1. Diagnosis

CONVERSION IN NAPLS: THOSE WHO DO NOT CONVERT TO PSYCHOSIS

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Background: A major focus in high risk research is determining the risk of conversion to psychosis and developing optimal algorithms of prediction. Although the reported rates of conversion vary in the literature, it always includes a minority of the samples. That is between 85% and 50% of putatively prodomal samples do not go on, at least in the duration of the studies (usually one year) to develop psychosis. Methods: The North American Prodrome Longitudinal Study (NAPLS 1) is an 8-site prospective, longitudinal study with up to 2.5 years of follow-up of over 300 prospectively identified treatment-seeking patients meeting Structured Interview for Prodromal Syndromes (SIPS) criteria for a psychosis risk syndrome. Over a 2.5 year follow-up 214 (71%) had not made the transition to psychosis. The sample being studied included 111 individuals who had at least 1 year of follow up, had not made the transition to psychosis within the duration of the study and were not on any antipsychotics. Results: Over time there was a significant reduction in those meeting prodromal criteria (100%–5.4%). In year one there was significant improvement in ratings on symptoms (SIPS) ($P < .0001$) although at least one attenuated positive symptom was present for 43% of the sample at one year and 41% at two years. Social and role functioning improved over time ($P < .01$) but remained significantly poorer compared to normal controls. Conclusion: Help seeking individuals who meet prodromal criteria appear to fall into 3 groups - those who develop a psychotic illness, those who remit in terms of the symptoms used to index risk status and who therefore may be considered to be "false-positives" and those who continue to have attenuated positive symptoms.
ID: 979236

PATERNAL AGE RELATED CHIZOPHRENIA (PARS): LATENT SUBGROUPS DETECTED BY K-MEANS CLUSTER ANALYSIS

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Background: Paternal age related schizophrenia (PARS) has been proposed as a subgroup of schizophrenia with distinct etiology, pathophysiology and symptoms. This study uses a data mining approach to generate hypotheses about differences between PARS and other cases of schizophrenia. Methods: We studied PARS (defined for exploratory purposes as not having any family history of schizophrenia among first and second-degree relatives and fathers' age at birth >35 years) in a case series recruited in a schizophrenia research unit. Data were available on numerous demographic variables, symptoms (Positive and Negative Syndrome Scale; PANSS), cognitive tests (Wechsler Adult Intelligence Scale—Revised; WAIS-R) and olfaction (UPSIT). We conducted a series of k-means clustering analyses to identify clusters of cases containing high concentrations of PARS. Results: Two analyses generated clusters with high concentrations of PARS cases. The first analysis (N = 136; PARS = 34) revealed a cluster containing 83% PARS cases, in which the patients showed a significant discrepancy between verbal and performance intelligence. The mean paternal and maternal ages were 41 and 33, respectively. The second analysis (N = 123; PARS = 30) revealed a cluster containing 71% PARS cases, of which 93% were females; the mean age of onset of psychosis, at 17.2, was significantly early. Conclusion: These results strengthen the evidence that PARS cases differ from other patients with schizophrenia. Hypothesis-generating findings suggest that features of PARS may include a discrepancy between verbal and performance and in females, an early age of onset. In future studies, these findings can provide a rationale for separating these phenotypes from others in clinical, genetic and pathophysiologic studies of schizophrenia and in considering responses to treatment.
ID: 979879

DIAGNOSTIC SPECIFICITY OF BIOLOGICAL MARKERS IN FIRST-EPISODE EARLY-ONSET PSYCHOSES

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Background: Several studies have shown neurobiological similarities in first-episode psychoses, including schizophrenia, bipolar disorder, and other psychoses. However, very few have assessed how the differences between the diagnoses persist during follow-up. We have examined the progression of brain changes, neuropsychological impairment, neurological soft signs, and oxidative markers in a sample of 200 first-episode early-onset psychosis patients and their relationship to diagnosis and prognosis at two-year follow-up. Methods: Prospective, multicenter, naturalistic study of 200 early-onset first-episode psychoses patients (mean age 15) and 110 healthy controls, with a follow-up time of 2 years. Results: Preliminary results show that volume changes in patients with schizophrenia, but not bipolar disorder or other psychoses, were significantly different than in controls for total gray matter (GM) and white matter (WM), and left frontal cerebrospinal fluid (CSF). There were no significant volume differences between diagnoses at baseline. Both in schizophrenia and bipolar patients, functional improvement correlated with less GM loss and lower rate of CSF volume increase in different brain areas. There were no significant differences at baseline between patients with different psychotic diagnoses in terms of neuropsychological performance and rate of neurological signs. However, at the two-year follow-up, patients who ended-up with a diagnosis of schizophrenia showed poorer functioning in those areas than patients with other psychoses. There were no differences between diagnostic groups in oxidative stress markers at baseline or follow-up. Conclusion: Differences between patients with a first psychotic episode with specific diagnoses are more obvious after two years of follow-up than at baseline. The use of biological markers for diagnostic purposes seems to be problematic after a first psychotic episode in children and adolescents. Progressive abnormalities seem to be more evident in patients that end-up with a diagnosis of schizophrenia. Changes in specific brain volumes and neuropsychological

performance may be related to markers of poorer prognosis and have diagnostic specificity.
ID: 978231

DISEASE BIOMARKERS FOR SCHIZOPHRENIA - FROM LABORATORY TO PATIENT BESIDE

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Background: Schizophrenia almost certainly presents a heterogeneous group of etiologies which may not be reflected in the symptomatic/clinical presentation of patients. Therefore, a better molecular understanding of the disease onset and progression is urgently needed. Methods: Multi-omics profiling approaches were employed to investigate large numbers of patient and control samples. These large scale experiments are required to identify disease intrinsic molecular signatures as well as patient subgroups with potentially distinct biochemical pathways underpinning their symptoms. Results: We have investigated serum and CSF from several hundred first-episode schizophrenia patients and were able to identify a number of highly significant peptides and proteins that distinguish first-onset paranoid schizophrenia patients from healthy controls. Our findings suggest alterations in glucoregulatory processes in CSF of drug-naïve patients with first-onset schizophrenia. Short-term treatment with atypical antipsychotic medication resulted in a normalization of the CSF disease signature in half the patients well before a clinical improvement would be expected. More recently, we have identified a candidate biomarker panel in patient serum, specifically up-or down-regulated in drug naive, first onset schizophrenia patients compared to healthy controls using high throughput proteomic profiling and multiplexed immunoassay profiling technology. A panel of 51 markers was found to yield an average sensitivity and specificity of >85% across five clinical centres comprising 572 first-onset drug-naive and recent onset schizophrenia patients vs 235 matched healthy control samples. Abnormalities remained significant after adjustment for all recorded baseline characteristics. As part of the EU Innovative Medicine Initiative NewMeds (http://www.newmeds-europe.com/) we have also evaluated the serum protein signatures of 14 animal models of schizophrenia (as used by the pharmaceutical industry in preclinical studies) and compared the changes with schizophrenia patients. We found that only few animal models show significantly similar serum signatures to the human disease. Conclusion: Our findings demonstrate the applicability of a rapid and non-invasive blood test to confirm the presence of schizophrenia. Several animal models of schizophrenia show significantly similar serum changes as observed in humans.
Thank you to the Stanley Medical Research Institute for Centre support.
ID: 996067

THE USE OF BLOOD BASED SIGNALS AS AN AID IN DIAGNOSIS AND TREATMENT PLAN DEVELOPMENT

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Background: While physicians are trained deeply in biochemical pathways as a context from which to perform diagnosis, most practicing physician revert to a role of pattern recognition, comparing the patient presently being diagnosed with similar past diagnostic challenges. Psychiatrists in particular tend to craft treatment plans based upon their own experience with patients and therapies, usually without any thought of underlying mechanism. Methods: The goal of this presentation is to present the underlying mathematical logic in developing a blood based test to help diagnose schizophrenia. Results: The talk considers the different mathematical steps needed to move from the selection of a multivariate blood based analyte panel likely to give good predictive power to inclusion of the result in the logic of diagnosis. The talk will examine machine learning, ROC curves, inductive vs deductive logic and Bayesian frameworks in turn. Conclusion: There is a place in psychiatric diagnosis for inductive aids that increase the probability of objective consistency based upon a biochemical profile.
ID: 996159

USING MULTI-MODAL NEUROIMAGING DATA TO PREDICT CONVERSION TO PSYCHOSIS IN CLINICALLY AT-RISK YOUTH

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Background: Early identification of youth at high risk for the development of psychosis is critical to advance our understanding of mechanisms underlying illness onset - and to apply preventive interventions to those truly at-risk- but current clinical criteria for risk prediction have achieved only modest accuracy. The goal of the current analysis was to determine whether improvement in predictive algorithms could be achieved by incorporating neuroanatomic data. Methods: Forty adolescents and young adults (aged 12–30; 67% male) who met criteria for clinical high-risk (CHR) for psychosis and 42 demographically comparable healthy controls were evaluated with high-resolution structural MRI and diffusion tensor imaging at baseline. Variables included in analyses were: baseline positive and negative symptoms, fractional anisotropy (FA) values in fronto-parietal and medial temporal white matter tracts; total gray and white matter volume; hippocampal and amygdala volume. Multiple logistic regression models were used to examine the joint predictive value of these measures for determining conversion to psychosis. Results: Fourteen (35%) of CHR participants converted to a psychotic disorder during the 1–2-year follow-up period. Baseline positive and negative symptom severity alone predicted conversion to psychosis with 72% accuracy. Of the neuroimaging variables examined, FA in the cingulum bundle was uniquely associated with conversion to psychosis. Inclusion of cingulum FA values in the model improved predictive accuracy to 82%. Overall gray and white matter volumes did not improve predictive value of the model, over and above clinical predictors. Conclusion: Myelination of the cingulum bundle, a key connection to the frontal lobe, is known to occur during late adolescence. Decreased white matter integrity in this tract was associated with conversion to psychosis in CHR youth. While global brain volumes did not significantly contribute to the model, localized gray matter reductions may make an important contribution to predictive accuracy, a possibility that will be explored in future analyses applying cortical mapping approaches. The development of multivariate prediction algorithms with improved positive predictive power will help to identify those at highest risk (minimizing exposure of false-positive cases to potential adverse events), and will facilitate studies of neurobiological mechanisms that occur proximal to the onset of psychosis.
ID: 979102

THE ABERRANT SALIENCE INVENTORY: VALIDATION OF A NEW MEASURE OF PSYCHOSIS PRONENESS

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Background: Aberrant salience is the unusual or incorrect assignment of salience, significance, or importance to otherwise innocuous stimuli and

has been hypothesized to be important for psychosis and psychotic disorders such as schizophrenia. However, despite the importance of this concept in psychosis research, no questionnaire measures are available to assess aberrant salience. The current research describes four studies designed to develop and validate the Aberrant Salience Inventory (ASI) as a measure of aberrant salience. Methods: In Study 1, an over-inclusive item pool was subjected to an exploratory factor analysis and items were kept or discarded based on factor loadings. In Study 2, the factor structure of the ASI was confirmed with a confirmatory factor analysis and a higher-order structure was tested. In Study 3 and Study 4, we tested whether participants with an increased risk for psychosis and a history of psychosis had elevated ASI scores compared to comparison groups. Results: The results of study 1 suggested that the ASI is composed of five correlated factors. The final ASI measure includes 29 items. In Study 2, the five-factor structure of the ASI was confirmed with a confirmatory factor analysis and a second-order factor analysis found evidence consistent with a single higher-order factor. Study 2 also provided support for the scale score's convergent validity as the ASI was strongly associated with psychosis-proneness measures and dissociation measures, and moderately correlated with measures associated with levels of dopamine. In addition, this study also provided support for its discriminant validity as the ASI was only weakly associated with social anhedonia. Study 3 found that participants with elevated psychosis proneness had increased ASI scores, but in contrast, participants with elevated social anhedonia had similar scores to comparison participants. Finally, Study 4 found that participants with a history of psychosis had elevated ASI scores compared to a psychiatric comparison group. Conclusion: Overall, the ASI demonstrated sound psychometric properties and may be useful for measuring aberrant salience and psychosis proneness in clinical and non-clinical samples. Future research could use the ASI to further explore the nomological network of aberrant salience as a construct.
ID: 978841

NEUROLOGICAL SOFT SIGNS IN NON-PSYCHOTIC PATIENTS WITH CANNABIS DEPENDENCE

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Background: Psychomotor performance has consistently been found to be altered in chronic cannabis users. Neurological soft signs (NSS) reflect neurological dysfunction involving integrative networks, especially those involving the cerebellum, where cannabinoid receptors are particularly concentrated. To our knowledge, there is no study assessing NSS in cannabis dependence. The objective of the present study was to assess NSS in a group of patients with cannabis dependence compared to a group of healthy control subjects, matched for age, gender and level of education. Methods: All outpatients seeking treatment for chronic cannabis use in the substance abuse department of Sainte-Anne Hospital in Paris, between June 2007 and May 2009, and meeting the cannabis dependence DSM-IV criteria, were included in the study ($n = 45$). Patients with psychotic disorders, bipolar 1 disorders, current (within five years before the assessment) alcohol, opioid or cocaine dependence were excluded. All patients and controls were assessed using the Diagnostic Interview for Genetic Studies (DIGS), which screens for lifetime DSM-IV diagnoses and the Standardized Neurological Examination of Neurological Soft Signs. Results: The mean age of the patients and healthy control subjects were 27.4 (±9.3) and 27.8 (±8.5) years, respectively (ANOVA $F = .05$, $P = .83$). Of the subjects in both groups, 82% were male and 18% were female. The mean levels of education were similar. In the group of patients with cannabis dependence, the mean ± SD age of onset of cannabis use, regular use and dependence were 15.8 ± 2.7 years, 19.0 ± 6.8 years, and 20.2 ± 7.3 years, respectively. All the patients smoked cannabis daily at the time of assessment. The mean number of cannabis cigarettes/day smoked was 6.9 ± 4.1. The mean duration of cannabis dependence was 7.30 ± 5.0 years. Neurological soft signs scores were significantly higher in patients with cannabis dependence compared to healthy subjects (8.90 ± 4.85 vs 6.71 ± 2.73, respectively, Mann-Whitney: $U = 775.0$, $P = .05$). Patients had particularly high scores on motor coordination and sensory integration NSS factors ($U = 769.0$, $P = .049$; $U = 585.5$, $P = .0001$, respectively). Conclusion: Cannabis dependence is associated with more neurological soft signs, and especially motor coordination and sensory integration signs. These results suggest that cannabinoids interact with the brain networks underlying NSS, known to be altered in schizophrenia.
ID: 986872

COMPARISON OF PUTATIVE ENDOPHENOTYPES IN SCHIZOPHRENIA PATIENTS WITH AND WITHOUT OBSESSIVE-COMPULSIVE DISORDER: IS THERE EVIDENCE FOR A SCHIZO-OBSESSIVE SUBTYPE?

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Background: Obsessive-compulsive symptoms (OCS) and obsessive-compulsive disorder (OCD) is estimated to occur in up to 30% of patients with schizophrenia, a much higher prevalence than is observed in the general population (1.2%–2.4%). OCS are also increased in the psychosis prodrome and are thought to involve basal ganglia and prefrontal areas. Studies have recently begun to investigate a possible OCD subtype of schizophrenia, but whether this subgroup of patients is cognitively, affectively, or physiologically distinct from non-OCD schizophrenia remains unclear. Methods: A total of 189 patients with a diagnosis of schizophrenia but not OCD, 15 schizophrenia-OCD-co-morbid patients, and 147 healthy comparison subjects were examined using measures of eye tracking dysfunction (ETD), craniofacial dysmorphology, and thought disorder. The Brief Psychiatric Rating Scale was used to examine symptom severity in the patient groups. Results: Two measures distinguished the OCD subgroup from the non-OCD schizophrenia patients. OCD patients showed elevations in anxiety and tension relative to non-OCD patients, and showed a significantly increased rate of smooth pursuit eye movement (SPEM) abnormalities (72%) relative to that observed in the non-OCD schizophrenia patients (44%; Controls = 12%). Patients with co-morbid OCD did not present with significantly worse craniofacial dysmorphology (using an embryologically-derived measure of primordia derivatives), higher levels of thought disorder, or more severe symptomatology compared with non-OCD schizophrenic patients. Both patient groups differed significantly from controls on these variables. Conclusion: Schizophrenia patients who also qualify for a diagnosis of OCD resemble non-co-morbid patients in most regards. However, the higher rate of eye-tracking dysfunction in the co-morbid group raises the possibility of selective involvement of specific brain regions, conceivably implicating striatal dysfunction in the pathophysiology of this subgroup. Given that fMRI studies of OCD have implicated basal ganglia and prefrontal dysfunction, it is plausible that these areas might be differentially affected in a subgroup of patients with schizophrenia. These findings suggest that it would be useful to examine the relation between OCS and ETD in nonpsychotic relatives of both subgroups of schizophrenia patients, as well as in relatives of OCD patients who are not co-morbid for schizophrenia.
ID: 976853

SUICIDAL BEHAVIOR IN HOMELESS VETERANS

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Background: A semi-structured interview was administered to 3595 homeless veterans in which psychiatric diagnosis was recorded and questions were asked about suicidal behaviors. The aim was to evaluate rates of suicidal behaviors across schizophrenia, mood disorder and substance abuse disorders and to calculate relative risk ratios across diagnostic groups. Methods: Comparisons were made using chi-square analyses to examine the strength of association between suicidal behaviors and diagnostic group status. Separate analyses were conducted for 30-day history of suicide attempts and current suicidal ideation. Group data were dichotomized and odds-ratios (OR) and 95% confidence intervals (95% CI) were computed to evaluate risk relative to the substance abuse group. Results: Reports of recent suicide attempts among individuals with schizophrenia (5.3%) and mood disorder (5.6%) each exceeded the rate for the substance abuse group (1.3%), $P < .001$. Likewise, rates for suicidal thoughts for the schizophrenia group (20.1%) and the mood disorder group (24.5%) each exceeded the rate for the substance abuse group (4.6%), $P < .001$). For schizophrenia and mood disorder groups combined (as contrasted with the substance abuse group), OR (95% CI) = 4.38 (2.12–9.03) for suicide attempts, and OR (95% CI) = 6.35 (4.28–9.41) for suicidal ideation. For the schizophrenia group (as contrasted with the substance abuse group), OR (95% CI) = 4.1 (1.8–9.5) for suicide attempts, and OR (95% CI) = 5.2 (3.28–8.10) for suicidal ideation. Conclusion: Higher rates of suicidal behaviors were observed among homeless veterans with schizophrenia or mood disorder as contrasted with homeless veterans with substance abuse disorders, but the schizophrenia and mood disorder groups did not differ substantially from each other. This finding is contrary to the belief that suicidal behaviors among homeless individuals occur, for the most part, in individuals with alcoholism or other forms of substance abuse.
ID: 986782

THE HOTEL STUDY: ADDICTION, MENTAL ILLNESS AND VIRAL INFECTION

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Background: The purpose of the study was to characterize clinically significant findings in people living in transitional housing, in the form of single-room occupancy (SRO) hotels. Methods: We recruited participants with the only inclusion criteria being current residence in an SRO hotel in Vancouver, Canada. The present report concerns substance exposure in the previous month, results from urine drug screens (UDS), evidence for active psychosis from the Positive and Negative Syndrome Scale (PANSS), depression from the Beck Depression Inventory (BDI), and viral serology. Results: From 230 study participants, only 5% of UDS were negative for non-prescribed drugs. The most common UDS positives were: cocaine 75%, cannabis 41%, opiates 37%, methamphetamine 25%, amphetamine 19%. More than one of these five drugs were detected in 63% of samples. In this SRO-living cohort, 117 (51%) had used intravenous drugs in the past 30 days, and 97 (42%) had shared crack pipes. Of the injection drug users, only 2 described sharing syringes, 86 (74%) used the supervised injection site in Vancouver. Previous treatment for mental illness was acknowledged by 50% of participants, 33% requiring hospital admission, but only 9% to a chronic or Provincial Hospital. Active psychotic symptoms were detected in 123 (53%) participants; only 29 (24%) of this group were treated with antipsychotic drugs. BDI scores ≥ 21 were present in 53 participants (23%); only 8 (15%) of this group were treated with antidepressant drugs. HIV seropositive status was detected in 45 participants (19%); 30 (71%) of this group were treated with antiretroviral drugs. Only 1 new case of HIV was detected. Hepatitis C seropositive status was detected in 154 participants (69%); 6 were new cases. Conclusion: Exposure to stimulant drugs was nearly ubiquitous in this cohort of people living in SRO hotels. Sharing crack pipes was common; this can increase risk of viral transmission. The majority experienced psychotic symptoms, and a substantial minority appeared depressed. HIV and HCV exposure was very high. These data confirm the previously suspected very high prevalence of psychotic and depressive symptomatology in this population and suggest that proportionately, treatment for HIV/AIDS was more frequent than treatment for psychosis or depression. Successful implementation of British Columbia's "seek and treat" model for HIV diagnosis and therapy may require integrated support for addictions and mental disorders.
ID: 977304

SUBSTANCE MISUSE AND FIRST EPISODE PSYCHOSIS, A STUDY OF ASSOCIATED RISKS

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Background: Studies have shown a link between substance misuse and development of psychotic disorders. The TIPS study has shown that 22% of patients meeting criteria for substance induced psychosis at screening later developed a schizophreniform spectrum psychosis. Methods: Patients are included from the early-detection sector of TIPS (Rogaland, Norway) into a naturalistic follow-up study. The sample consists of 100 consecutive first-episode psychosis patients consenting to study inclusion from 2006 to 2010. Patients are compared for possible baseline characteristics and differences. Comparing a group of consecutive patients with SIP (Substance Induced Psychosis) with a group that has primary psychosis (PPS) with substance misuse and a group that has primary psychosis (PP) without substance misuse at baseline. Results: The sample consisted of 24 SIP patients, 21 PPS patients and 55 PP patients. There were no differences in terms of age, sex, or suicidality between the groups. Duration of untreated psychosis (DUP) did not differ statistically, but there was a trend towards SIP patients being picked up earlier. ($P = .052$, median: SIP-2,00; PPS-5,00; PP-20,00. Furthermore, a difference was found in the PANSS Excitement component between SIP- and PPS patients ($P = .49$) and between SIP- and PP patients ($P = .006$) indicating a higher level of hypervigilance in SIP patients ANOVA showed a difference between groups in terms of GAF functioning ($P = .025$; SIP-37,00; PPS-37.14; PP-42,44). Conclusion: Preliminary results indicate that SIP patients are picked up earlier, have higher scores in the PANSS excitement component and lower GAF functioning scores compared with primary psychosis patients.
ID: 979214

RELIABILITY AND VALIDITY OF THE CLINICAL ASSESSMENT INTERVIEW FOR NEGATIVE SYMPTOMS (CAINS): A REPORT FROM THE COLLABORATION TO ADVANCE NEGATIVE SYMPTOM ASSESSMENT

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Background: Negative symptoms remain an unmet treatment need in schizophrenia, and treatment development and refinement has been stalled, in part, due to the lack of a current, comprehensive clinical assessment measure of negative symptoms. The Collaboration to Advance Negative Symptom Assessment in Schizophrenia (CANSAS) is an NIMH-funded, multi-site study designed to develop and validate a new clinical rating scale for negative symptoms using a data-driven, iterative process. The CAINS includes items covering the five consensus negative symptoms: asociality, avolition, anhedonia, blunted affect, and alogia. Methods: The first phase of the CANSAS project has now been completed, and in this paper, we present data from 277 ethnically diverse men and women with schizophrenia and schizoaffective disorder. Participants were interviewed with the CAINS along with the BPRS, Calgary Depression Scale for Schizophrenia (CDSS), and a measure of general cognitive ability (WTAR) in order to establish the initial convergent and discriminant validity of the CAINS To examine the reliability of the CAINS, we adopted a rigorous procedure whereby interrater agreement was assessed both within each of the four study sites (UC Berkeley, Penn, UCLA, and Maryland) as well as between the sites. Results: Internal consistency estimates (alphas) of the CAINS total and subscales were high, ranging from .83 to .88. Within site rater agreement was high, with intraclass correlations (ICCs) ranging from .75 to .94 for the five negative symptom domains. In addition, agreement between raters at different sites was also excellent (ICCs from .75 to .95). The CAINS total and subscales were positively correlated with the BPRS anergia subscale (r's ranging from .30 to .66), demonstrating good convergent validity. Good discriminant validity was observed with the non-significant correlations between the CAINS and other BPRS subscales, the CDSS, and WTAR. Conclusion: Results demonstrate that the CAINS scales are internally consistent, show good convergent validity, and good discriminant validity with little shared variance with non-negative symptoms. Further, rater agreement for the CAINS was high within and across sites. We will discuss the processes by which the CAINS has been revised and shortened, as well as additional validity and test-retest reliability that are part of Phase 2 of the CANSAS project.
ID: 976312

TREATMENT NEEDS OF INDIVIDUALS SEEKING PSYCHIATRIC HELP FOR PSYCHOTIC SYMPTOMS LINKED TO METHAMPHETAMINE ABUSE

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Background: Recent studies suggest that MA users with psychosis are much more likely to experience psychotic symptoms again if they use MA, and are also more likely to have a psychotic relapse when confronted with stressful events, even years after cessation of MA use. MA users with persistent or recurrent psychotic symptoms become vulnerable to stress and may benefit from antipsychotic medication the same way individuals with schizophrenia do. Our study aimed at describing the trajectories of symptoms and substance abuse over time of individuals with methamphetamine (MA) abuse and psychotic symptoms. We also wished to determine services and treatments received during this period. Methods: 295 individuals needing psychiatric help for MA psychosis were assessed at baseline on various profile measures, as well as monthly for six months regarding their substance abuse patterns and psychiatric symptoms. File reviews were also conducted to determine treatments received. Results: Trajectory analyses on positive symptoms revealed two principal groups: sustained-high (30%), and decreasing-low 70%). Logistic regression revealed that the strongest predictors (forward Wald) of having the sustained-high psychosis overtime were more years of use of amphetamines and more severe depressive symptoms. This group was also significantly older. There were trends toward more individuals in the high psychosis group with antisocial personality disorder, more years of alcohol abuse. Diagnoses and treatments received for each group during the six months of the study will also be described. Conclusion: Close to one third of individuals presenting with methamphetamine abuse and psychosis seem to present with higher treatment needs, in terms of higher and more sustained psychotic symptoms, more severe depressive symptoms, more substance abuse (MA and alcohol) and more personality problems. Previous baseline results from this study had also revealed high comorbidities in this sample, namely regarding PTSD. Future directions, such as ways of targeting these "higher treatment needs" individuals in order to offer them better tailored treatments, will be discussed.
Predictors of worst psychotic profile in MA abusers

Variable	B	Wald	Exp(B)
MA (y)	.62	4.9	1.06
BDI	1.19	12.4	.30

ID: 975802

CHILDHOOD TRAUMA AND STRESS RESPONSIVITY IN ADOLESCENTS AND YOUNG ADULTS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: In the stress-vulnerability model of schizophrenia, early childhood trauma has been posited to contribute to the development of a dysregulated stress-response system, with downstream effects on neural systems involved in psychosis, potentially increasing risk for development of the disorder. However, little prospective work has been done assessing early trauma in young people at "ultra-high-risk" (UHR) for psychosis. Methods: In this study, participants age 12–30 diagnosed as having a UHR syndrome on the Structured Interview for Prodromal Syndromes ($N = 30$) and a group of age-matched healthy control adolescents ($N = 19$) completed comprehensive clinical and neuropsychological batteries at study entry. Participants in both groups provided saliva samples to assess diurnal cortisol rhythms, response to a social evaluative lab stressor task and response to administration of dexamethasone. UHR participants

were followed for up to 24 months after baseline. Results: Preliminary analyses show that more UHR participants reported a history of 1 or more traumatic events prior to age 13 (57%) than did healthy controls (28%; $P < .05$). By 6-month follow-up, 3 of 21 UHR subjects (14%) had converted to a full psychotic disorder and 6 of 13 subjects had converted by 12 months (46%). Secondary analyses of outcome prediction among UHR subjects and results of salivary cortisol assessments will also be reported. Conclusion: Consistent with the growing literature on early trauma and schizophrenia, adolescents and young adults at ultra-high-risk for psychosis report experiencing more traumatic events in childhood than their age-matched healthy control counterparts. Ongoing work will assess whether this early trauma is related to psychotic-like symptoms and hypothalamic-pituitary-adrenal (HPA) axis functioning in UHR individuals, and whether trauma history and dysregulated stress responsivity are risk factors for developing full psychosis. This research was supported by a grant from the NIMH K23 MH086618 and a NARSAD Young Investigator award to Rachel Loewy.
ID: 979002

FACTOR STRUCTURE OF THE POSITIVE AND NEGATIVE SYNDROME SCALE DIFFERS BY SEX

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Background: The factor structure of the Positive and Negative Syndrome Scale (PANSS; Kay et al, 1987), one of the most widely used measures in schizophrenia research, has been studied extensively to determine the best way to categorize the underlying symptom constructs associated with schizophrenia. However, results of numerous factor analyses have been inconsistent and questions about the underlying factor structure remain. The purpose of this study was to examine whether the factor structure of the PANSS differs in men and women with schizophrenia. Methods: Principal components analysis (PCA) with equamax rotation was used to examine the factor structure of the Positive and Negative Syndrome Scale (PANSS) separately in 124 males and 74 females with schizophrenia spectrum disorders. Rotated factor patterns were observed for simple structure (items loading >.4 on one factor and <.4 on other factors). The number of factors retained was based on observation of the scree plot as well as the number of high loading items on each factor. Items that did not load on any factor or loaded on more than one factor were excluded and the PCA was repeated until at least three items loaded onto each factor and simple structure was maintained. Results: In males, five items were dropped from the analyses resulting in a four factor structure, accounting for 54.54% of the total variance: (1) Negative (25.91%), (2) Cognitive (12.04%), (3) Positive (9.84%) and (4) Hostility (6.75%). In females, nine items were dropped from the analyses resulting in a four factor structure, accounting for 59.54% of the total variance: (1) Negative (28.12%), (2) Cognitive (13.68%), (3) Positive (11.34%) and (4) Depression (6.39%). The most notable difference between the male and female PCAs is the presence of a depression factor in the females and a hostility factor in males. With the exception of lack of insight (which loaded on the depression factor in females and the hostility factor in males), the items that make up the depression factor in females loaded on the positive factor in males, and the items that make up the hostility factor in males loaded on the cognitive factor in females. Conclusion: These results show important sex differences in the factor structure of schizophrenia symptoms. These effects may have contributed to the prior conflicting results in the literature. Research in the field must account for sex differences in examining the effects of treatment and other sources of heterogeneity in the factor structure of the PANSS.
ID: 977231

DIAGNOSTIC OUTCOMES OF CASES REFERRED AS CHILDHOOD-ONSET SCHIZOPHRENIA AFTER INPATIENT EVALUATION AND MEDICATION WASHOUT: A LONGITUDINAL FOLLOW-UP.

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Background: The NIMH childhood onset schizophrenia (COS) study has offered the unique opportunity to examine a cohort of children who have been diagnosed with schizophrenia in the community but who fail to meet the criteria for schizophrenia after a careful inpatient observation that includes complete medication wash-out. Methods: Since 1991, through nationwide recruitment, over 200 children were accepted with a provisional diagnosis of COS for further inpatient evaluation that included up to three weeks of medication free observation. A 2010 follow up of patients who did not meet criteria for COS was made by telephone and in-person interviews. 34 of 85 identified patients participated in the follow-up. Results: 117 patients received the diagnosis of COS. Of the remaining 85 rule-outs there were 34 participants available for interview. Of this group, 19 met the diagnosis of affective syndromes (14 bipolar, 4 MDD, 1 mood disorder NOS), 10 psychotic disorders (5 PNOS, 2 PNOS in full remission, 1 PNOS in partial remission, 1 schizoaffective, 1 schizophrenia), 2 anxiety disorders, 1 intermittent explosive disorder, and 1 had ADHD as the current primary diagnosis. Incidence of comorbid diagnosis was high. Only 1 no longer met criteria for any diagnosis and only 1 proband's diagnosis was changed back to COS. Conclusion: Among the patients admitted with suspected COS diagnosis, only 117 (58%) met criteria for COS while 85 (42%) did not have a COS diagnosis. In general, among the rule outs very few converted to COS prior to follow up suggesting the importance of careful diagnostic evaluation in each case, and longer term follow up to assess diagnostic stability. Many of these rule-out patients continued to experience significant psychiatric disorders.
ID: 978949

ULTRA HIGH RISK (UHR) FOR PSYCHOSIS GROUPS: ARE THERE DIFFERENT LEVELS OF RISK FOR TRANSITION TO PSYCHOSIS?

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Background: The "ultra-high risk" (UHR) approach consists of identifying three help-seeking groups: 1. Individuals with attenuated psychotic symptoms (APS), 2. Individuals with brief limited intermittent psychotic symptoms (BLIPS), 3. Individuals with a trait vulnerability combined with a recent deterioration in functioning (Trait). It is unclear whether a particular UHR group, or combination of groups, has a higher risk of transition to psychosis than other groups. In this study, we investigated this issue over a six-month follow up period. We a priori hypothesized that the transition rate would be BLIPS>APS>Trait. Methods: 817 UHR subjects were recruited from the PACE clinic, Orygen Youth Health, Melbourne. Results: 72 subjects (8.8%) transitioned to psychosis within 6 months. After adjusting for sex, age, antipsychotic medication, year of presentation and type of intervention, intake group remained a significant factor ($P = .024$). As hypothesized, the BLIPS group (regardless of whether they also met criteria for other groups) displayed the highest transition rate, followed by the APS group (regardless of whether they also met criteria for other groups) and then the Trait group alone. Conclusion: The current data indicate that within the UHR population the BLIPS group are at highest risk of transition over the short term, followed by subjects with APS, followed by those who meet the Trait group alone. This stratification of risk within the UHR

population may provide a means of further "closing in" on those at highest risk of frank psychosis and inform treatment approaches.
ID: 978234

ALTERATIONS IN WHITE MATTER INTEGRITY CORRELATED WITH COGNITIVE DYSFUNCTION IN FIRST EPISODE SCHIZOPHRENIA

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Background: Schizophrenia is a devastating illness with multiple symptoms domains, including positive, negative and cognitive deficits. Evidence is growing that outcome maybe be improved with early detection and treatment. Diffusion tensor imaging has shown structural abnormalities in white matter in people in the early and chronic stages of schizophrenia. The possibility of using DTI as a biomarker has been suggested by Moriya et al 2009 when they found structural abnormalities in the brain present during the early stage of first-episode schizophrenia. Recent studies have demonstrated an association in deficits in executive and motor function in patients with first-episode psychosis with reductions in white matter integrity in major fasciculi (Perez-Iglesias et al 2010). Few studies have examined both white matter integrity and associated neuropsychological function in First Episode Psychosis. Decreased fractional anisotropy of the left SLF has been associated with verbal working memory performance (Karlsgodt et al 2008). We propose that there will be an association between fractional anisotropy and cognitive tasks measuring verbal memory. Methods: 30 adults with first-episode schizophrenia and 30 healthy, age, sex, and handedness matched controls were scanned on a Siemens 3 Tesla MRI scanner. Connectivity distributions were generated with FSL BEDPOST/PROBTRACKX for the Superior Longitudinal Fasciculus (SLF). Mean fractional anisotropy will be determined for the left tract. Cognitive tasks completed to estimate verbal memory included the WAIS-III Wechsler Memory Scale III and the CVLT-II. Results: Currently analyzing data. Conclusion: At the time of submission we are analyzing the data, however this is important follow-up to recent studies published associating specific cognitive deficits and white matter abnormalities.
ID: 979803

ANXIETY DISORDERS AND SUBSTANCE USE DISORDERS IN FIRST-EPISODE PSYCHOSIS

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Background: Our recent meta-analysis (Achim et al, Schizophrenia Bulletin, 2010) reported elevated yet highly variable rates of anxiety disorders (AD) in SZ spectrum related psychoses (SZSPD). We herein seek estimating AD rates in recent onset SZSPD using a novel instrument, the Diagnostic and Dimensional Assessment of Psychoses and Comorbidities (DDAPC). Furthermore, we seek to verify whether the association between anxiety and substance use disorders found in general population studies can be found in psychotic disorders. Methods: Fifty-four SZSPD recent-onset subjects were interviewed using the DDAPC, a semi-structured instrument combining the SCID, CASH, PANSS, SDS, PSYRATS to comprehensively assess several pathology domains. It also includes the Yale-Brown Obsessive-Compulsive Scale (YBOCS) and the Liebowitz Social Anxiety Scale (LSAS) to finely assess OCD and social phobia with a procedure that allows determining if their addition improves AD detection over information yielded by SCID probes. We added probes assessing DSM-IV hierarchy criteria and developed detailed standardized instructions on applying these rules. Results: We observed the following lifetime prevalence rates of probable or definite AD: panic disorder: 9.3%, social phobia: 48.1%; specific phobias: 5.6%; post-traumatic stress disorder 3.7%; generalized anxiety disorders 9.3%; OCD: 14.3%; at least one AD: 61.1% $n = 33$, among whom 84.9% ($n = 28$) had at least one AD occurring prior to psychosis onset. Roughly half of our OCD and social phobias were detected with the YBOCS or LSAS respectively after not being identified through the SCID probes. Among patients with AD, 77.3 % had a lifetime history of substance use disorders vs. 50% among patients without AD (odds ratio =3.5; $P \leq .05$). Conclusion: AD rates in recent onset SZSPD may be higher than previously assessed. The use of additional probings such as included in the YBOCS and LSAS may increase the sensitivity of AD diagnoses. The association between AD and substance use disorders suggests that successfull treatment of AD may contribute to decreasing substance use. These results warrant further investigation of the nature of AD/SZSPD comorbidity.
ID: 979789

AT-RISK FOR DEVELOPING PSYCHOSIS - ADVANCING CRITERIA FOR PREDICTION

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Background: The major challenge for prevention of psychosis is the definition of criteria which likewise allow sufficiently early intervention and sufficient enrichment of risk. Recent studies indicated that ultra-high risk (UHR) criteria produce a higher variance of risk enrichment than required for time limited prevention studies. A combination with basic symptoms (BS) may be useful. BS are assumed to be closer related to disturbed cerebral processes than the hypothetically later emerging, epiphenomenal psychotic symptoms. Methods: The naturalistic European Prediction of Psychosis Study (EPOS) included 245 help-seeking individuals at six specialized centers by UHR criteria and/or the basic symptom criterion "cognitive disturbances" (COGDIS). Follow-up period was 18 months (T0, T1, T2). Based on a multivariate Cox model, a prognostic index (EPOS-PI) with four risk classes was developed. Results: At T0, 59.6% reported a combination of UHR and COGDIS [A], 30.2% UHR alone [B] and 10.2% COGDIS [C] alone. The overall 18-month transition (hazard) rate was 19%; the transition rates per subgroup were [A] 22%; [B] 18% and [C] 5%. In group [C], 4% showed a prognostic score equivalent to EPOS-PI risk class 4, 7% in [B] and 20% in [A]. Within this highest risk class of the EPOS-PI, which was associated with a 18-month transition rate of 85%, 83% belonged to condition [C], only 14% to condition [B] and 3% to condition [A]. Comparing T0 and T2 in subjects (yet) without a transition to psychosis, [C] and also [A] were associated with a three times higher percentage of subjects progressing to worse SIPS-positive scores than [B] (13%; 15%; 4%). Attenuated positive symptoms as part of UHR were still present in 33% of [C], 25% of [B] and newly developed in 14% of [A]. Worsening of GAF scores was high across all groups ([A] 60%, [B] 77%, [C] 76%). Conclusion: Findings of this and another equally large study from the FETZ in Cologne demonstrate that a simultaneous use of both criteria improves sensitivity even for the relatively short observation periods of prevention studies. Furthermore,

the combined presence is associated with a higher risk for psychosis and a more sustained risk over time. Using both UHR and COGDIS as risk detection criteria (accompanied by the EPOS-PI for 2nd step risk stratification) is recommended and might serve as a reliable starting point for further risk assessments including also non-specific variables such as functional decline and/or (attenuated) negative symptoms.
ID: 985406

REDEFINING AT-RISK: CLINICAL AND FUNCTIONAL OUTCOMES OF PUTATIVELY PRODROMAL YOUTH WHO DO NOT DEVELOP PSYCHOSIS

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Background: The ''prodromal risk syndrome'' construct was designed to identify individuals at clinical-high-risk (CHR) of developing psychosis. However, most individuals identified as putatively prodromal do not convert to psychosis over follow-up, and it is unknown whether these non-converting individuals actually recover from an at-risk state. A question of major importance is whether the non-converting CHR patients represent ''false positives'' from the perspective of risk ascertainment. The ability to prospectively differentiate those individuals who are most likely to recover clinically and functionally from those who do not would aid in efforts to refine the risk syndrome criteria and limit exposure of false positive cases to interventions that carry some side effect burden. Methods: Eighty-seven prospectively identified patients meeting Structured Interview for Prodromal Syndromes (SIPS) prodromal criteria and 58 healthy comparison subjects were followed in a two-year longitudinal study. Clinical and functional recovery algorithms were developed to represent remission of positive symptoms and achievement of normative functioning. Analyses examined the course, rate and time to clinical and functional recovery from a CHR state. Results: Survival analyses modeling time to remission among non-converting CHR patients indicated that 47% reached remission of positive symptoms, but only 26% reached a normative level of functioning over the follow-up period. Profile analyses confirmed distinct trajectories in symptoms and functioning among subgroups of non-converters, with about half experiencing a significant decline in positive symptom severity over time and the remainder showing stable levels of positive symptoms and functional deficits but without converting. Functional deficits in non-converters were significantly associated with co-morbid mood and anxiety symptoms. Conclusion: Non-converting CHR cases represent a heterogeneous group, but about 50% show remission of attenuated positive symptoms and on that basis could be considered false positives. Given that non-converters who remitted also presented initially with lower prodromal symptomatology and better psychosocial functioning than both converters and non-converters who remained symptomatic, refinement of prodromal risk criteria targeting subjects who experience more severe attenuated positive symptoms and functional deficits would result in a substantial increase in positive predictive power.
ID: 939639

PSYCHOPATHOLOGY AND ADAPTIVE FUNCTIONING IN INDIVIDUALS WITH FIRST EPISODE SCHIZOPHRENIA, CLINICAL-HIGH-RISK FOR PSYCHOSIS, AND AUTISM SPECTRUM DISORDERS

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Background: Few studies have systematically compared adolescents with autism spectrum disorders (ASD) and first-episode schizophrenia (FEP) on parent-report measures designed to assess psychopathology and adaptive behavior deficits. This study compares both of the above groups, with the addition of a clinical-high-risk (CHR) group consisting of individuals exhibiting sub-threshold psychotic symptoms. Methods: We recruited four groups of FEP, CHR, ASD patients and typically developing (TYP) (n = 20 per group) participants aged 11–20 that were ascertained using gold standard diagnostic measures. Caregivers completed, along with other measures, the Behavior Assessment System for Children (BASC-2), which contains two composite scales assessing symptoms of both externalizing and internalizing psychopathology (Clinical Scale) and behaviors associated with social functioning, adaptability and leadership (Adaptive Scale). Results: On almost all Clinical and Adaptive domains of the BASC, TYP were rated as significantly different from their clinical counterparts, reflecting a more positive assessment. In the Clinical domains of Hyperactivity, and Internalizing Problems CHR and ASD showed equivalent impairment. On Aggression, CHR scored the highest, reflecting a lack of control over behavior. On Conduct, CHR and FEP showed significant impairment, with FEP averaging in the at-risk level. On the Atypicality and Withdrawal scales, all clinical groups were equivalent, with ASD reaching clinically significant levels of impairment on both scales, while CHR and FEP were at-risk. Atypicality is a scale designed to assess psychosis, so it is interesting that the ASD participants were most impaired. On the Adaptive domains Attention Problems, Social Skills, Leadership, and Activities of Daily Living, TYP were rated as less impaired in comparison to all three clinical groups. Conclusion: Individuals with FEP, CHR, and ASD exhibit significant difficulties in clinical and adaptive domains relative to TYP. The psychotic disorder groups show more conduct related psychopathology. ASD and CHR show the most symptoms of hyperactivity. Although all the clinical groups showed significant adaptive behavior problems, the ASD group was the most behaviorally rigid. This deep phenotyping work is important to assist in differential diagnosis, to suggest opportunities for interventions, and to guide investigations of the neural circuitry underlying psychopathology.
ID: 979963

DIFFERENCES AND SIMILARITIES BETWEEN VOICES OF NON-PSYCHOTIC INDIVIDUALS AND SCHIZOPHRENIA PATIENTS

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Background: The presence of auditory verbal hallucinations (AVH) in otherwise healthy individuals has frequently been described in epidemiological studies. However, doubt has remained concerning the issue whether this is indeed the same phenomenon as observed in patients with schizophrenia. Methods: To answer this question, the phenomenology of AVH was compared in 118 patients with schizophrenia, and 111 non-psychotic individuals experiencing AVH. In a subgroup of 21 non-psychotic individuals

we could visualize cerebral activation during the experience of AVH with fMRI. Participants indicated the presence of AVH by balloon-squeezes, while functional scans were obtained continuously. Activation maps were obtained using a Philips Achieva 3 Tesla MRI scanner. Eight-hundred blood-oxygenation-level-dependent (BOLD) fMRI images were acquired with the following parameter settings: 40 (coronal) slices, TR/TE 21.75/32.4 ms, flip angle 10°, FOV 224 × 256 × 160, matrix 64 × 64 × 40, voxelsize 4 mm isotropic. These activation patterns were compared to those of 21 schizophrenia patients matched for duration and frequency of AVH experienced in the scanner, as well as for sex and handedness. Results: Many characteristics, such as loudness, perceived location, number of voices, personification, and voices speaking in single words were comparable for both groups. Differences were observed for the frequency of AVH, the emotional content, and associated beliefs. These differences were all related to the higher associated distress in the patient group. Cerebral activation during AVH revealed activation of the bilateral postcentral gyrus, the left inferior parietal lobule, precentral gyrus, insula, inferior frontal gyrus, right cerebellum and bilateral superior temporal gyrus in both groups. The two-sample T-test revealed no significant difference in activation during AVH between the two groups. Conclusion: These phenomenological and fMRI data strongly suggest that AVH consist of a similar phenomenon in non-psychotic individuals and schizophrenia patients, with differences mainly in verbal content, frequency and associated distress.
ID: 954702

CLINICAL AND FAMILY CHARACTERISTICS OF THE 5-SITE B-SNIP COHORT: DOES DSM DIAGNOSIS OR DISEASE DIMENSION DISTINGUISH GROUPS MORE PRECISELY?

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Background: Dimensional characteristics of serious mental illness with psychosis (SMI-P) have been put forward as more sensitive predictors of treatment outcome and possibly more stringent predictors of disease mechanisms than DSM diagnosis. The B-SNIP study has collected intermediate- and endo-phenotypes of psychosis in large proband and relative populations to contrast the two approaches. Here we develop that contrast across the clinical and family characteristics of SMI-P in probands and relatives. Methods: Dense phenotyping will ultimately provide clinical symptom, outcome, and family data in over 2500 individual SMI-P probands, relatives and healthy controls. Standardized rating for Axis1 and Axis2 disorders, and ratings of psychosis, depression, anxiety and personality characteristics, as well as detailed family history will be available. In a preliminary sample, we will examine these outcomes in five populations of probands (SZ and BDP), relatives and healthy controls and examine unique and overlapping characteristics. Results: Preliminary analyses show expected differences in demographic and symptom data, including increased age of relative compared with proband groups and decreased education of the SZ probands. Both proband groups showed similar levels of psychosocial function, which is lower than the relative groups and still lower than healthy controls. Approximately 40% of all SZ or BDP probands ''bred true'' with respect to the Axis1 diagnoses in their pedigrees; however, 25%–30% of either proband pedigrees are mixed, showing both SZ and BD in relatives. Characteristics of schizotypal personality disorder, of narsassistic personality disorders and others will be examined in the relative groups. Conclusion: Traditionally, clinical symptom and disease outcome criteria have been used to distinguish SZ and BD diagnoses. In this sample, the dimension of ''psychosis'' in SZ or BD was the target of recruitment; this may have added more phenomenological variety to the group. Markers of outcome have not so far distinguished between SZ and BDP probands. SZ and BD often ''bred true'', however, not inevitably, with a significant number of kindred with both SZ and BD cases. We will be able to contrast schizotypal relatives with those with no such personality characteristics with respect to clinical and demographic outcomes.
ID: 987464

THE EXPERIENCE OF TREATMENT IN INDIVIDUALS PRESENTING CONCOMITANT PSYCHOTIC AND BORDERLINE PERSONALITY DISORDERS

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Background: There is a growing interest in the link between psychosis and borderline pathology. Empirical studies have confirmed the existence of a heterogeneous group of people who present with both psychotic and borderline pathology. Clinical and anecdotal information suggest that these individuals often experience a tumultuous course of treatment in the mental health care system. However, this has yet to be confirmed with empirical data. Methods: The objective of this study is to investigate in more depth the experience of treatment of individuals presenting with both psychotic and borderline personality disorders. To do so, we undertook a qualitative methodology. This methodology permitted us to explore in more depth and more openly the subject at study than by using existing questionnaires. Ten interviews were completed with individuals presenting with both psychotic and borderline disorders according to DSM-IV criteria. Diagnoses were clinically attributed by the treating psychiatrist and were confirmed with the participant's medical file. The semi-structured interview lasted approximately 45–60 minutes. Each participant was asked to provide an account of their treatment experiences as well as their perception of these experiences as helpful or detrimental. The interviews were audio-taped and transcribed into verbatim. They were then entered into QDA Miner 3.2. for analysis. Results: Preliminary analyses of the results confirm the presence of a tumultuous course of treatment. This course is characterized by numerous diagnoses and ''shipping'' of the participants from one service to another. Participants with a primary diagnosis of borderline personality disorder equally expressed that psychiatrists in general mentioned not believing them regarding their experience of psychotic symptoms - which they felt were quite real. Some also mentioned feeling uncared for and/or judged and therefore did not disclose other potentially valuable information to the treatment team. More detailed analyses will be presented and discussed. Conclusion: In conclusion, people presenting with a dual diagnosis of psychosis and borderline personality disorder can experience a complicated course of treatment. Suggested treatment guidelines will be discussed.
ID: 976604

DISABILITY IN YOUNG PEOPLE CLINICALLY AT HIGH RISK OF PSYCHOSIS

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Background: Decline in social functioning occurs in individuals who later develop psychosis. We investigated whether baseline differences in disability are present in those who do and those who do not make a transition to psychosis in a group clinically at high risk and if disability is a risk factor for transition. Methods: Prospective multicentre, naturalistic field study with an 18-month follow-up period on 245 help-seeking clinically at high risk individuals. Disability was assessed with the Disability Assessment Schedule of the World Health Organization(WHODAS-II). Results: At baseline, the transition group displayed significantly greater difficulties in making new friends ($z = 73.40$, $P = .001$), maintaining a friendship ($z = 73.00$, $P = .003$), dealing with people they do not know ($z = 72.28$, $P = .023$) and joining community activities ($z = 72.0$, $P = .05$) compared with the non-transition group. In Cox regression, difficulties in getting along with people significantly contributed to the prediction of transition to psychosis in our sample (b = .569, s.e. = .184, Wald = 9.548, $P = .002$, hazard ratio (HR) = 1.767, 95% CI 1.238–2.550). Conclusion: Certain domains of social disability might contribute to the prediction of psychosis in a sample who are clinically at high risk.
ID: 975775

HOMICIDE AND SELF-CONTROL AMONG MALES SUFFERING FROM PSYCHOSIS AND A CLUSTER B PERSONALITY DISORDER

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Background: Studies show a relationship between psychotic symptoms and violence. Some research postulates that personality features may help better explain this relationship. In fact, almost 50% of homicidal psychotic individuals have a comorbid diagnosis of a cluster B personality disorder. Impulsivity is an important characteristic in the understanding of human behaviour, and often correlates with the development of violent behaviors. Studies of human impulsiveness have relied primarily on college students and control populations, who rarely have significant histories of violence or major mental health problems. This study investigates the role of impulsivity and lack of self-control on homicide in individuals with a dual diagnosis of psychosis and cluster B personality disorder. Methods: Fifty-nine males diagnosed with psychosis (SCIDI) and a cluster B personality Disorder (SCIDII) were administered the PANSS and the HCR-20. Fifteen of the participants had committed or attempted to commit homicide. Inclusion criteria for this study require the participant to belong to one of the following legal statuses: incarcerated in a Québec institution; hospitalized involuntarily; or have been found guilty of an offense but held not responsible due to mental disorder. Spearman's correlation coefficients and Mann-Whitney U statistics were calculated, followed by a hierarchical regression. Results: Impulsivity was negatively correlated with Homicide (rho = −.343, $P = .008$), and did not correlated with Violent (rho = .162) or Non-Violent (rho = .239) behaviors. The U-statistic revealed that the Homicide group was significantly more controlled (Impulsivity, Mean rank = 20.17; Poor impulse control, Mean rank = 20.20) and experienced an equal amount of psychotic symptoms (Positive symptom scale, Mean rank = 24.07) than the non-homicidal (Impulsivity, Mean rank = 33.35; Poor impulse control, Mean rank = 31.54; Positive symptom scale, Mean rank = 30.12) individuals ($P = .006$; $P = .012$; $P = .217$, respectively). A regression confirmed that impulsivity and poor impulse control accounted for 38% of the total variance explained in Homicide (39%) by the model including the three variables. Conclusion: Those who are dually diagnosed with a psychotic and a cluster B personality disorder and who commit or attempt to commit a homicide may be different characteristically from those who are violent but do not have homicidal tendencies or who have committed non-violent crimes. Understanding risk factors can help to better predict and reduce future risk.
ID: 978967

2. Phenomenology

THE IMPORTANCE OF REVIVING THE TERMS ''EGO'' AND ''‘EGO STRENGTH'' TO UNDERSTANDING AND EXPLAINING PSYCHOPATHOLOGY AND RESILIENCE

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Background: Ego is not the exclusive purview of psychoanalysis, as many modern behavioral scientists seem to view it. Of course, ego and ego strength are abstract concepts, used liberally by psychologists and psychiatrists, prior to the renaissance of ''biological psychiatry'' in the 1950s. Ego maybe viewed as the central ''magnetic sphere'' of the psyche that integrates and coordinates the autonomous cognitive fragments consisted of ''percept units'' and (reactive and non-reactive) ''thought units,'' and ego strength as the centripetal, cohesive force with which the integration and coordination of these cognitive fragments are prosecuted. Methods: Hypothetical constructs based on literature search. Results: Kaplan and Sadock (1998) write, ''The synthetic function [of ego] refers to the ego's capacity to integrate diverse elements into an overall unity … [It] involves organizing, coordinating, and generalizing or simplifying large amounts of data.'' Andreasen et al (1998) have coined the term, ''cognitive dysmetria,'' meaning ''difficulty in prioritizing … coordinating, and responding to information.'' They postulated that a disruption in the circuitry among nodes located in the prefrontal regions, the thalamic nuclei, and the cerebellum produces cognitive dysmetria. They write ''This poor 'mental coordination' is a fundamental cognitive deficit in schizophrenia and can account for its broad diversity of symptoms.'' I had suggested that schizoid and schizotypal/schizothymic dispositions, as well as schizophrenia itself, were reflections of ''ego weakening'' in varying degrees, and that ''cognitive dysmetria could also be viewed as an end-result of ego weakening (Alias AG. Biol Psychiatry 1974; 9: 61–72; Med Hypotheses 2000; 54: 537–552). Conclusion: Ego may be difficult to define in neuroanatomical terms. But ''sometime in the not-too-distant future, the neurophysiological circuits that potentiate ego strength, and even the genes for the development of them will be discovered'' (AGA, 2000). It may be noted that the MMPI scoring is adjusted for sex differences as well, since ''ego strength'' is significantly higher in men than in women.
ID: 986602

PARANOID IDEATION: ITS RELATIONS WITH ATTRIBUTION STYLE, NEURO-COGNITION, AND THEORY OF MIND

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Background: Paranoia was proposed to be associated with attribution biases, poor executive function, and deficits of theory of mind (ToM). The aim of this was to investigate the relationship of paranoid ideation with biases of the perceived hostility and blaming, neuro-cognitive function, and ToM in normal population. Methods: Normal persons were asked to complete the Ambiguous Intentions Hostility Questionnares (AIHQ), paranoia scale, and other psychosocial measures of Rosenberg's self-esteem, Spielberg state anxiety, Chapman's magical thinking and perceptual aberration scales and Beck depression inventory ($n = 90$), ToM picture stories task ($n = 30$), and comprehensive neuro-cognitive tests ($n = 30$). Hierarchical regression analyses were conducted. Results: Paranoid score ($n = 90$) was found to be explained by female, magical thinking, perceptual aberration, self-esteem and perceived hostility bias in ambiguous situations [adjusted R square = .449, $F(5, 77)=14.34$, $P < .001$], not by age, state anxiety, and depression scores. Paranoid score ($n = 30$) was also found to be associated with perceived hostility bias and blaming bias in ambiguous situations [adjusted R square = .240, $F(2, 26) = 5.43$, $P = .011$], not by age, sex, and ToM scores. Paranoid ideation ($n = 30$) was also found to be related with female and blaming bias in ambiguous situations [adjusted R square = .198, $F(2, 27) = 4.59$, $P = .019$], not by age, executive function, attention and working memory, verbal memory, and spatial memory subdomain scores. Conclusion: Subclinical paranoia may be associated with female, self-esteem, magical ideation and perceptual aberration, and biased attribution styles of perceived hostility and blaming in ambiguous situations. In near future, the role of attribution style, self-esteem, neurocognitive function, and ToM in paranoia process should be assessed in clinical paranoia subjects such as schizophrenia patients.
ID: 978988

INSIGHT IN A LARGE COHORT OF FIRST-EPISODE EARLY ONSET PSYCHOSIS

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Background: Increasing evidence supports the important role of illness state and individual characteristics in insight. There have been not many studies assessing insight longitudinally in a cohort of first episode patients, even less with pediatric populations (1, 2). The purpose of this study is to explore prospectively (2 year follow-up) the relationship between insight and psychopathology, specifically depressive symptomatology, neurocognitive performance, function in life, treatment adherence, sociodemographic and clinical factors and gray matter volumes in a large cohort of first-episode early onset psychoses ($n = 200$, approximately 35% schizophrenia). Methods: Insight, as measured with the Scale to Assess Unawareness of Mental Disorder, over the first 2 years of early-onset first-episode psychosis and its correlations with clinical, socio-demographic, cognitive, and structural brain variables are studied. Results: Preliminary results with 110 patients show that (1) Insight at 2 years is poorer in schizophrenia spectrum disorders (SSD) than in subjects with other psychoses; (2) The more severe the psychosis, the worse the insight. In SSD, depressive symptoms, poorer baseline executive functioning, lower IQ, longer duration of untreated psychosis (DUP), and poorer premorbid infancy adjustment are associated with poorer insight; frontal and parietal gray matter reductions at baseline correlate with worse insight into having psychotic symptoms at 2 years; (3) IQ and SUMD1 at 1 year, together with left frontal and parietal gray matter volumes, explain 80% of the variance of insight into having specific psychotic symptoms in SSD patients (Adjusted $R^2 = .795$, $F =$

15.576, $P < .001$). Conclusion: Insight is a complex phenomenon that depends both on severity of psychopathology and also on disease and subject characteristics, such as IQ, DUP, cognitive functioning, frontal and parietal gray matter volumes, and age, gender, and ethnicity. These results may have clinical implications in the treatment of this vulnerable population.

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ID: 975368

EXAMINING RISK FACTORS FOR DELUSIONS OF CONTROL, REFERENCE, AND GRANDIOSITY IN THE DAILY LIFE OF PEOPLE WITH SCHIZOPHRENIA

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Background: Delusions are considered to be among the core symptoms of severe psychiatric illnesses such as schizophrenia and schizoaffective disorder. A cognitive model of the positive symptoms of psychosis suggests that a number of trait and state risk factors including reasoning biases, negative self-esteem, negative emotional states, and anomalous experiences (eg hallucinations) may contribute to the formation and maintenance of various delusions. The current study examined whether these factors prospectively predict the occurrence of delusions of control, reference, and grandiosity in real-time/real-world settings using a computerized Experience Sampling Method (ESM). Methods: One hundred and thirty community-dwelling participants with schizophrenia or schizoaffective disorder completed laboratory measures (probabilistic reasoning: Bead Task; Self-Esteem Rating Scale: SERS) and momentary self-reports (anxiety, sadness, hallucinations, and delusional belief items) generated by a personal digital assistant multiple times per day, over 7 consecutive days. Multilevel modeling of the time-lagged data permitted simultaneous examination of person-level and within-person time-varying relationships among the variables, allowing for stronger directional inferences than simply examining cross-sectional associations. Results: Approximately half of the participants reported having at least one delusional experience during the week; 37% reported experiencing delusions of control, 31% experienced delusions of reference, and 28% experienced delusions of grandiosity. A quarter of the sample reported experiencing all three delusion subtypes. The occurrence of each delusion subtype was predicted by a different combination of factors; negative self-esteem, a reasoning style characterized by a tendency to ''jump to conclusions'', and momentary hallucinatory experiences predicted the subsequent occurrence of delusions of control. Increased negative self-esteem and hallucinations also predicted the occurrence of delusions of reference, but reasoning style did not. Only negative self-esteem was a significant predictor of delusions of grandiosity. Surprisingly, negative emotional states of increased anxiety and sadness did not predict the occurrence of any delusion subtype. Conclusion: The findings suggest that negative self-esteem, a ''jumping to conclusions'' cognitive bias, and momentary hallucinatory experiences may serve as possible treatment targets in emerging cognitive-behavioral interventions for delusions.

ID: 975136

THE EXPERIENCE OF SOCIAL AND PHYSICAL PLEASURE IN SCHIZOPHRENIA

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Background: Negative symptoms are often characteristic of schizophrenia, with anhedonia as a particularly common feature. Previous research has found that schizophrenia patients associate less enjoyment with various activities compared to their healthy counterparts; however, they do not appear to differ in their in-the-moment experience of emotions. This study explored this distinction between anticipatory and consummatory pleasure further, by assessing social and physical anhedonia separately and examining their relationship specifically with social and non-social stimuli. Methods: The data were collected from 65 individuals with schizophrenia and 65 matched healthy controls in the greater Chicago area. Anticipatory pleasure was assessed using the Chapman Anhedonia social and physical subscales, while consummatory pleasure was measured by self-reported arousal and valence ratings for 131 social and non-social stimuli from the International Affective Picture System (IAPS). Results: To determine whether the expected pattern of anticipatory and consummatory pleasure arose, we ran a series of 2 (Diagnosis: schizophrenia, healthy control) X 2 (Anhedonia: anticipatory, consummatory) mixed design analyses of variance (ANOVAs); 2 ANOVAs were used for social anhedonia and 2 ANOVAs were used for physical anhedonia. All 4 ANOVAs found significant interaction effects, and follow-up tests revealed that schizophrenia patients and healthy controls did not differ on their ratings of consummatory pleasure, but that they were significantly different in their ratings of anticipatory pleasure. Conclusion: These findings provide additional support for the hypothesis that schizophrenia patients do indeed experience in-the-moment pleasure from both social and physical stimuli that does not significantly differ from that of healthy individuals, yet they are unable to indicate these feelings when asked to report on past or future enjoyment from these activities. One possible explanation for this pattern of results is a memory deficit in schizophrenia; although schizophrenia patients may have normal emotional experiences, they are unable to recall these experiences when asked to report them. As this was beyond the scope of the present study, more research is needed on emotional memory in schizophrenia in order to explore this phenomenon further.

ID: 979678

FAILURE TO UTILISE STANDARD ASSESSMENTS IN PSYCHIATRY MAY HINDER SCIENTIFIC & CLINICAL PROGRESS

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Background: Most UK and European psychiatrists do not regularly use any standardized assessments instruments (SAI) when assessing history, symptomatology, cognition, outcome or other aspects of clinical presentation. This is in marked contrast to the introduction of SAIs by physicians in other specialties, or indeed by other mental health professionals such as psychologists and nurses. This paper investigates the reasons behind this conservatism and will stimulate debate about the implications for the practice and scientific development of psychiatry. Methods: Literature was reviewed and standard qualitative methods including focus meetings and questionnaires were used to explore the attitudes of psychiatrists to employing SAI in their practice. The reasons behind the reluctance of psychiatrists to utilise such standardized assessments compared with physicians in other medical specialties, and psychologists was investigated. Results: Psychiatrists surveyed appear reluctant to use rating scales in their clinical practice. Yet most psychiatrists surveyed felt that rating scales for assessment were appropriate in research. The reasons given for this disparity include: too

little time, unwillingness to reduce clinical practice to numbers, fears about transparency of process and peer review of skills. Some psychiatrists highlighted the lack of managerial support & appropriate resources (eg IT support) for such assessments. Conclusion: There is marked conservatism of attitude in relation to adopting new and standardized methods of information gathering in clinical practice. As a consequence most clinical data is not available in a format where it can be used for clinical effectiveness studies or to provide phenotype for studies of biomarkers or genetic variants. In a few areas of the UK attempts have been made to introduce outcome measures but usually only where driven by a management rather than by clinicians for clinical purposes. Successful attempts have been made in Australia to use OMs where appropriate investment by government has been made. The implication of these findings for clinical and scientific development of psychiatry will be discussed.
ID: 981202

LANGUAGE, THOUGHT DISORDER, AND DEVELOPMENTAL ABNORMALITIES IN CHILDHOOD SCHIZOPHRENIA

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Background: Children (1) and adolescents with schizophrenia (2, 3) have thought disorder. A study conducted on language scores in children with schizophrenia, included children with symptoms of autism spectrum disorder (ASD), language delay, epilepsy and intellectual disability (4), conditions associated with impaired language (5). Since language delay is found in 44%–72% (6–8) and ASD in 25%–87% of children with schizophrenia (7, 9–11), we compared language and thought disorder in children with schizophrenia with/without delayed language, ASD, and early motor abnormalities. Methods: The Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version, Test of Language Development-2, Wechsler Intelligence Scale for Children-III, Story Game, and Kiddie Formal Thought Disorder Rating Scale were administered to 37 children with schizophrenia aged 13.6 (SD 2.7). Parents provided language development, ASD symptom, early motor abnormalities, and age of illness onset information. We compared patients with linguistic deficits to those with average language scores on developmental variables using chi-square tests and *t* tests as appropriate. Developmental measures included age of onset, language delay, ASD diagnosis, and motor abnormalities (postural abnormalities, stereotyped body movements, repetitive behaviors, fascination with movement). We also investigated the association of thought disorder with these variables using Pearson's correlations and non-parametric Wilcoxon tests as appropriate. All tests were two-tailed with a significance level of .05. Results: Controlling for non-verbal intelligence and age differences, 59.5% of the patients had linguistic deficits with mean (age standardized) language scores one standard deviation below the healthy population. Other than a trend for more patients with language deficits to exhibit motor abnormalities (76% vs 47%; $X^2(1) = 3.31$, $P < .07$), children with linguistic deficits did not differ from those with average language scores on language delay (48% vs 21%) and ASD (59% vs 53%). The severity of thought disorder was also not associated with the developmental variables. Other than poor on-line monitoring, planning and editing of speech errors, thought disorder severity was unrelated to the presence of linguistic deficits. Conclusion: Similar to adult schizophrenia, impaired basic and higher-level linguistic skills (thought disorder) appear to be core deficits in childhood schizophrenia.
ID: 979261

SELF-REPORTED PLEASURE AND CANNABIS USE IN FIRST-EPISODE PSYCHOSIS AND CONTROL SUBJECTS

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Background: Dysfunctional reward processing is becoming recognised as an important deficit in psychotic illness and is also seen in drug addiction. Therefore research is needed to explore whether it could be a candidate mechanism explaining a portion of the comorbidity between these two disorders. Our objective is to test whether deficits in anticipatory pleasure are related to the presence of and intensity of cannabis use in a first episode psychosis (FEP) population and healthy controls. Methods: 91 FEP patients and 91 controls were administered the Temporal Experience of Pleasure Scale (TEPS), a self report which measures anticipatory and consummatory pleasure, as well as the Behavioural Inhibition and Behavioural Activation Scale (BIS/BAS). Substance use was measured via the Structured Clinical Interview for DSM IV (SCID) and recording the amount and frequency of recent use. Results: Contrary to previous findings, patients did not show a significant deficit in anticipatory pleasure compared to controls ($F(1, 180) = 1.9$, $P = .17$) but did show deficient consummatory pleasure ($F(1, 180) = 4.3$, $P = .040$). Pooled patients and controls with a lifetime SCID diagnosis of cannabis abuse or dependence reported significantly higher consummatory pleasure compared to those without cannabis diagnosis ($F(1, 180) = 6.9$, $P = .009$). Patients who had continuing cannabis use during treatment of their FEP reported significantly lower anticipatory pleasure compared to patients who had a cannabis diagnosis but were able to stop use throughout treatment (Tukey's post hoc, $P = .013$). Frequency of cannabis use was negatively correlated to anticipatory and consummatory pleasure and BAS reward response (Beta's = −.42, −.40, and −.45 respectively) in 37 FEP patients currently using cannabis but not in 46 currently using controls. All analyses controlled for gender. Conclusion: The results suggest that the relationship between reward and cannabis use may be complex, with higher pleasure a risk factor to be drawn to problematic cannabis use but also protective against sustained and heavy cannabis use in FEP.
ID: 978700

CLINICAL CORRELATES OF MALTREATMENT AND TRAUMATIC EXPERIENCES IN CHILDHOOD/ADOLESCENCE AMONG SOCIALLY DISADVANTAGED, HOSPITALIZED FIRST-EPISODE PSYCHOSIS PATIENTS

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Background: Associations between maltreatment/traumatic experiences in childhood/adolescence, substance use, and key domains of psychopathology have been initially explored in previous studies; however, research on these factors in socially disadvantaged patients with first-episode psychosis is unavailable. Methods: Among 61 first-episode patients, this correlational analysis examined associations between eight maltreatment and trauma-related variables (eg, traumatic experiences, parental harsh discipline, violence exposure) and: (1) substance abuse (age at initiation of alcohol and cannabis use, as well as lifetime intake of both), (2) select social variables (years of education and number of Axis IV problems), and (3) symptom severity at initial hospitalization. Results: Several key findings emerged; first, the rates of childhood abuse and traumatic events were remarkably high in the sample. Second, years of educational attainment and number of current Axis IV problems were substantially correlated with sev-

eral domains of childhood abuse/traumatic experiences. Third, age at initiation of alcohol and cannabis use, and lifetime alcohol and cannabis intake, were correlated with a number of trauma domains. Lastly, positive symptom severity was correlated with four of the trauma variables, though negative symptom severity was only correlated with emotional neglect. Conclusion: These results provide insights into the relationships between childhood traumatic events, substance use, and clinical features of first-episode psychosis. More attention should be given to the problem of past maltreatment and traumatic experiences among young adults with newly diagnosed psychotic disorders.
ID: 977390

QUALITY OF LIFE AS AN OUTCOME OF PSYCHOSIS: IMPLICATIONS FOR RECOVERY

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Background: Quality of life (QoL) is an important outcome from a patient's perspective, but remains poorly understood in first episode psychosis (FEP) research. The overall aim of this paper is to describe methodological and conceptual issues associated with QoL as an outcome measure. Methods: QoL data from two studies conducted at the Early Psychosis Prevention and Intervention Centre Melbourne, Australia will be presented. The two studies include: (1) the Episode II relapse prevention RCT; and (2) the EPPIC800 medium term follow-up study of patients with FEP. Heinrich's Quality of Life Scale and the World Health Organization's Quality of Life Scale - Brief Version (WHOQoL-Bref) were used as measures of objective and subjective QoL, respectively. Results: In the Episode II study, reduced QoL in FEP patients currently meeting remission criteria was associated with increased likelihood of personality disorder and depression, more severe positive symptoms and impaired functioning. In the medium term follow-up study, a median of 7.4 years after incipient psychotic episode, there was a moderate correlation ($r = .53$, $P < .01$) between the total scores of the objective and subjective QoL measures. Both objective and subjective QoL were related to severity of psychopathology. Conclusion: Families and patients are keen to understand illness trajectory and the impact on QoL. Thus, QoL is a key constituent of any definitional model of recovery. In the context of recovery, it is important to consider that QoL not only depends on severity of psychopathology but level of functioning. Further, subjective and objective measures of QoL do not necessarily assess the same construct.
ID: 979075

THE ETIOLOGY OF LACK OF INSIGHT IN SCHIZOPHRENIA

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Background: Lack of insight in psychosis can be conceptualized in a number of ways: (i) phenomenologically - as a set of beliefs or attitudes which are inextricably linked to psychopathological abnormalities (eg an aspect of delusions); (ii) psychosocially - involving cognitive mechanisms such as appraisal biases, self or other deception (denial) or the expression of culturally shared beliefs; (iii) neuropsychiatrically - as a result of cognitive impairment with neurophysiological correlates. Support for the last of these comes clinical studies in neurological disorders and the syndrome of anosognosia and also from studies showing that lower insight scores in schizophrenia patients tend to be associated with cognitive impairments, both generalized and specific (ie executive functioning). Similarly, a literature is emerging from structural neuroimaging which indicates correlates between low insight and brain anatomy - both generalized and specific. Methods: Systematic literature review; structural and functional MRI with patients with psychosis and healthy controls. Results: Research using voxel based morphometry with structural MRI on a first episode cohort of 82 patients from South East London points to gray matter deficits in the cingulate cortex, part of the 'cortical midline system', thought to support self awareness. Furthermore, preliminary new findings from functional MRI based on 11 psychosis patients with a range for insight scores shows increased activity in medial frontal systems during self appraisal compared with 8 healthy controls. This suggests increased activity in systems related to insight in those with serious mental disorder. Conclusion: This kind of work may improve our understanding of how brain-function might be relevant to lack of insight. However, it is likely that phenomenological and psychosocially mediated process co-exist with neurophysiological processes related to awareness of illness and that a complete understanding of insight in psychosis will require integration of all three. Purely cognitive mechanisms for poor insight in schizophrenia are relatively under-explored.
ID: 975781

MULTIDIMENSIONAL SCALING OF RELATIONSHIPS BETWEEN EXPERIENCES DUE TO CANNABIS

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Background: We investigated the inter-relationships of items within the self-report Cannabis Experiences Questionnaire (CEQ), which records acute effects of cannabis intoxication (42 items) and its after-effects (12 items), using multi-dimensional scaling (MDS) of data from an otherwise healthy volunteer sample. Methods: Students at three universities in the north-west of England were recruited via e-mail and intranet popup and asked to complete the CEQ, details of demographics and other substance misuse. Data from cannabis users were analysed using MDS with the ALSCAL package within SPSS 15. Data was entered as ordinal (all items score 1–5). Analysis of the intoxication items was performed first; after effects were then included. Results: 760 responded. 532 smoked cannabis; their median age was 20 (IQR 19–23); median age of first use was 16 (IQR 15–17). 58% were male. Model indices marginally favored 3 dimensions, particularly when after effects were included (Kruskall's stress .08, RSQ .98). Plotting in 3 dimensions revealed that similar items were adjacent. In fact, items formed two circuits: i) ecstasy-excitement-paranoia/dysphoria-psychosis-grandiosity-ecstasy; and ii) time distortion-sedation/lethargy-relaxation/euphoria-appetite-time. After-effects and acute intoxication items for similar experiences clustered together. Conclusion: This methodology is a unique tool for exploring relationships between experiences, which were not random. The existence of circuits suggests that processes producing any one experience predispose to adjacent, similar ones in a coherent way, possibly in sequence. One circuit has a variety of experiences common to dopaminergic psychoses, the other not. The findings are of interest given cannabis intoxication's status as a model for schizophrenia and this exploratory analysis should be replicated.
ID: 979914

SEMANTIC MEMORY PROCESSING STRATEGIES IN SCHIZOPHRENIA

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Background: Despite the long-recognized prevalence of language abnormalities in schizophrenia, their cognitive and neural mechanisms are unknown. After these mechanisms are identified, it can be determined whether patients can learn to use more efficient processing strategies, leading to both neural patterns that resemble controls' and better quality of life. One prominent hypothesis is that individuals with schizophrenia have difficulty using semantic information in an appropriate context. The Deese/Roediger-McDermott (DRM) paradigm is useful for exploring use of semantic information as it requires participants to learn lists of words (eg, ''night'', ''bed'', etc.) that are associated with a lure (eg, ''sleep'') that is not presented. The presented words create a context around a semantic category. Following encoding, a recognition phase is given in which the lure (''sleep'') is presented, in addition to words that were already presented and words that are new. Intact context maintenance leads to higher rates of false alarms (FA) to the lure, and is routinely observed in healthy individuals. Prior research that has used the DRM paradigm with patients with schizophrenia determined that patients made fewer FA than controls. These studies did not examine neural activity, so inferences about why patients make fewer FA could not be made. Methods: A DRM-based task was presented with Eprime software. EEG was recorded using a 64 Ag/AgCl electrode cap and reduced using Neuroscan software. Components were scored from average waveforms. fMRI scanning was performed on a Siemens 3T magnet. Data preprocessing and analysis were done with Statistical Parametric Mapping (SPM8) software. Results: N100 (indexes attention to perceptual features) was larger for patients. P300 (indexes categorization) and N400 (indexes semantic integration) were reduced in patients. Activation of the left inferior frontal gyrus (BA 45), which is associated with lexical search, was greater in controls compared to patients, whereas left parahippocampal gyrus activation (associated with episodic encoding) was greater in patients compared to controls. Conclusion: Patients attend to perceptual features of words, consistent with a superficial encoding strategy and self-report which indicated attention to orthographic information. In contrast, controls used a semantic strategy, and reported noticing semantic relationships. Future work will use these findings to design neurally-guided cognitive therapies for patients.
Funding: NARSAD 2008 YI Award
ID: 979601

HOW DOES ONE BECOME ADHERENT TO ANTIPSYCHOTIC MEDICATION? A QUALITATIVE STUDY OF THE PERSPECTIVES OF TREATMENT-EXPERIENCED SCHIZOPHRENIA PATIENTS

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Background: Poor antipsychotic medication adherence is a pervasive clinical problem in the long-term treatment of patients with chronic psychotic illnesses. An extensive quantitative literature has identified over 200 risk factors related to medication non-adherence, including lack of insight, negative attitudes to medication, perceived treatment efficacy and tolerability and past non-adherence. In contrast to quantitative methods, qualitative research with its focus on subjective experience allows an in-depth study of the dynamic and subtle interplay of factors operating at the level of the individual. However, such qualitative inquiries in the field of antipsychotic non-adherence are scarce. Methods: We performed in-depth semi-structured interviews with 20 subjects suffering from schizophrenia-spectrum disorders who had experience with antipsychotic treatment. We elicited illness narratives and a timeline of medication use emphasizing key turning points such as periods of non-adherence and illness relapses. Results: In contrast with the common view of medication adherence as a rational behavior aimed to maximize benefit for the patient, our subjects described a more complex picture of medication use or refusal. Most medication use was initiated or continued because of external factors (family, clinicians, secondary benefits and a variety of coercive measures). Moreover, personal factors transcended rational models, stressing the importance of trust, emotional reactions, subjective experiences with medication and stigma. Conclusion: Our qualitative study questions the validity of a purely voluntaristic model of medication use. Antipsychotic use was part of a long and painful fight with a debilitating disorder and off-medication periods were essential parts of a learning process.
ID: 977345

LONGITUDINAL TRAJECTORY OF HALLUCINATIONS IN PATIENTS WITH SCHIZOPHRENIA, SCHIZOAFFECTIVE DISORDER, BIPOLAR DISORDER WITH PSYCHOSIS, AND UNIPOLAR DEPRESSION

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Background: With the DSM-V well underway there is renewed interest in the diagnostic classification of common psychiatric disorders. One key interest is in the diagnostic relationship and long-term trajectory of related psychotic and mood disorders. The goal of this study was to evaluate the 20-year longitudinal trajectory of hallucinations, one of the core symptoms that can be present in schizophrenia, schizoaffective disorder, bipolar disorder, and depression. Methods: The current investigation is based on data from the Chicago Follow-up Study, a longitudinal, multi-follow-up research program of psychiatric disorders. One hundred seventy-six young patients were studied prospectively at the acute phase of hospitalization for hallucinations and then reassessed on at least 5 of the 6 subsequent follow-ups over a 20-year period. The follow-ups occurred at 2, 4.5, 7.5, 10, 15, and 20 years posthospitalization. Results: A 4 (psychiatric group) × 6 (follow-ups) mixed-model ANOVA assessed the longitudinal trajectory of these patients with regards to their hallucination frequency. There was a main effect of psychiatric group ($F(3, 74) = 7.66$, $P < .001$, $\eta^2 = .24$) and a trend towards a time by psychiatric group interaction ($F(14, 339) = 1.55$, $P = .09$, $\eta^2 = .06$). Schizophrenia patients had a greater frequency of hallucinations than schizoaffective patients at the 2 ($P = .04$) and 7.5 ($P = .007$) year follow-ups and trend-wise at the 10 ($P = .07$) and 15 year ($P = .08$) follow-ups. In addition, schizophrenia patients had a greater frequency of hallucinations than bipolar patients with psychosis (P's $<.001$–$.03$) and depression patients (P's $<.001$–$.003$) at all 6 follow-ups. Schizoaffective patients had a greater frequency of hallucinations than bipolar with psychosis patients at the 2 year follow-up ($P = .05$) and trend-wise at the 4.5 year follow-up ($P = .10$). Schizoaffective patients differed from depression patients at the 2.5, 4.5, 10, 20 year follow-ups (P's = .004–.05). Bipolar patients with psychosis did not differ from the depression patients at any of the follow-ups over the 20 years. Conclusion: The longitudinal trajectory of hallucinations can differentiate between the different psychotic and mood disorders. The longitudinal course of hallucinations clearly differentiated between schizophrenia and bipolar disorder with psychosis and suggested some diagnostic similarities between schizophrenia and schizoaffective disorder and bipolar disorder with schizoaffective disorder and depression.
ID: 978132

THEORY OF MIND, REFERENTIAL THINKING, AND SCHIZOTYPY

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Background: Schizophrenia patients display impairments in the ability to attribute mental states to oneself or others, ie, Theory of Mind (ToM). It is unclear whether ToM impairments are present prior to the manifestation of the illness. To date, findings regarding the association between schizotypy and ToM performance have been mixed. The primary aim of our study was to examine the association between ToM and schizotypy, as assessed by the Wisconsin psychosis-proneness scales. Referential thinking, while less pathological than delusions, reflects reality distortion. A secondary aim of the study was to examine whether referential thinking, as a schizotypic feature, would be associated with performance on measures of Theory of Mind. Methods: In the present study, we assessed Theory of Mind (ToM) and referential thinking in 134 individuals classified into three groups: two groups of psychometrically-identified schizotypes (namely, a positive schizotypy group [characterized by perceptual aberrations and magical ideation; $n = 36$], and a negative schizotypy group [characterized by social anhedonia; $n = 30$]) and controls [$n = 68$]. ToM was assessed in two ways: a composite Hinting Task including Corcoran's (l995) Hinting Task measure and the Reading the Mind in the Eyes Task (RMET; Baron-Cohen et al, 2001). Referential thinking was assessed using the Referential Thinking Scale (Lenzenweger et al, 1997). Results: The positive schizotypy group differed from the negative schizotypy and control groups in terms of performance on the Hinting Task, $P < .05$ and $P < .01$, respectively. The groups did not differ in terms of RMET performance. Both schizotypy groups differed from the controls in terms of referential thinking. Referential thinking was significantly associated with RMET performance but not the Hinting Task. Conclusion: These results suggest that different aspects of schizotypy are associated differentially with Theory of Mind abilities. The results also provide a rationale for the inclusion of multiple measures when attempting to study multifaceted constructs such as Theory of Mind.
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ID: 978682

TRAUMA HISTORIES IN CHILDREN AND ADOLESCENTS WITH PSYCHOTIC SYMPTOMS

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Background: Children and adolescents who have experienced trauma are more likely to report affect dysregulation, reduced behavioral control, and perceptual disturbances. Some of the perceptual disturbances can mimic psychotic symptoms. There is currently debate as to whether trauma produces a pseudo-psychotic state that can be clearly differentiated from early onset psychosis, or whether trauma is a general risk factor for all psychotic disorders. Methods: This study describes 60 children and adolescents with a history of trauma from a sample of 118, with psychotic symptoms, who were seen at The Children's Hospital Westmead between July 2005 and June 2008. Their average age was 13.7% and 72% were female. Their history, presenting symptoms and diagnosis were obtained from a file review. Results: Recorded trauma included sexual assault (34/60), neglect (16/60), physical abuse (13/60), loss and death (23/60), war/disaster 9/60 and domestic violence (8/60). Females were significantly more likely to report trauma. Traumatised young people were significantly more likely to report hallucinations and less likely to report delusions than those without a trauma history. Traumatised young people were also significantly more likely to be aggressive, have flashbacks, run away from home, attempt suicide and have higher levels of poor self care than those without a trauma history. Conclusion: This study found that 51% of young people who presented to hospital with one or more psychotic symptoms had a history of trauma. The symptomatic overlap of these syndromes and the growing body of evidence linking trauma and psychotic symptoms suggests further investigation is warranted.
ID: 979019

THE RELATIONSHIP BETWEEN HEART RATE VARIABILITY AND PHASE OF ILLNESS IN SCHIZOPHRENIA

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Background: Although findings of autonomic nervous system dysregulation are common in schizophrenia, limited research has focused on the contribution of the balance between sympathetic and parasympathetic nervous system functions to the course of the disorder. Heart rate variability (HRV) provides an index of such an interplay, and reflects psychological and behavioral adaptability (eg, Friedman & Thayer, 1998; Porges, 1992). The present study examined the relationship between HRV and phase of illness in schizophrenia across different phases of the illness. Methods: HRV was derived from resting cardiovascular data obtained from 46 first-episode schizophrenia patients, 33 chronic schizophrenia patients, 41 prodromal patients, and demographically-matched healthy comparison subjects. Results: As predicted, first-episode patients in the initial stabilization phase exhibited significantly lower HRV than comparison subjects ($P = .039$). A further comparison of first-episode patients at three time points demonstrated that patients had comparable HRV from the initial acute psychotic episode to clinical stabilization to one year following stabilization. When HRV of first-episode patients was compared to that of stable chronic patients, decreased HRV was significantly related to duration of illness over and above the effects of age ($P = .004$). Additionally, HRV within each patient group was not found to be related to self-reported depression. However, HRV was significantly associated with self-reported state ($r = -.41$, $P = .020$) and trait ($r = -.37$, $P = .038$) anxiety but only in schizophrenia patients who had reached the chronic phase of the illness. Analyses examining HRV in individuals in the prodromal phase of illness and in their healthy comparison subjects, as well as whether HRV may be of value in predicting later conversion to psychosis, will also be reported. Conclusion: Overall, these data suggest that disrupted HRV appears to be a relatively stable trait during the early course of schizophrenia. Further decreases in HRV appear to be associated with the duration of illness, reflecting heightened impairment in psychological flexibility in response to situational demands as the illness progresses.
ID: 978123

WHAT DOES PREMORBID SOCIAL ADJUSTMENT TELL US ABOUT INDIVIDUALS WITH SCHIZOPHRENIA?

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Background: Schizophrenia is a multifaceted disorder and course of premorbid social adjustment has been shown to have three trajectories: good premorbid functioning with sudden illness onset; poor premorbid functioning with no clear onset; and slow downward course (Haas & Sweeney, 1992). We characterized a sample of 147 inpatients with schizophrenia and schizoaffective disorder into the 3 premorbid groups in terms of clinical presentation, neuropsychological functioning, paternal age related schizophrenia, and comorbid conditions. Methods: The premorbid adjustment scale (PAS; Cannon Spoor et al, 1982) was administered to 147 individuals with schizophrenia and schizoaffective disorder. Participants were approximately equally distributed among the 3 premorbid groups . A comprehensive clinical and neuropsychological assessment was conducted using standardized interview and self-report measures. Areas assessed include clinical symptoms, comorbid psychiatric disorders and neuropsychological functioning. Results: There were distince differences between the three groups with respect to most areas assessed. The poor premorbid functioning group presented with more negative symptoms and poorer performance on most neuropsychological tests. The good premorbid social adjustment group reported more depressive symptoms. Differences between the good functioning group and the group with declining functioning were more subtle. Conclusion: Premorbid social functioning is informative in patients who later develop schizophrenia. Group differences have implications for etiology and treatment, especially with respect to psychopharmacological, psychotherapeutic and cognitive interventions. It is essential that premorbid social functioning be considered in future research in prodromal syndromes and schizophrenia.

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ID: 985797

THE STRUCTURE OF NEGATIVE SYMPTOMS: FINDINGS FROM THE COLLABORATION TO ADVANCE NEGATIVE SYMPTOM ASSESSMENT IN SCHIZOPHRENIA (CANSAS)

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Background: Negative symptoms are key determinants of poor functional outcome and are only minimally responsive to available treatments. There is widespread agreement that progress in treatment development is impeded by limitations in our understanding of the dimensional structure of the negative symptom construct and in existing assessment technologies. The CANSAS project is a NIMH-funded multi-site study that is constructing a new instrument, the Clinical Assessment Interview for Negative Symptoms (CAINS). Methods: In a recently completed first phase of the CANSAS project, a diverse sample of 281 schizophrenia and schizoaffective outpatients completed a beta-version of the CAINS designed to measure five consensus-based sub-domains of negative symptoms, including asociality, avolition, anhedonia, affective blunting, and alogia. A critical issue in refining the assessment of negative symptoms is whether these five domains best reflect the latent structure of negative symptoms. This study applied multiple exploratory factor and cluster analytic methods to the newly developed CAINS items to address this issue. Results: Converging results indicated that the beta-version of the CAINS was best characterized by a two-factor solution – one reflecting experience-related impairments (diminished motivation for social, vocational, and recreational activities) and one reflecting expression-related impairments (diminished non-verbal and verbal expressivity). These two factors were only moderately correlated (r = .39). Conclusion: These results converge with prior factor analytic studies of interview-based measures suggesting a two-factor structure of negative symptoms. The broader meaning of this structure will be addressed, as well the implications of these results for guiding the development of a refined, briefer version of the CAINS. An ongoing multi-site validation study of the revised CAINS will be described.

ID: 976027

DIAGNOSTIC STABILITY OF BRIEF PSYCHOTIC DISORDER

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Background: The diagnostic stability of brief psychotic disorder (BPD) is known to be between 30% and 60%. The diagnosis was changed to schizophrenia, bipolar disorder, etc. The aim of this study was to investigate the diagnostic stability of BPD using retrospective chart review. Methods: This retrospective chart review was based on all BPD patients who had a first-ever admission, and were readmitted at least once, to the psychiatric ward of the Asan Medical Center, from 1988 to 2010. All diagnoses were reviewed by an experienced research psychiatrist. Results: Thirty-five subjects met our inclusion criteria. The mean age at first admission with BPD was 32.2 ± 9.3 (14–64) years and the majority (71.4%) of patients was female. At a median follow-up of 2782.5 ± 1838.8 (92–7140) days, 3.3 ± 1.6 (2–9) episodes developed so mean interepisode interval was 959.5 ± 679.5 (46–3570) days. The number of cases in the ''diagnostically stable'' group was 11, with an overall stability rate of only 31.4%. The number of subjects whose diagnosis changed increased with each subsequent admission; the diagnosis of more than half was changed to bipolar I disorder (n = 13), schizophrenia (n = 5), schizophreniform disorder (n = 2), or schizoaffective disorder (n = 4). Except for just one episode, bipolar I disorder patients relapsed with a manic episode, with or without psychotic features. Almost no interepisode depressive features were observed. And a substantial proportion (63.6%) had maintained their jobs including subjects whose diagnosis was changed later to schizophrenia. This indicates patients with either schizophrenia or Bipolar disorders, with an onset as BPD may have a better prognosis compared to those who do not. Conclusion: BPD patients had a high possibility of conversion to schizophrenia or bipolar spectrum disorder. However, in those cases, they still showed prominently better outcomes compared to patients who were originally diagnosed with schizophrenia or bipolar disorder.

ID: 980250

FAILURES IN LEARNING-DEPENDENT PREDICTIVE PERCEPTION AS THE KEY VULNERABILITY TO PSYCHOSIS IN SCHIZOPHRENIA

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Background: Human perception, thought and action - the basic elements of maintaining reality - are based upon a hierarchical process that conjoins

memory and external stimuli, which we refer to as learning-dependent predictive perception. We propose that impairments in this elemental process lead to psychosis in patients with schizophrenia. Methods: The hierarchical model posits that the nature of the output from a given area of cortex depends on temporal coincidence with the patterns of the bottom-up input it receives. If an individual experiences stimuli that do not clearly fit any top-down hypotheses derived from previous experience, a given area of cortex relays the details of the patterns it receives to higher cortical areas; the signals are passed on to the next highest layer and this pattern extends until a match is achieved. The correct identification of objects, sensations, and processes in the environment is based upon probabilistic prediction determined by evolutionary development and the accumulation of memories of how the perceptual world is organized and operates. Results: In schizophrenia, the formation and storage of invariant representations at higher hierarchical levels may be insufficient. The higher levels do not provide enough input to lower levels for solving the nature of stimuli, and the lower levels do not provide adequate perceptual details to enable a sufficient establishment of perceptual context. Reduction in the correct identification of percepts in the context of real-world information-processing demands affords the opportunity for arbitrary internally-generated interpretations of reality to intrude upon perception and thought, leading to an accumulation of inaccurate but internally-meaningful perceptions that build into incorrect beliefs. Context-based perceptions of real objects and events are overwhelmed by an interpretation of reality that is individually determined and disconnected from the experiences and beliefs shared by others. Recent work supports this concept. Patients with schizophrenia have great difficulty perceiving visual and auditory objects among noise and are unable to identify incongruous events in a virtual reality context. Individuals who are soon to develop psychosis experience the perception of more elaborate sequences of verbal stimuli in auditory noise conditions. Conclusion: Deficits in learning-dependent predictive perception may be the mechanism behind the development of delusions and hallucinations in patients with schizophrenia.
ID: 977276

DISORDERS OF THE BASIC SELF AS A MARKER OF RISK FOR EMERGING PSYCHOSIS: A PILOT STUDY AMONG NON-PSYCHOTIC HELP-SEEKING ADOLESCENTS

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Background: The overarching goal of this study was to test the hypothesis that anomalies in self experience (ASE) are a core, "not-yet-psychotic" pathogenetic feature of emerging schizophrenia and its spectrum. Methods: To estimate the prevalence and nature of accomplish this goal we administered the Examination of Anomalous Self-Experience (EASE: Parnas et al, 2005) to a representative sample of 87 help-seeking, non-psychotic adolescents (age 14–18). In addition, to examine the relationship between ASEs and other common risk markers, we administered the Prodromal Questionnaire (PQ; Loewy et al, 2005) and the Structured Inteview for Prodromal Syndromes (SIPS; Miller et al, 2003) to assess prodromal symptoms, Cornblatt et al's (2007) Social and Role Functioning Scales to assess deterioration in psychosocial functioning, and the Mood and Anxiety States Questionnaire [MASQ: Watson & Clark, 1991]) to assess overall level of distress. Results: About 23% of the sample reported ASEs at a clinically meaningful level. This proportion was smaller than the number of participants (32%) who met diagnostic criteria for a prodromal syndrome. The degree of overlap between the two conditions was moderate (14%) but not significant (Chi-square = 2.9, $P = .09$). Similarly, an exploratory factor analysis revealed that ASEs load on a different factor than prodromal symptoms and deterioration in functioning, but that there is a modest correlation between the three factors. Conclusion: If further validated, these preliminary findings suggest that ASEs have the potential to enrich current early detection models by providing a means of further "closing in" on a smaller subgroup of individuals truly at high risk of schizophrenia spectrum disorders.
ID: 986932

AFFILIATIVE DEFICITS AND SOCIAL ANHEDONIA: RESULTS FROM A BEHAVIORAL INTERACTION TASK

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Background: Research suggests that social anhedonia (SocAnh) is a promising indicator for the vulnerability towards developing schizophrenia-spectrum disorders (Kwapil, 1998, Meehl, 1962) as well as an important determinant of the social impairment associated within these disorders. Although individuals elevated on SocAnh display deficits in a variety of social functioning domains, few studies have examined how these individuals actually behave in affiliative interactions. In this study we sought to examine the hypothesis that, within social affiliative interactions, social anhedonia is associated with problematic behavioral skills and experiential deficits. Methods: The current study compared normally hedonic controls (n = 54) to individuals elevated on SocAnh (n = 42) within a videotaped social interaction focusing on an initial affiliative interaction. Participants provided self-reports of their reactions to the social interaction and videos were coded for participant social skill and facial affect. Results: Compared to controls, participants with SocAnh were rated as less behaviorally affiliative and they were rated as having overall lower social skills ($ps < .05$). There were no group differences on ratings of facial affect. SocAnh participants' self-report indicated that, compared to controls, they experienced less positive affect in response to the social interaction, were less willing to engage in future social interactions with their interaction partner, and had less affiliative reactions toward the interaction partner (all $ps < .05$). Conclusion: Results converge with prior findings in that individuals with SocAnh may experience less positive and affiliative reactions in response to social interactions. They may also be less apt in interacting with social partners in an affiliative and meaningful way. Notably, results of the current study also demonstrate that the simulated live social interaction developed for the current study may better elicit social affiliative behaviors and experiences than previous stimuli, and may help clarify the affective components of SocAnh.
ID: 976685

INSIGHT INTO NEUROCOGNITIVE DEFICITS IN SCHIZOPHRENIA

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Background: Insight into neurocognitive deficits (I-COG) is an aspect of insight that has recently received attention, because neurocognitive deficits are a prominent symptom of schizophrenia that are linked to functional outcome. As more treatments for neurocognitive deficits become available, it is important to ascertain if patients are aware that they have cognitive deficits, if I-COG is stable from one assessment to the next, if I-COG is associated with clinical and neurocognitive symptoms, and if I-COG predicts adherence to neurocognitive treatment. Methods: Results from three different trials with schizophrenia outpatients aged 18–65 addressed these questions. The MIC-CR and MIC -SR were used to assess I-COG in a total of 162 subjects who were determined to have neurocognitve impairment on

the basis of neuropsychological testing. Results: In all three trials ($N = 71$, $N = 39$, $N = 52$) schizophrenia outpatients on average demonstrated low levels of I-COG. Although all demonstrated cognitive impairment on standardized tests, on average the subjective experience of the cognitive deficits was that they rarely impacted daily functioning. For the subset of 24 SS who were reassessed after a week, their self report of I-COG was quite stable ($r = .92$) and their clinician rated insight was also fairly stable ($r = .77$). There was little evidence across the three studies that degree of neuropsychological dysfunction was significantly related to I-COG, but level of depression was significantly correlated with greater awareness. Greater insight into neurocognitive deficit was significantly associated with lower adherence to cognitive treatment in 39 outpatients with schizophrenia ($r = -.45$, $P = .008$), and better cognition was significantly associated with better adherence ($r = .46$, $P = .007$). Conclusion: These findings indicate that people with schizophrenia reliably report low levels of awareness of their neuro-cognitive deficits regardless of the degree of their neuro-cognitive impairment, and higher insight is associated with lower adherence to neurocognitive treatment. This suggests that I-COG is in several ways different from insight into psychotic symptoms, which has been shown to be related to neuropsychological dysfunction and to predict treatment adherence. Implications for an understanding of insight as a multi-determined construct will be discussed.
ID: 976412

PHENOMENOLOGY OF SELF IN DELUSIONS OF REFERENCE IN BEGINNING SCHIZOPHRENIA

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Background: Despite claims that neuroimaging experiments access human 1rst-person-perspective, studies to date examine self from a 3rd-person-perspective, eg, retrospective reports, higher-order self-referential judgments, unconstrained default-mode activity putatively reflecting relaxed daydreaming or personal memories. These approaches do not provide information about schizophrenia patients' 1rst-person experience of their disorder. Using phenomenologic analysis of the reports of patients with beginning schizophrenia, however, the German psychiatrist Klaus Conrad found that the experience of self plays a key role in the development and maintenance of delusions. We operationalize Conard's observations to examine whether they can be studied empirically. Methods: Conrad's careful analysis of the subjective reports of patients with beginning schizophrenia is examined to see what extent the self plays a role in delusions. We operationalize Conrad's observations into 3 areas of disruption to experience of self: (1) random occurrences are seen as having special meaning directed towards the patient; (2) the delusional mood spreads from just a few salient events to an ever greater scope of the patient's experience which is then related back to the patient; (3) the self is experienced as passive centerpoint of the delusions. These three criteria are coded and evaluated by 2 independent raters in a sample of early schizophrenia patients with ($n = 12$) and without ($n = 14$) paranoid delusions. Results: We found Conrad' model to apply to the patients with paranoid delusions according to the three operationalized criteria of disruption to self-experience which were absent in the non-paranoid group. Conrad's observations are supported in the patients in our sample. Conclusion: Conrad's phenomenologic analysis of the role of self in delusions in beginning schizophrenia provides a first step to studying patients' 1rst-person experience of their disorder. His phenomenologic observations may be operationalized into testable hypotheses which can be further investigated as indicated by the present study. By demonstrating a spreading of delusional mood from a few salient aspects to more and more realms of the patient's experience, we also provide testable hypotheses about the underlying neurobiology.
ID: 979901

OLFACTORY HALLUCINATIONS IN SCHIZOPHRENIA: RELATIONSHIP TO PSYCHOPHYSICAL OLFACTORY PERFORMANCE AND CLINICAL INDICES

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Background: Abnormalities in the structure and function of the olfactory network have been well-documented in schizophrenia. However, few studies have examined the prevalence and severity of olfactory hallucinations in schizophrenia samples and the overlap between olfactory hallucination severity and performance on psychophysical olfactory testing. Thus, the aim of the current study was to extend previous research by investigating the relationship between self-reported severity of olfactory hallucinations and performance on two well-established measures of olfactory processing in a large sample of schizophrenia patients. Methods: One hundred eighty-seven schizophrenia outpatients (40% female; mean age = 34.36 ± 10.54 years; mean education = 12.89 ± 2.14 years) were administered the Scale for the Assessment of Positive Symptoms in order to characterize presence and severity of hallucinatory experiences. In addition, measures of depressive symptomatology and quality of life were administered. Each individual underwent unirhinal psychophysical testing of odor identification and odor detection threshold sensitivity. Results: Female patients performed better on odor identification but not detection threshold sensitivity compared to male patients. There were no significant differences in the distribution of hallucination subtype across either sex. Patients reporting the presence of olfactory hallucinations did not differ on olfactory task performance when compared to patients reporting the absence of olfactory hallucinations. Similarly, no relationships were observed between olfactory psychophysical performance and olfactory hallucination severity across the entire sample, or when examined separately in male and female patients. Of note, longer duration of illness and earlier age of onset were significantly correlated with increased severity of olfactory hallucinations. Conclusion: Despite no observed relationship between olfactory hallucinations and olfactory test performance, both the severity of olfactory hallucinatory experiences and level of impairment on olfactory testing appear to increase with illness duration. These findings raise the possibility that while separate mechanisms may underlie olfactory hallucinatory experiences and olfactory abilities in schizophrenia, degradation in related neural pathways during the progression of the illness may impact both of these processes. Future studies are needed to further elucidate potential mediating factors.
ID: 977442

PREDICTING COMPLIANCE IN SCHIZOPHRENIA: THE VALUE OF INSIGHT AND ATTITUDES TOWARD TREATMENT

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Background: Even effective drugs are useless when not taken (Hogan, 1986). The aim of this study is to assess whether attitudes toward treatment were a better predictor of compliance than insight (both assessed by self-report and clinicians ratings), in schizophrenia. Methods: 98 inpatients diagnosed with schizophrenia (according to DSM-IV-TR criteria) were evaluated within one week after being admitted to a psychiatric ward. Compliance with medication was based on medical records review. Insight and attitudes toward treatment were assessed using the Scale of Unaware-

ness of Mental Disorder, the Birchwood Insight Scale and the Drug Attitude Inventory (DAI), respectively. Results: 49% of patients were non compliant and compliance with injectable medication (52%) was similar to oral medication treatments (50%, $P = .83$). DAI-10 scores discriminated compliers from non-compliers: Mann-Whitney test demonstrated a statistically significant difference between compliant and non- compliant patients on DAI-10 total score and factor 2 ''patient's assessment of need for medication''. Attitudes toward treatment were largely correlated to patient's self-report of insight into illness and to patient's insight into the need for medication: The better the insight into the need for treatment the more positive the attitudes toward medication. Assessing jointly DAI and insight scores optimize the prediction of compliance to antipsychotic medication: results from a logistic regression indicated that compliance is better predicted by DAI factor 2 score ''patient's assessment of need for medications'' combined to SUMD global insight score ''insight into mental disorder''(ROC AUC = .776). Independently taken DAI-10 total score and factor 2 ''patient's assessment of need for medications'' score are less of a strong predictors (ROC AUC = .663 and ROC AUC = .726 respectively). Conclusion: Independently clinical insight and attitudes toward treatment are strong predictors of adherence to treatment, they are an even stronger predictor when combined. It is possible that there is a conceptual overlap between patient's assessment of need for medication and clinical insight. Strengths of the experimental design include a large sample size ($N = 98$), inpatient setting and double assessment of insight (self-reported and clinician-rated). Among the limitations of the present study was the lack of measure of insight into cognition.

ID: 946678

SEX DIFFERENCES IN THE INVOLVEMENT OF DISRUPTED-IN-SCHIZOPHRENIA-1 IN THE BEHAVIORAL EFFECTS OF METHAMPHETAMINE IN MICE

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Background: Co-morbidity between schizophrenia and drug abuse is prominent. Disrupted-In-Schizophrenia-1 (DISC1) gene identified in a large Scottish pedigree with a balanced (1:11) translocation co-segregates with major psychiatric disorders. DISC1 is a major hub protein that has been implicated in synaptic plasticity. Since drug abuse involves operation of the brain's learning and memory systems that may be affected by DISC1, we set out to determine how alterations in DISC1 function may impact the behavioral effects of methamphetamine (METH), a widely abused form of amphetamines. We employed our Tet-off transgenic dominant-negative model of inducible expression of mutant DISC1 in the forebrain neurons. Methods: Subjects were tTA mice as a control and DBL - double transgenic (tTA and mutant DISC1 transgene) mice. They received either saline or an escalating dosing (ED) with METH (.5–12 mg/kg/day in 1–4 injections over 2 weeks) and were put into the open field (OF) after the first injection. One week later mice were sacrificed 10 minutes after receiving 1 mg/kg METH in the OF; striatum was dissected and subjected to Western blotting for phosphorylated ERK (p-ERK). Conditioned place preference (CPP) was run in naïve subjects with .5 mg/kg METH in a biased design. Results: METH ED did not result in any overt brain neurotoxicity as evidenced by unchanged regional tissue concentrations of dopamine, serotonin, and their metabolites. Mice displayed sensitization of motor activity in OF that was significantly delayed in female but not male DBL mice compared to tTA mice. CPP in naïve subjects was also significantly impaired in the DBL female mice only. Sensitized tTA mice had a significant increase in p-ERK levels in striatum after METH in OF compared with controls. By contrast, it was absent in sensitized female DBL mice and diminished in saline-treated DBL mice. Conclusion: Our results suggest that DISC1 participates in the mechanisms of neuroplasticity underlying METH-induced sensitization and reward; this is reflected in dampened activation of ERK pathway in DBL females. Alterations in the DISC1 function may contribute to the co-morbidity between drug abuse and major psychiatric disorders through common signaling pathways.

Escalating Dose of Methamphetamine

Week	Monday	Tuesday	Wednesday	Thursday	Friday
One time	9	9	9 17	9 11 14 17	9 11 14 17
Dose mg/kg	.5	1.0	1.0 1.0	1.0 1.0 1.0 1.0	1.5 1.5 1.5 1.5
Two time	9 11 14 17	9 11 14 17	9 11 14 17	9 11 14 17	9 11 14 17
Dose mg/kg	1.0 1.0 1.0 1.0	1.5 1.5 1.5 1.5	2.0 2.0 2.0 2.0	2.5 2.5 2.5 2.5	3.0 3.0 3.0 3.0

ID: 979771

NEGATIVE SYMPTOMS AND TRANSITION TO A FIRST EPISODE OF PSYCHOSIS - FINDINGS FROM EPOS

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Background: Retrospective studies showed that negative symptoms develop already in the prodromal phase. Their emergence may reflect unfavorable neurobiological processes, which may underlie the worse functional outcome associated with negative symptoms. Hence, their early detection in the pre-psychotic phase may allow intervening more successful than in later stages of the illness. However, current risk criteria focus on either positive or cognitive symptoms and negative symptoms alone are too unspecific for a valid prediction. Methods: The European Prediction of Psychosis Study (EPOS) is a prospective multi-center study funded by the European Commission. 245 at-risk patients were included by Ultra-High Risk criteria and/or the COGDIS criterion (composed of 9 cognitive basic symptoms), follow-up was 18 months. Considering clinical and demographical variables, a Cox regression model was developed. From this model, a prognostic index (EPOS-PI) with four risk classes was derived to stratify the general transition risk of the total sample. Associations of negative symptoms (subscale and single items of the Structured Interview for Prodromal Syndromes, SIPS) with PI-classes and with transition to psychosis were analyzed. Results: Although the regression model underlying the PI did not include any negative symptoms, higher risk classes were associated with higher SIPS-N scores. Corresponding patterns emerged for ''social anhedonia or withdrawal'' (N1), ''decreased expression of emotion'' (N3) and ''deterioration in role functioning'' (N6). Patients with a transition to psychosis showed significantly higher SIPS-N and N1 scores, almost 50% of transitions lay within the upper SIPS-N quartile. Hazard Ratios (HR) for N1 and SIPS-N (dichotomized at the upper quartile) were significant, but not included into the model underlying the PI. Conclusion: The association of severity of negative symptoms with higher risk classes of the EPOS-PI, the differences between patients with and without a transition to psychosis and the predictive value of SIPS-N scores support the assumed importance

of negative symptoms in the pre-psychotic prodrome. Results further indicate that a stratification of risk based on more psychosis-specific predictors may also facilitate biological investigations of negative symptoms in the pre-psychotic phase, as it allows an enrichment of cases with a better defined association between these symptoms and psychosis.
ID: 979446

THE HIERARCHICAL ORGANIZATION OF SYMPTOM DIMENSIONS IN FIRST EPISODE PSYCHOSIS AND THE RELATIONSHIP TO DIAGNOSTIC CLASSIFICATION

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Background: The categorical approach to psychosis is under increasing criticism due to its inability to explain the heterogeneity of psychotic disorders. A multi-dimensional approach may be a useful supplement to discrete nosological entities for clinicians and research workers. There is, however, no definitive dimensional model to describe psychosis. This study aims to examine the organization of symptom severity in early psychosis and to determine the interchangeability of categorical and dimensional approaches to psychosis. Methods: First episode psychosis patients participating in an epidemiological study ($n = 500$) were included. Symptom severity was assessed using the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) and rated through the SCAN's Item Group Checklist (IGC). To assess the organization of symptoms Principal Component Analysis with oblique rotation (Promax) was used. Schimd-Leiman solution was applied to explain direct and indirect relationships between lower and higher order factors. Concordance between categorical diagnosis and the dimensional model was evaluated with Recursive Partitioning and Multinomial Logistic Regression modelling. Results: Using a parallel scree plot, a first order six-factor model was identified that accounted for 63% of the variance and best fitted the data. The factors that emerged were: Mania, Negative, Disorganization, Depression, Hallucinations and Delusions. Higher order factor analysis was performed on the first order factors and gave rise to two second order factors accounting for 49.5% of variance and discriminating the affective (Disorganization/Mania/Depression) from the non-affective (Hallucinations/Negative/Delusions) characteristics of psychosis. Concordance rate between categorical and dimensional classification methods was 74%. Conclusion: Findings are consistent with a hierarchical organization of psychosis characterized by 6 symptoms dimensions that split into 2 higher-order factors discriminating affective from non affective psychosis. The dimensional model showed an overall good agreement with the traditional diagnostic categories.
ID: 979114

PSYCHOBIOLOGICAL DETERMINANTS OF STRESS REACTIVITY IN SCHIZOPHRENIA

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Background: The notion that life stressors precede symptom exacerbation in schizophrenia has been well supported in the literature but important questions still remain (Phillips et al, 2007). For example, there is significant inter-individual variability in how patients react to life stressors. Many studies describe an increase in the frequency of stressful life events before elevations in clinical symptoms, however, this effect has not been replicated for all patients (eg, Docherty et al, 2009). These inconsistent findings in how stressors impact illness expression were examined within the framework of the neural-diathesis stress model of schizophrenia, which provides considerable support for the role of the stress hormone, cortisol, in the production of psychotic symptoms (Walker et al, 2008). Although previous research has commonly conceptualized life stress as a homogenous construct, the neural-diathesis model suggests that specific stressor attributes might be more closely linked to symptom exacerbation. Specifically, it was hypothesized that stressor domains that elicit greater cortisol activity, such as social evaluative threat and uncontrollability (Dickerson & Kemeny, 2004), would be more strongly associated with symptom elevations relative to other stress domains. Additionally, individual difference characteristics that increase cortisol output (eg, trait affect, coping styles, early life adversity) and may place patients at greater risk for experiencing elevated symptom levels following life stress were also investigated. Methods: Interview, self report, and cortisol data were obtained from 125 schizophrenia patients and 95 healthy subjects. Beyond traditional indices, life stress interviews were coded for social evaluative and uncontrollable content. Results: Initial results indicated significant positive associations between social evaluative stressors and both negative and positive symptoms ($P < .05$); however, no significant correlations were found when life stressors were combined into a single construct. Psychosocial factors (eg, trait anxiety and parental loss) also moderated stress-symptom associations ($P < .01$); that is, patients with greater trait anxiety and parental loss were more likely to show elevations in clinical symptoms following life stress relative to patients who scored lower on these psychosocial constructs. Conclusion: Thus, specific stressor and patient characteristics are important to consider when examining stress-symptom associations in schizophrenia.
ID: 978147

PSYCHOLOGICAL EFFECTS OF CANNABIS IN PATIENTS WITH SUBSTANCE-INDUCED PSYCHOSIS

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Background: The cannabis experiences questionnaire [CEQ] is a short self-report measure designed to capture the essential concurrent- and after-effects of the drug. Normative data has now been collected from 892 "healthy" cannabis users (Barkus and Lewis, 2008; Stirling et al, 2008). In this pilot study, we sought to record effects of cannabis in currently psychotic patients using the CEQ. Methods: 16 individuals (12 males, 4 females; average age: 27years 8 months, range 17–45 years), currently hospitalized with a diagnosis of substance [cannabis] induced psychosis, completed the CEQ, and their responses were compared to those of non-patient controls. Results: Patients reported significantly higher levels of concurrent aversive experiences and after-effects compared to healthy controls (both $P < .001$), but comparable levels of positive (appetitive) experiences. Item analysis indicated that patients evinced significantly elevated scores (alpha adjusted for multiple significance testing) on 14/20 "dysphoric" experiences previously associated with high levels of schizotypy in "healthy" cannabis users. Conclusion: These results suggest that patients whose psychotic illness is complicated by cannabis use display a marked increased sensitivity to aversive effects of the drug.
ID: 976117

PREMORBID ADJUSTMENT IN AFFECTIVE AND NON-AFFECTIVE PSYCHOSIS: A FIRST EPISODE STUDY

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Background: There is substantial evidence that on average, individuals with schizophrenia have worse premorbid social and academic adjustment compared to individuals with non-psychotic diagnoses. However, it is unclear if premorbid social and academic functioning differs among psychotic disorders. Methods: This study examined premorbid social and academic adjustment in 105 individuals with a first-episode psychotic disorder: schizophrenia ($n = 68$), schizoaffective disorder ($n = 22$), and affective disorder with psychotic features ($n = 15$). Social and academic adjustment in childhood (5–11 years), early adolescence (12–15 years), and late adolescence (16–18 years) was assessed at first-episode using the Premorbid Adjustment Scale (Cannon-Spoor, 1982). Results: The three diagnostic groups were compared simultaneously utilizing multinomial logistic regression analysis. Worse social adjustment in childhood was associated with higher odds of schizoaffective disorder compared to odds of schizophrenia (OR = 3.7; $X^2 = 6.6$, $P = .010$) or affective disorder with psychotic features (trend) (OR = 3.0; $X^2 = 3.1$, $P = .079$), accounting for effects of early and late adolescent social adjustment. In contrast, worse social adjustment in late adolescence was associated with higher odds of schizophrenia compared to odds of schizoaffective disorder (trend) (OR = 2.9; $X^2 = 3.0$, $P = .086$) or affective disorder with psychotic features (trend) (OR = 4.4; $X^2 = 3.1$, $P = .079$), above contributions of childhood and early adolescent adjustment. Premorbid academic adjustment did not differentiate odds of the three diagnoses. Premorbid social adjustment was further examined in non-affective (schizophrenia, $n = 68$) vs affective psychosis (schizoaffective and affective disorder with psychotic features, $n = 37$) utilizing binomial logistic regression analysis. Worse childhood social adjustment was associated with higher odds of affective psychosis vs schizophrenia (OR = 3.1; $X^2 = 6.0$, $P = .015$), whereas worse social adjustment in late adolescence was associated with higher odds of schizophrenia (OR = 3.1; $X^2 = 4.9$, $P = .027$). Conclusion: Overall, results suggest that poor premorbid social (but not academic) adjustment in childhood is associated with greater odds of affective psychosis (vs non-affective), whereas poor social adjustment in late adolescence is associated with increased odds of non-affective psychotic disorder (ie, schizophrenia).
ID: 979551

AFFECTIVE DEFICITS IN SCHIZOPHRENIA REVISITED: THE ROLE OF AMBIVALENCE AND ALEXITHYMIA

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Background: Affective research in schizophrenia has repeatedly brought discrepant results: compared to healthy controls, schizophrenia subjects show lower positive temperament and higher negative temperament on trait questionnaires, whereas they report similar levels of positive and negative affective reactivity in laboratory evocative tasks. Those findings question the coherence between trait measures and online ratings. However, the role of early-stage ambivalence and alexithymia (impaired emotional clarity) has rarely been examined. Methods: Eighty individuals with schizophrenia and 36 non-patient control participants completed an evocative affective task consisting of pictures and sounds. Following each presentation, participants rated their induced levels of pleasantness and unpleasantness on two separate ratings, and three scores were obtained: on-line global pleasantness, on-line global unpleasantness and ambivalence. All participants completed two trait questionnaires: the General Temperament Survey to measure positive temperament and negative temperament, and the Toronto Alexithymia Scale. Results: In the evocative task, schizophrenia participants showed higher ambivalence but no impairment in positive and negative emotional reactivity. Schizophrenia participants self-reported higher negative temperament and higher alexithymia. In both groups, negative temperament moderately correlated with on-line global unpleasantness, but positive temperament did not correlate with global pleasantness. Regression analyses were conducted to test whether trait measures predicted on-line ratings, and negative temperament predicted on-line global unpleasantness in the schizophrenia group only. More importantly, in the schizophrenia group, ambivalence and alexithymia predicted negative temperament, accounting for 40% of the variance, and groups did not differ on negative temperament after controlling for ambivalence and alexithymia ($P = .99$). Conclusion: The coherence between affective state and trait measures was limited within the negative affect system, and quite poor within the positive affect system. In schizophrenia, increased early-stage ambivalence was a central affective deficit. Increased ambivalence and alexithymia explained the higher negative temperament of individuals with schizophrenia, which is consistent with the view that emotional clarity helps to regulate negative emotions.
ID: 974976

CAN OBSESSIONS DRIVE YOU MAD? LONGITUDINAL EVIDENCE THAT OBSESSIVE-COMPULSIVE SYMPTOMS WORSEN THE OUTCOME OF EARLY PSYCHOTIC EXPERIENCES

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Background: Although there is substantial comorbidity between psychotic disorder and OCD, little is known about how these clinical phenotypes, and their subclinical extended phenotypes, co-vary and impact on each other over time. This study examined cross-sectional and longitudinal associations between (subclinical) OCD and (subclinical) psychosis in the general population. Methods: Data were obtained from the three measurements of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). A representative population sample of 7075 participants were assessed using the Composite International Diagnostic Interview (CIDI) at baseline (T0), 1 year later at T1 and again 2 years later at T2. Results: At T0, a lifetime diagnosis of psychotic disorder was present in 1.5% of the entire sample, in 11.5% of the people with any OC symptom and in 23.0% of individuals diagnosed with OCD. OC symptoms at T0 predicted incident psychotic symptoms at T2 (OR: 4.2, $P < .0005$, 95% CI: 2.4–7.5). Similarly, T0 psychotic symptoms predicted T2 OC symptoms (OR: 7.7, $P < .0005$, 95% CI: 3.2–18.4). Given the early presence of psychotic symptoms, the likelihood of persistence of psychotic symptoms or transition to psychotic disorder was higher if early psychosis was accompanied by co-occurring OC symptoms, but not the other way round. Conclusion: OCD and the psychosis phenotype cluster together and predict each other at clinical and subclinical level. The co-occurrence of subclinical OC and psychosis may facilitate the formation of a more "toxic" form of persistent psychosis with a higher probability of transition to need for care.
ID: 980131

LONG TERM OUTCOME IN AN ULTRA HIGH RISK ("PRODROMAL") GROUP

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Background: Criteria have now been developed that identify individuals at ''ultra high risk'' (UHR) of psychotic disorder. These individuals have been found to have a rate of ''transition'' to psychotic disorder of about 35% over 1 year, with risk decreasing over the next 2.5 years. The longest follow up to date of a UHR cohort has been 3.5 years. In this study we sought to determine the longer term (up to15 year) outcome of a UHR sample. Outcomes of interest were transition to psychotic disorder and persistence of UHR status. We also aimed to examine predictors of psychosis over the longer term. Methods: Of 412 subjects followed up, 114 developed a psychotic disorder by the time of follow up (27.4%). Estimated rates of transition to psychotic disorder were: within the first year after entry: 16.6%, within 2 years after entry: 20.6%, within 3 years after entry: 24.7%, within 5 years 30%, within 10 years 34.8%. There were no further transitions after 10 years. Ninety subjects (21.6%) met UHR criteria at follow up. Results: Individual predictors of transition were: disorders of thought content, conceptual disorganization, negative symptoms, poor psychosocial functioning and long duration of symptoms. After applying a stepwise procedure in conjunction with Cox regression the significant predictors were poor psychosocial functioning and long duration of symptoms. Additionally, subjects from earlier cohorts (initial assessment between 1995 and 2000) had a higher transition rate than subjects from later cohorts (2001–2006). Conclusion: This study suggests that UHR individuals continue to be at risk of psychosis even 10 years after initial presentation, but with greatest risk in the early years after recruitment. The transition rate appeared to have decreased over the past 15 years. This may be partly because later cohorts have not yet moved through the period of greatest risk. For example, previously we had found that subjects recruited before 1998 had a significantly higher transition rate compared to those recruited between 1998 and 2000. However this longer term follow up found that the transition rate in the 1998–2000 cohort caught up to the earlier cohort, suggesting a lead time effect. It is also possible that changes in recruitment and clinical practice over time may have decreased the transition rate. The finding that low functioning predicts psychosis is consistent with previous studies.
ID: 979209

3. Drug Side Effects & Physical Illness

METFORMIN AND IMPAIRED GLUCOSE TOLERANCE IN OVERWEIGHT PERSONS WITH SCHIZOPHRENIA

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Background: People with schizophrenia are at elevated risk for obesity, diabetes, and dyslipidemia, and antipsychotic medications contribute to this risk. Metformin is a safe and well-tolerated anti-hyperglycemic medication for the treatment of type II diabetes. Metformin produces modest weight loss in patients with diabetes while also improving measures of glucose and lipid metabolism. We recently found that 16 weeks of adjunctive metformin produced a differential 2 kg weight loss over placebo in non-diabetic, overweight individuals with chronic schizophrenia or schizoaffective disorder. Triglyceride levels were also differentially improved with metformin. In this exploratory sub-analysis, subjects with impaired fasting glucose (IFG) at baseline were examined to determine whether baseline fasting glucose influenced the effects of metformin on weight and selected metabolic parameters. Methods: In a 16-week, randomized, double-blind trial, 146 outpatients with schizophrenia or schizoaffective disorder with a body mass index (BMI) >27 kg/m^2 received metformin, titrated to 2000 mg/d, or placebo. Subjects were taking stable doses of either one or two antipsychotic medications. All subjects received counseling on improving diet and exercise habits. IFG was defined by a baseline fasting glucose >100 mg/dL. Results: Of 43 subjects who met criteria for IFG, 18 received metformin and 25 received placebo. In the IFG subjects, metformin produced a mean weight loss of 3.0 kg compared to .9 kg for placebo (P = .012). Non-HDL cholesterol was lower by 13 mg/dL for metformin compared to .9 mg/dL lower for placebo, at a trend level (P = .071). Absolute reductions in fasting glucose were 8 mg/dL for metformin and 4 mg/dL for placebo (P >.1 for group difference). Conclusion: Metformin appears to be equally effective for weight loss in overweight individuals with schizophrenia or schizoaffective disorder, whether fasting glucose is normal or impaired. The analysis suggests an advantage for metformin on non-HDL cholesterol in the IFG group that was not found in the larger group. The reduction in fasting glucose by metformin in the IFG group suggest a potential preventive role for antipsychotic-treated patients at risk for diabetes. While the findings from the current analysis must be considered exploratory due to limited power, it highlights the potential benefits of metformin in preventing metabolic complications from antipsychotic medications.
ID: 979374

EPIDEMIOLOGY OF THREE COMMON SURGERIES IN VETERANS WITH SCHIZOPHRENIA

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Background: Patients in the Veterans Health Administration (VA), the largest integrated healthcare system in the United States, become eligible for VA care as veterans of US military service with service-connected disability, low income or service factors. Veterans with schizophrenia may get care for both mental and physical illnesses. Yet the meager evidence base on surgical experiences of patients with schizophrenia suggests systematic differences compared to patients without severe mental illness (SMI), in that surgical care for persons with schizophrenia may be less timely. The Surgical Treatment Outcomes of Psychiatric Patients (STOPP) study examined 3 of the most common surgeries performed in the VA: coronary-artery bypass graft (CABG), endarterectomy (ENDA), and arthroscopic knee surgery (ARTS) for the period 2006–2009, contrasting veterans with and without schizophrenia or other SMI. Methods: Administrative data extracts from the VA's all-electronic medical record were aggregated to examine SMI diagnosis and 90-day mortality associated with these 3 surgeries. Diagnosis on 2 or more dates in 1 year identified schizophrenia, other SMI (bipolar disorder, major depressive disorder, post-traumatic stress disorder) and no SMI. CPT and ICD-9-A procedure codes identified invasive surgeries. Results: Over the 4-year period, the VA treated 7.5 million patients, including 380 000 with 829 000 invasive procedures. The cohort of surgery patients was 4% female, 18% black, 78% white, 3% other race, and 6% of patients were Hispanic. 40% of patients were VA-eligible via low income. Comorbidity status was assessed as 2.6 (SD 2.5) conditions per Charlson score, 4.3 (SD 2.3) chronic conditions per Selim score. CABG was performed on 27 753 patients, ENDA on 14 069, and ARTS on 8436. Roughly 90 000 schizophrenia patients underwent 2000 invasive surgeries each year. Patients with schizophrenia were less likely to experience any surgery (2.2% vs 4.1% for non-SMI patients) or to receive the common surgeries (eg in 2006, CABG: 4% of schizophrenia vs 6% other SMI vs 7% non-SMI patients; ENDA: 3% schizophrenia vs 5% other SMI vs 6% non-SMI). Conclusion: In spite of two decades of attention to excess cardiovascular mortality among VA patients with schizophrenia, common surgical treatments, the coronary artery bypass graft and endarterectomy, appear to be performed relatively less often on these vulnerable patients. [VA HSRD Grant #IIR-09-335]
ID: 986656

ENDOTHELIAL FUNCTIONING AND OMEGA 3 FATTY ACIDS IN SCHIZOPHRENIA SUBJECTS RECEIVING ANTIPSYCHOTICS

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Background: Within schizophrenia, cardiovascular disease (CVD) is highly prevalent. Those with mental illness lose more than 25 years of life due to CVD, which may be due to atypical antipsychotic (AAP) risk. Thorough assessments of diet, lifestyle, and endothelial functioning have not been done in the schizophrenia population. Recently omega-3-fatty acids (O3FAs) have garnered much attention in relation to mental illness psychopathology as well as their cardioprotective effects. We sought to assess endothelial functioning in schizophrenia subjects and determine if lifestyle behaviors, such O3FA intake, were significantly associated with endothelial functioning in this population. Methods: Schizophrenia subjects receiving antipsychotic treatment >6 months were included in this cross-sectional analysis. Endothelial function was measured using non-invasive peripheral arterial tonometry (EndoPAT2000). A 24 hour dietary food recall on three occasions was used to construct average intake profiles using the Nutrition Data Systems for Research software (NDSR) (Schakel 2001). We explored possible associations between O3FA dietary intake, AAP use, and endothelial functioning (RHI values). Results: A total of 93 subjects were included. The mean age (±s.d.) of the cohort was 45.89 (±11.49), 64% were Caucasian, 64% were male, and 77% were receiving AAP treatment. A significant

positive relationship was found between RHI values and O3FA intake (P = .00070) as well as the ratio of polyunsaturated fatty acids to saturated fatty acids (PUFA/SFA; P = .0066) in subjects not receiving AAPs. This relationship was erased in those treated with AAPs (P >.6). Regression analysis confirmed the interaction effect of AAP treatment on the relationship between RHI and O3FA (P = .0105) as well as PUFA/SFA (P = .05). Conclusion: The use of AAP may negate some of the CV benefits of a diet high in PUFAs, specifically O3FAs. Thus AAP use may necessitate a higher O3FA dose in subjects to regain their cardioprotective effects, but additional research involving more subjects is necessary to strengthen the preliminary findings. Lifestyle modifications, particularly dietary interventions, may represent a cost-effective method of reducing the morbidity and mortality associated with CVD in patients diagnosed with schizophrenia
ID: 976579

EARLY CANNABINOID EXPOSURE LEADS TO SCHIZOPHRENIA-LIKE BEHAVIORS IN MICE

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Background: Cannabis is the most commonly used drug in the United States, especially among adolescents. In 2001 67% of new marijuana users were under the age of 18 (DHHS, SAMHSA). Epidemiologic studies consistently find an association between early cannabis use and later onset of schizophrenia. Schizophrenia did not develop days or weeks later, but rather years later, suggesting that cannabis use during a critical period of brain development/maturation may have long term consequences. Methods: This study was designed to examine the long-term molecular and behavioral effects of early cannabinoid exposure. C57BL6 mice were administered a CB1 agonist, (WIN55,212-2), CB1 antagonist (AM251), both agonist and antagonist or vehicle for 10 days by intraperitoneal injection at different developmental time points (5, 7 and 9 weeks). The mice were left undisturbed until 16 weeks of age when a series of behavioral tests - fear conditioning, social interaction, loco motor activity, and pre-pulse inhibition - were conducted. One week after the last behavioral test, mice were sacrificed and the prefrontal cortex (PFC) dissected. Immunoblotting studies were conducted to determine expression levels of endocannabinoid system proteins. Activation of group I metabotropic glutamate receptors (mGluRs) is one mechanism by which endocannabinoids are synthesize and released. Accordingly, we measured protein levels of CB1, mGluR1a and mGluR5. Results: Mice that received the CB1 agonist at 5 weeks of age display significant deficits in PPI and in both contextual and cue fear conditioning tasks. There were no deficits in social learning or locomotor activity. Mice treated with CB1 agonist at later developmental time points did not show deficits in any of the four behaviors tested. Compared to controls, 5 week old mice treated with the CB1 agonist show significant increases in CB1 and mGluR5 protein levels but a significant decrease in mGluR1a levels. Further, we find striking correlations between contextual learning and CB1 and mGluR5 protein levels in CB1-treated but not vehicle-treated mice. Conclusion: These data demonstrate that early cannabinoid exposure leads to schizophrenia-like behaviors in the long term. Further, some of the learning and memory deficits are associated with an upregulation of the endocannabinoid system. More broadly, these data suggest that ''adolescent'', but not ''adult'' cannabinoid exposure may alter the developmental trajectory of specific brain systems.
ID: 978600

FOLATE AND ANTIPSYCHOTIC LINKED METABOLIC OUTCOMES: AN INTERIM ANALYSIS

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Background: In schizophrenia (SCZ) patients, our group reported that the methylenetetrahydrofolate reductase (MTHFR) 677C/T variant, responsible for aberrant folate and homocysteine (HCY) metabolism, is a risk factor for atypical antipsychotics (AAPs) linked metabolic syndrome. It is unknown if folate supplementation can overcome MTHFR's effects and reduce these complications. The purpose of this pilot study is to examine the effects of folate supplementation on metabolic measures, endothelial functioning, and inflammatory markers in SCZ subjects treated with AAPs. Methods: Subjects who previously screened positive for metabolic syndrome (NCEP-ATP-III) criteria were given 5mg of folate daily for three months in an open-label trial. Endothelial function was assessed using peripheral arterial tonometry (PAT) using the EndoPAT 2000. Baseline measurements included the PAT index, BMI, and fasting laboratory measures, (glucose, lipids, homocysteine, IL-6, leptin). These were reassessed after three months. Results: A total of 11 subjects are part of this interim analysis. Three subjects had a MTHFR T allele. Overall, the mean PAT index increased by 15% from (1.72–1.87, P = .07) indicating better endothelial functioning. Mean HCY levels decreased by 11% (10.6–9.3 umol/L, P <.06). Mean BMI did not change significantly between baseline and endpoint, from 40 to 39. Mean IL-6 and CRP significantly decreased from 3.79 to 2.49 pg/ml, (P <.05) and 9.9 to 7.7 mg/L, (P <.05) respectively; however mean leptin levels increased from 34.5 to 40.5 ng/mL (P = .06). Differences in the PAT index were seen in relation to the MTHFR genotype. Those with a CC genotype experienced an 18% increase compared to a 6% decrease in those with the T allele, although this was not statistically significant (P = .29) in the very small sample. Conclusion: The results of this interim analysis are encouraging in terms of the endothelial and inflammatory effects of folate supplementation in SCZ subjects receiving AAPs. Folate use may help reduce some of the AAP linked metabolic risks. Increases in endothelial functioning could signal reductions in overall cardiovascular risk. Those with the MTHFR T allele (associated with reduced folate metabolism) may not fully benefit from folate supplementation, although the small sample size precludes a definitive conclusion. Overall, these preliminary results suggest that folate supplementation may have a role to play in managing the metabolic syndrome of SCZ patients taking AAPs.
ID: 979346

ATYPICAL ANTIPSYCHOTICS AND EFFECTS OF MUSCARINIC, SEROTONERGIC, DOPAMINERGIC AND HISTAMINERGIC RECEPTOR BINDING ON INSULIN SECRETION IN VIVO: AN ANIMAL MODEL

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Background: The atypical antipsychotics (AAPs) have been associated with increased risk of metabolic abnormalities, including type 2 diabetes. Evidence suggests direct, drug-related effects independent of changes in weight. Previously we demonstrated in an animal model that a single dose of risperidone, olanzapine or clozapine results in decreased insulin sensitivity, with findings highlighting a clozapine- and olanzapine-induced deficit in β-cell functioning. Although mechanisms underlying this phenomenon are unclear, it has been suggested that the heterogeneous binding profile of the AAPs may influence neurotransmitters and receptors implicated in glucose metabolism. This study aimed to clarify the weight gain-independent mechanisms of AAP-induced changes in insulin secretion by deconstructing their heterogenous receptor binding profile with representative

and selective antagonists. Methods: Healthy Sprague-Dawley rats were pretreated with a single subcutaneous dose of darifenacin 6 mg/kg (n = 8), a selective M3 muscarinic antagonist; ketanserin 2 mg/kg (n = 8), a 5HT2A antagonist; raclopride .3 mg/kg (n = 7) a selective D2/D3 antagonist; terfenadine 20 mg/kg (n = 7) a selective H1 antagonist; or, vehicle (n = 7). A hyperglycemic clamp was employed 90 minutes following drug or vehicle injection, providing an index of secretory capacity of pancreatic β-cells. Results: Acute treatment with darifenacin significantly decreased insulin response to glucose challenge (P = .03), while treatment with ketanserin tended towards decreased insulin levels (P = .09) as compared to vehicle. C-peptide assay confirmed these results, with a reduction in C-peptide levels after darifenacin (P = .007) and ketansarin (P = .04). Acute treatment with raclopride resulted in an increase in insulin levels (P = .02) and a strong tendency to increased C-peptide levels (P = .07), suggesting increased insulin secretion. H1 blockade did not result in acute effects on insulin or C-peptide secretion. Conclusion: Our results suggest that the weight gain-independent effects of antipsychotics on glucose dysregulation may be related to direct inhibitory effects of muscarinic (M3) and serotonergic (5HT2) antagonism on insulin secretion. Based on the presence of D2-like receptors in pancreatic β-cells, which mediate inhibition of insulin secretion, we propose that prolonged D2 blockade with antipsychotics may predispose to depletion of insulin stores and an eventual defect in pancreatic compensation.
ID: 978839

METABOLIC SYNDROME MANAGEMENT FOR THE SEVERELY MENTALLY ILL: A QUALITATIVE ANALYSIS OF PATIENT AND PROVIDER PERSPECTIVES

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Background: The life expectancy of persons with schizophrenia and other forms of severe mental illness (SMI) is decreased by nearly 33% due in large part to health related problems of the metabolic syndrome (eg, dyslipidemia, insulin resistance, diabetes, hypertension, obesity). Screening and treatment rates for this debilitating disease are low for patients with SMI despite the increased efforts to improve medical care for this population. Methods: To better understand the barriers which continue to impede effective metabolic care, the current study conducted 20 qualitative interviews with mental health and medical treatment providers, as well as 10 patients who suffer from SMI receiving mental and physical health care at a large county hospital. Results: A deductive content analysis revealed several major themes including systemic (eg, lack of access to medical care), provider (eg, differential treatment of adults with SMI) and patient level barriers (eg, cognitive limitations) as well as solutions to treating comorbid SMI and metabolic syndrome (eg, greater involvement of case management). An additional theme concerned psychiatric provider involvement in delivering primary care to SMI patients (eg, what primary care treatment psychiatrists and psychiatric nurses could and could not provide in a community mental health setting). Sub-themes within these categories were broken down and arranged hierarchically, each with textual evidence to support the theme's inclusion. Barriers to metabolic care for SMI patients are discussed along with successful strategies for treating metabolic syndrome. Conclusion: The importance of effective collaboration between psychiatric and primary care was highlighted within the interviews and discussed along with suggestions for future care models.
ID: 977799

METABOLIC ABNORMALITIES IN NEWLY DIAGNOSED, ANTIPSYCHOTIC-NAIVE PATIENTS WITH SCHIZOPHRENIA AND RELATED DISORDERS

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Background: Patients with schizophrenia and related disorders have an increased prevalence of diabetes; some of the burden is due to antipsychotic medications. However, schizophrenia is also associated with abnormalities in the periphery independently of medications, and shares some early-life risk factors with diabetes. Methods: We administered a glucose tolerance test to newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis and control subjects. Results: Compared to the control subjects, the antipsychotic-naïve patients had (1) an increased prevalence of diabetes or impaired glucose tolerance on the glucose tolerance test, and other abnormalities associated with diabetes and cardiovascular disease: (2) increased interleukin-6, (3) a wide pulse pressure, (4) a short telomere, (5) a decrease in stromal-derived factor 1-alpha (SDF1α), the main chemokine for adult, circulating stem cells, and the focus of recent diabetes research; (6) an increased prevalence of type 2 diabetes in the parents of schizophrenia probands, and (7) abnormal glucose tolerance in their siblings. In a comparison of patients in the same study who did or did not have primary, enduring negative symptoms (deficit features), those with such features had less severe glucose intolerance than did those without these features; both groups had significantly more severe intolerance than did matched control subjects. In contrast, those with deficit features had higher concentrations of IL6 and c-reactive protein than those without these features. These group differences could not be attributed to group differences in body mass index, demographics, smoking, diet, aerobic conditioning, or duration of untreated psychosis. Most of the differences had effect sizes ranging from "medium" to "large" or even greater. In a 16- week open trial of olanzapine in previously antipsychotic-naïve patients, there was a significant, linear increase in fasting glucose, weight, BMI, cholesterol, triglycerides, and LDL, but not hemoglobin A1c, fasting insulin, IL-6, or HDL. An abnormal baseline IL-6 was a significant predictor of a greater increase in cholesterol and LDL. Otherwise, neither parental history of DM2 nor baseline IL-6 predicted changes in metabolic measures. Conclusion: People with schizophrenia and related disorders have metabolic abnormalities, including an increased risk of diabetes, prior to the administration of antipsychotics.
ID: 978709

EFFECTS OF SECOND GENERATION ANTIPSYCHOTICS ON PERIPHERAL ARTERIAL COMPLIANCE

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Background: Treatment with second generation antipsychotics (SGAs) has been associated with adverse metabolic changes such as weight gain, hyperglycemia, and hyperlipidemia, which in turn is associated with increased

risk of myocardial infarction and stroke. Thus, it is crucial that we increase our understanding of metabolic changes and enhance our prediction of metabolic risk with SGAs in order to prevent such potentially life-threatening events. Arterial compliance (CMP) is the flexibility or the elasticity of arteries. It can be measured in a non-invasive manner with the use of an air plethysmography device called a vasogram, a device that measures volume/pressure changes to quantify CMP in the large arteries of the lower extremity. Reduced CMP has been shown to correlate with coronary and aortic lesions in asymptomatic patients as measured by angiography and MRI. The objective of this study was to compare CMP in subjects treated with SGAs to healthy controls and to psychiatric controls not on any antipsychotic medication. Methods: The subject groups consisted of 19 patients treated with risperidone (RISP), 18 on quetiapine (QUET), 27 psychiatric controls who had been off all antipsychotics for at least two months (NOMED), and 111 historical healthy controls (CONT). Subjects were excluded if they were over 70 years old, had diabetes, weight >300 lbs, or triglycerides >600 mg/dl. Results: One-way ANOVAs indicated that the four subject groups differed in BMI and Framingham risk group but not in age or height. A MANCOVA with thigh and calf CMP as dependent variables, subject group as a between-subjects factor, and BMI and Framingham risk group as covariates was used to assess medication effects on CMP. The main effect for subject group was robustly significant for CMP in both thigh ($F(3, 169) = 4.61$, $P = .004$) and calf ($F(3, 169) = 8.95$, $P < .001$). Follow-up pairwise comparisons for thigh CMP indicated that CONT were higher than RISP ($P = .04$) and QUET ($P = .001$). For calf, CMP in the CONT exceeded that of RISP ($P = .002$), QUET ($P < .001$), and NOMED subjects ($P = .003$). Conclusion: To our knowledge, this is the first pilot study that has examined CMP in subjects treated with antipsychotics. As hypothesized, subjects treated with RISP or QUET had reduced CMP compared to healthy control subjects independent of the effects of BMI and Framingham risk. CMP measures assessed using the vasogram method may prove useful in assessing the advancement of arteriosclerosis during treatment with SGAs.
ID: 956838

THE FIRST 100 WOMEN IN THE NATIONAL REGISTER OF ANTIPSYCHOTIC MEDICATION IN PREGNANCY (NRAMP)

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Background: It is important to evaluate the safety of antipsychotic medication use during pregnancy. Current data on the use of antipsychotic medication in pregnancy is limited. The National Register of Antipsychotic Medication in Pregnancy (NRAMP) will provide evidence-based clinical guidelines for the best use and effect of antipsychotic medication during pregnancy. Methods: NRAMP is an Australia-wide, observational, longitudinal study involving female participants of child-bearing age who are taking, or have taken, antipsychotic medication during pregnancy. Maternal information gathered antenatally includes demographic, social, medical, psychiatric, medication and obstetric history. Measures of maternal psychopathology are also conducted during this time. Further information is collected postnatally, on the general health and well-being for mother and baby including baby developmental milestones, up to the first 12 months of the baby's life. Results: This observational study is current and ongoing. Our presentation will focus on results for the first 100 women consented to take part in NRAMP, and will relate to medications, neonatal outcomes and maternal health and well-being. In the absence of clinical trials, which are the gold standard for medication safety research, but are unlikely given ethical considerations, we must rely on observational studies. Data collected by this method can be a useful source of evidence-based information, providing strategies for achieving and maintaining maternal mental health and well-being with minimal risk to the fetus. Conclusion: The resultant evidence-based guidelines arising from The National Register of Antipsychotic Medication in Pregnancy (NRAMP) have the potential to provide regular, contemporary updates to clinical treating teams for the management of women in this vulnerable population group. We plan to fill a void in mental health services where currently there is a distinct lack of information available to treating clinicians, as they strive to improve the safety and quality of care for women who take antipsychotic medication during pregnancy.
This tudy is supported by AstraZeneca, Janssen-Cilag, Mayne Pharmaceuticals and the Australian Rotary Health Research Fund.
ID: 982367

PATIENT REPORTS OF ANTIPSYCHOTIC-INDUCED DEPRESSIVE SYMPTOMS

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Background: Depressive symptoms are found in a large number of patients with psychotic disorders. The dopamine blockade by antipsychotics may contribute substantially to the emergence of depressive symptoms. Here we study the relationship between patient-reported depressive symptoms and the prescribed antipsychotic treatment. Methods: Data were collected between 2007 and 2010 by the PHArmacotherapy Monitoring and Outcome Survey (PHAMOUS-project). This cross-sectional study included consecutive patients with psychotic disorders receiving an annual routine outcome monitoring in the North of the Netherlands. The Subjects' Reaction to Antipsychotics (SRA), a validated self-report questionnaire, was used to determine if patients perceived depressive symptoms as a side effect of their antipsychotic treatment. Results: Included were 1521 patients with a mean age of 40.4 (SD 11.5) years, a mean duration of illness of 14.1 (SD 10.1) years; 1032 (68%) were male and 913 (61%) were outpatients. 561 (37%) patients perceived depressive symptoms as a side effect of their antipsychotic medication. 359 (24%) patients received combined antipsychotic therapy of two or more antipsychotics. Patients in this group reported significantly more antipsychotic-induced depressive symptoms than the monotherapy group (Chi-square = 10.26; $df = 1$, $P < .001$). Regarding the group of patients using mono-therapy, a typical antipsychotic was prescribed in 248 (21%) patients. Dosing of the typical antipsychotics was within the low to moderate range of haloperidol equivalents. Mono-therapy with atypical antipsychotics included: risperidone (25%), olanzapine (22%) quetiapine (8%) clozapine (16%) and aripiprazol (6%). In a logistic regression model, atypical antipsychotics did not differ from typical antipsychotics in their risk to induce depressive symptoms, when controlled for antipsychotic dose and antidepressant use. Conclusion: A considerable number (37%) of patients attributed depressive symptoms to their antipsychotic medication, with both typical and atypical antipsychotic users affected equally. However, combined antipsychotic treatment was associated with more depressive symptoms as compared to monotherapy.
ID: 979154

GENOME-WIDE ASSOCIATION STUDY OF ANTIPSYCHOTIC-INDUCED WEIGHT GAIN IN PREVIOUSLY-UNTREATED PATIENTS

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Background: Weight gain and related metabolic abnormalities are a significant side effect associated with antipsychotic drug treatment. Treatment studies comprised of chronic patients may underestimate the severity of this side effect, as prior treatments may have caused weight gain and obscure the true weight liability of the current drug treatment. In a recent study (Correll et al 2009, JAMA), we showed that pediatric patients without significant prior exposure to antipsychotic medications experienced marked weight gain at 12 weeks of treatment with each of the study drugs; the weight gain was far greater than reported for previously treated patients and the weight change was highly variable. Therefore, we have focused our pharmacogenetic efforts on the identification of genes that predict weight gain in this largely antipsychotic-naïve population of subjects. Methods: We have comprehensively characterized a cohort of antipsychotic-naïve (or minimally-exposed) pediatric patients undergoing initial clinical treatment with second generation antipsychotic drugs including risperidone, aripiprazole, and quetiapine (Correll et al 2009). Subjects were confirmed to be receiving antipsychotic drug by plasma blood levels, and were weighed at baseline, 4, 8 and 12 weeks of treatment. DNA was collected via blood sample and genotyping conducted with the Illumina 1M OmniQuad platform. Regression analysis of BMI change at 12 weeks of treatment vs baseline was conducted using both additive and recessive models. Results: QTL analysis revealed a region of the genome significantly associated with antipsychotic induced weight gain. The top SNPs that achieved genome-wide significance under the recessive model are located near a previously identified candidate gene for antipsychotic -induced weight gain. Conclusion: Pharmacogenetic studies of antipsychotic-induced weight gain may be most powerful if comprised of previously untreated patient populations with documented adherence to treatment. Our preliminary data suggest that specific candidate genes may be associated with antipsychotic induced weight gain in these populations. Replication studies are underway to confirm and extend these results.
ID: 986938

CARDIOMETABOLIC RISK INDICATORS IN CHILDREN BEFORE AND AFTER 3 MONTHS OF INITIAL ANTIPSYCHOTIC EXPOSURE

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Background: The present analysis, conducted in a dataset of children undergoing their initial exposure to antipsychotic treatment from the ongoing Metabolic Effects of Antipsychotics in Children study (MEAC; PI Newcomer, MH072912) aimed to (1) compare metabolic risk levels in the general pediatric population with untreated baseline MEAC sample, (2) determine whether change in clinical measures of adiposity in children are predictive of changes in gold-standard, laboratory measures, (3) determine whether plasma measures of risk predict change in a laboratory measure of whole body insulin sensitivity. Methods: Participants ages 6–18 (n = 113) were assessed before and after 3 months of randomized antipsychotic therapy with lab and clinical measures of adiposity, metabolic risk and insulin sensitivity. Lab measures include DEXA total and % total fat, abdominal MRI (visceral and subcutaneous fat), and hyperinsulinemic-euglycemic glucose clamps with stable isotope tracing. Clinical measures include anthropomorphic assessment (height, weight and BMI%ile), fasting lipids and glucose, HgbA1c and insulin. Results: Participants entered the MEAC study with a baseline prevalence of overweight or obesity of 34% (13% overweight, 21% obese), compared to a general population prevalence of 32% (15% overweight, 17% obese). Baseline prevalence of ''at-risk'' fasting triglyceride was 1.8%, lower than the general population rate of 12%–14%. After 3 months of antipsychotic treatment, 51% of the population met criteria for overweight (24%) or obesity (27%). The number of children with ''at-risk'' triglyceride values increased to 5.3%. Change in BMI%ile strongly predicted change in DEXA % fat (F[1,110] = 112.20, $P < .0001$) and change in visceral and total (visceral + subcutaneous) abdominal adiposity measured by MRI. Among measured plasma variables, change in fasting HDL (F[1,90] = 4.02, P = .048) alone significantly predicted change in clamp-derived change in insulin sensitivity. Conclusion: Children with mental disorders entering the MEAC study have untreated, baseline prevalence of overweight, obesity and ''at-risk'' lipid values similar to that in the general population. Rates of overweight, obesity and elevated fasting triglyceride increased markedly after 3 months of initial antipsychotic exposure. These results indicate that antipsychotic treatment, and not the untreated psychiatric state of this pediatric sample, is associated with clinically measurable increases in cardiometabolic risk.
ID: 977897

CARDIOVASCULAR RISK IN A FIRST-EPISODE PSYCHOSIS SAMPLE: A CRITICAL PERIOD FOR PREVENTION?

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Background: Studies in first episode psychosis samples about status of cardiovascular risk factors have shown discordant results. The 10-year coronary heart disease risk in patients with chronic schizophrenia from CATIE study was significantly higher as compared to their controls. We aimed to determine the 10-year risk of developing coronary heart disease in a sample of first episode psychosis patients and compared the same with controls. Methods: We conducted a cross-sectional analysis of baseline data of 56 subjects enrolled in the first episode psychosis clinic, the ''Specialized Treatment Early in Psychosis (STEP)'' from April 2006–January 2010 at Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA. This sample was compared with the age, gender, and race matched 145 individuals drawn from the U.S. National Health and Nutrition Examination Survey (NHANES) 2005–2006 database. Socio-demographic and clinical variables were collected. Physical examination including laboratory evaluation was used to screen for common medical illnesses. The 10-year risk of developing coronary heart disease was calculated by using a tool developed by National Cholesterol Education Program (NCEP-ATP III). Results: There was no significant difference in smoking status, weight, body mass index, total and HDL cholesterol, fasting plasma glucose, status of diabetes and impaired fasting plasma glucose, and HbA1C level. The patients had high rates of systolic as well as diastolic hypertension. The 10-year median (range) risk of developing coronary heart disease in patients and controls was 1 (0–5) % and 0 (0–9) % respectively. The difference was not statistically significant. Conclusion: First episode psychosis patients do not present with significantly high cardiovascular risk. To the best of our knowledge, this is the first study where the 10-year risk of developing coronary heart disease was measured in patients with first-episode psychosis. The evidence of the markedly increased coronary heart disease risk in patients with chronic schizophrenia make a compelling case for ameliorative strategies. Early intervention programs give an opportunity to alter the

cardiovascular risk factors in the early stages of schizophrenia and subsequently reduce the mortality.
ID: 938364

METABOLIC SIDE EFFECTS IN ANTIPSYCHOTIC-NAÏVE ADOLESCENTS AFTER 12 MONTHS OF TREATMENT WITH SECOND-GENERATION ANTIPSYCHOTICS

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Background: The prescribing of second-generation antipsychotics (SGA) has increased in recent years in the pediatric population, despite of increasing concern that it may constitute a group vulnerable to metabolic adverse effects and weight gain (Fraguas, Merchan-Naranjo et al 2008). Recent studies have reported significant increases in these parameters in the first months of treatment with SGA in young people (Fraguas, Merchan-Naranjo et al 2008), but there is insufficient data about their long-term safety in this population group. Methods: This longitudinal observational uncontrolled study compares metabolic changes after 12 months of treatment with risperidone, olanzapine or quetiapine in antipsychotic-naïve adolescent patients (defined as no prior treatment with antipsychotic medication or with a total lifetime exposure of fewer than 30 days). Baseline, 6 month, and 12 month measurements, including body mass index (BMI) *z*-score and metabolic parameters, were compared across treatment groups. The outcome measure was defined as a $\geq$.5 increase in BMI *z*-score (Correll and Carlson 2006). Results: The study sample was composed of 61 patients, 14.1 ± 3.3 years of age, 79% males. No significant differences in BMI were found among treatments groups at baseline. After 12 months of follow-up, BMI *z*-scores increased significantly in young people in all the SGA treatment groups ($P < .001$). The increase in BMI *z*-score was significantly greater in the first six months of treatment ($P < .001$), as was the increase in total cholesterol ($P = .008$) and triglycerides ($P = .005$). The BMI z-score increased by more than .5 in 89% of patients receiving olanzapine in the first six months ($P < .05$). Free-T4 decreased after 12 months in patients treated with quetiapine ($P < .05$). Conclusion: Weight and metabolic profile should be monitored closely in children and adolescents treated with SGAs, this being particularly important in the first six months of treatment and especially in patients treated with olanzapine.
ID: 978875

EFFECTS OF THE CANNABINOID-1 RECEPTOR ANTAGONIST RIMONABANT ON SATIETY SIGNALING IN OVERWEIGHT PEOPLE WITH SCHIZOPHRENIA: A RANDOMIZED, DOUBLE-BLIND PILOT STUDY

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Background: Weight gain is a serious side-effect of several second-generation antipsychotic (SGA) medications which may be due to a disruption in satiety signaling. Activation of cannabinoid-1 (CB1) receptors have been shown to stimulate hunger and inhibit satiety in rats (Escartin-Perez, 2009). Rimonabant, a CB1 receptor antagonist, promotes weight loss in the general population (Leite, 2009). Methods: In a 16-week, double-blind, placebo-controlled study of rimonabant (20 mg/day) in people with DSM-IV schizophrenia or schizoaffective disorder, who were clinically stable on SGAs, we tested satiety signaling at baseline and after 7- and 16-weeks of treatment. Participants had a BMI $\geq$30 or $\geq$27 kg/m^2 with hyperlipidemia, no recent depressive symptoms/suicidality, no current substance abuse/dependence (with the exception of nicotine), and < weekly cannabis use. An exercise and dietary counseling group was offered weekly. Because the trial terminated early, due to withdrawal of rimonabant from the European market, target enrollment of 60 was not met. Upon fasting, a standardized breakfast preload was administered followed by a pre-weighed test meal (Wheat Thins® and Nilla Wafers®) using a 60-minutes inter-meal interval; and hunger ratings (visual-analogue scale) were taken pre- and post-preload, then every 30 minutes, for both behavioral and self-report indices of satiety. Results: Fifteen participants were randomized (7 rimonabant, 8 placebo); 5 completed in each group. Rimonabant was not associated with a significant increase in satiety, as measured by self-reported or behavioral measurements. There were trends for decreased test meal consumption in the rimonabant group, compared to placebo, for total kcal ($P = .053$, $ES = .73$) and Wheat Thin kcal ($P = .089$, $ES = .44$). Least square means showed that treatment differences were consistent at visits 7 and 16. Nilla Wafer consumption did not differ between groups. There were no significant group differences in weight or BMI. Conclusion: No statistically significant changes in eating behavior were associated with rimonabant in this small sample of people with schizophrenia. However, there was a trend toward lower caloric consumption in the rimonabant group compared to placebo. This suggests that the endocannabinoid system may be involved with satiety signaling. Future work is needed to confirm and extend these findings. Supported by the NIMH 1 R34 MH077839 (PI: R.W. Buchanan), NIDA Contract N01DA59909 (PI: D.L. Kelly), and the Intramural Research Program, NIH, NIDA
ID: 979447

AKATHISIA PROFILE OF ILOPERIDONE IS SIMILAR TO PLACEBO: RESULTS FROM A POOLED ANALYSIS OF 2 PHASE III CLINICAL TRIALS

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Background: Akathisia is a serious complication of antipsychotic treatment. The current analysis evaluates the propensity of iloperidone (ILO) to induce akathisia in patients with schizophrenia and schizoaffective disorder, with comparisons to placebo (PBO) and 2 active controls, risperidone (RIS) and ziprasidone (ZIP). Methods: In a pooled, post-hoc analysis of 2 phase III studies (4–6 weeks' duration; $N = 1286$) including schizophrenia ($n = 1133$) and schizoaffective patients ($n = 153$), 2 dose ranges of ILO (10–16 mg/d and 20–24 mg/d), RIS (6–8 mg/d), and ZIP (160 mg/d) were compared with PBO regarding their propensity to induce akathisia, using the following definitions: (1) akathisia as recorded by investigator as an adverse event (AE) and (2) new-onset akathisia, as defined by the proportion of patients without akathisia at baseline who met the Barnes akathisia scale (BAS) criteria during the trial. Data were analyzed for patients receiving $\geq$1 study medication dose and having $\geq$1 BAS score during treatment (observed-case analysis). Time-to-first akathisia event analyses were conducted using the Kaplan-Meier method. Results: Akathisia occurred as an AE in 1.7% (4/234) of ILO 10–16 mg/d patients and 2.5% (11/444) of ILO 20–24 mg/d patients vs. 2.3% (7/305) with PBO ($P > .05$ for both ILO groups, pairwise log-rank test); higher rates of akathisia were

observed with RIS (7.8% [12/153]; $P < .05$ vs. ILO and vs. PBO) and ZIP (7.3% [11/150]; $P < .01$ vs. ILO and vs. PBO). New-onset akathisia meeting Barnes criteria was observed in 11.3% (26/230) of patients receiving ILO 10–16 mg/d, 8.9% (38/429) of patients receiving ILO 20–24 mg/d, and 12.5% (37/295) of patients receiving PBO. Using the same criteria, akathisia rates were 20.9% (31/148) with RIS and 21.8% (32/147) with ZIP. Time-to-event analyses showed a consistent pattern of comparability of both doses of ILO to PBO ($P > .05$, pairwise log-rank test). When comparing ILO 20–24 mg/d to RIS and ZIP, statistical separation was observed between the treatments over the treatment period ($P < .01$ and $P < .0001$, respectively; pairwise log-rank test). Conclusion: During short-term (ie, up to 6 weeks) treatment, the frequency of akathisia with ILO was similar to PBO and lower than with ZIP and RIS.
Support: Novartis Pharmaceuticals Corporation
ID: 987381

ADVERSE DRUG EFFECTS NOT DETECTED AT LICENSING REVIEW: REGULATORY AUTOPSY OF OLANZAPINE

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Background: Olanzapine is one of several commonly prescribed medications for which important safety concerns have been identified only after licensing approval, in this case risks of hyperglycemia/diabetes, hyperlipidemia, and marked weight gain. Given the small exposed populations during premarket studies, a proportion of risks must always escape initial detection; however, re-evaluation of the premarket database may improve our capacity to avoid missing some risks going forward. Methods: Review of the 1996 olanzapine Food and Drug Administration Approval Package and European Medicines Agency Assessment Report and published and unpublished analyses of premarket safety data. The unpublished analyses were conducted by the sponsor and were made public through litigation. Results: In retrospect, substantial evidence was available in 1996 raising safety concerns with olanzapine about diabetes, hyperlipidemia, and weight gain that was not identified in the agency reviews or initial labeling, including excess outliers for plasma glucose and cholesterol and glucosuria and statistically significant glucose and cholesterol mean differences. Fasting glucose and triglycerides were not acquired in the pivotal studies. Several processes contributed to overlooking safety signals, including limited reliance on active-controlled and longer-term data, limited consideration of adequacy of safety measures and analytic plans, inappropriately high laboratory safety cut-offs, and under-appreciation of clinical relationships among safety measures and dose-relationships. Conclusion: The present "regulatory autopsy" suggests that warnings/precautions included and then progressively strengthened in prescribing labels 1999–2009 could have been justified at approval in 1996. Hindsight is always 20:20, but regulatory autopsy of premarket safety data can detect overlooked safety signals and potentially benefit future safety evaluations. In the case of olanzapine, the current findings suggest that regulatory premarket review should take a more prescriptive approach to safety design and analytic exploration, analogous to the prescriptive approach to design and hypothesis-testing of efficacy data. Fully informative regulatory autopsies will require that all premarket safety analyses become public when a drug is approved for marketing. Such public availability of safety data would also promote post-marketing surveillance by helping to identify possible safety signals to guide surveillance.
ID: 977068

EFFECTS OF EXTRACT OF GINKGO BILOBA ON TARDIVE DYSKINESIA AND SERUM BDNF: ASSOCIATION WITH THE BDNF VAL66MET POLYMORPHISM

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Background: Tardive dyskinesia (TD) has no well-accepted treatments or known pathophysiology, but low brain-derived neurotrophic factor (BDNF) may play an important role in its pathophysiology. Ginkgo biloba (EGb-761) is a potent antioxidant that has neuroprotective effects mediated through enhancing BDNF levels. We hypothesized that treatment with EGb-761 would increase serum BDNF levels and reduce TD dyskinesia, particularly among schizophrenics who have the BDNF Val66Met genotype (Val/Val) because it is associated with greater neuronal release of BDNF. Methods: Serum BDNF levels and genotyping for the BDNF gene Val66Met polymorphism were assessed in Chinese schizophrenic patients with TD ($n = 333$) and without TD ($n = 482$) as well as healthy control subjects ($n = 546$). About half of the TD patients ($n = 157$) then participated in a double blind, randomized and placebo-controlled 12-week treatment with 240 mg/day of EGb-761. These TD patients' serum BDNF levels were measured again after treatment. Clinical efficacy was determined using the abnormal involuntary movement scale (AIMS), and the Positive and Negative Syndrome Scale (PANSS). Results: TD patients had lower serum BDNF levels than the non-TD patients (8.9 ± 3.0 ng/mL vs. 10.0 ± 2.1 ng/ml, $P < .002$) and healthy controls (10.9 ± 4.2 ng/ml; both $P < .001$).EGb-761 improved symptoms of TD (7.0 ± 2.9 for pre-treatment vs 4.9 ± 2.2 for post-treatment)and increased BDNF serum levels (9.6 ± 3.3 ng/mL for pre-treatment vs 10.8 ± 2.9 ng/mL for post-treatment) compared to placebo treatment. Moreover, the improvement of AIMS total score correlated with the increase in BDNF levels [give r value]. Furthermore, improvement in the AIMS score was greatest in those with the Val/Val allele and lowest with the Met/Met allele. Conclusion: The BDNF system may be implicated in the pathophysiology of TD and its improvement with antioxidant treatment in schizophrenia. Furthermore, patients with the genetic potential for greater BDNF release (Val/Val at 66) may obtain a greater reduction in TD from EGb-761 treatment.
ID: 978729

4. Electrophysiology

PROLONGED AUTONOMIC REACTION TO MENTAL ARITHMETIC STRESS IN FIRST DEGREE RELATIVES OF SCHIZOPHRENIA PATIENTS: A STUDY USING HEART RATE VARIABILITY

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Background: Several have reported abnormal heart rate variability (HRV) in schizophrenia patients suggesting a pathophysiological link between central autonomic function and schizophrenic symptoms. Recent studies suggest that these HRV abnormalities are heritable. This study aimed at evaluating cardiac autonomic response to stress in first degree relatives of schizophrenia patients employing HRV analysis. Methods: Time and frequency domain measures of HRV and QT variability (QTvi) as well as, non linear measures such as Approximate entropy (ApEn), Fractal Dimension (FD) of HRV were computed for 25 healthy adult first degree relatives of schizophrenia patients (siblings/offspring) and 25 healthy age and gender matched controls during rest, mental arithmetic stress task and recovery period. Results: Both groups showed similar response during stress task in time and frequency domain measures. After stress termination, controls recovered completely, showing HRV pattern similar to their baseline. However, first degree relatives did not show a similar recovery pattern with reference to SDNN, LF power, LF/HF ratio, maintaining a pattern similar to that in stress. Conclusion: Poor recovery from cardiac autonomic functions (CAF) changes induced by arithmetic-stress may be a heritable trait marker of schizophrenia. Our study supports endophenotypic potential of HRV in schizophrenia research.
ID: 977577

NEURODEVELOPMENT AND RESTING STATE EEG ACTIVITY AMONG EARLY-ONSET SCHIZOPHRENIA PATIENTS, ADOLESCENTS AT CLINICAL HIGH RISK, AND TYPICALLY DEVELOPING ADOLESCENTS

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Background: Schizophrenia (SZ) is seen increasingly as a syndrome involving abnormal connectivity among neural networks. Nevertheless, how normal neurodevelopmental processes interact with illness risk factors to generate this ''dysconnective'' state remains unknown. A growing number of fMRI investigations have examined the default mode network (DMN), an array of interconnected brain regions shown to be most active when individuals are not engaged in a cognitive task, to assess the activity of task-independent neural networks at a given point in time. Resting EEG activity also reflects ongoing activity in large-scale, task-independent networks, and may provide additional insight into network dynamics underlying the DMN's oscillatory behavior. However, the relationship between the two modalities, and how that relationship may be affected by SZ risk and by the illness itself, requires specification. Methods: The present study aimed to address this issue through an examination of task-independent neural network activity in typically developing adolescents, age-matched individuals at clinical high risk (CHR) for psychotic disorder, and age-matched patients with a diagnosis of a SZ-spectrum illness. The former sample permits disambiguation of the effects of age from the effects of latent risk for psychosis during a developmentally sensitive period, and the latter helps untangle the effects of age from the effects of that risk once it has been fully expressed. We investigated the extent to which the spatiotemporal distribution of resting alpha band (8–12 Hz) EEG generators, derived in source space, overlaps with known sources of activity in the DMN. Results: The present results point to precuneus/posterior cingulate cortex and to medial prefrontal cortex as points of overlap between the two modalities. Next, we investigated age effects on the derived EEG source activity recorded from controls. Consistent with the earlier findings, control adolescents displayed an increase in alpha generator activity with increasing age. Next, we investigated possible age effects in the three samples, showing a divergent developmental trajectory in the adolescent SZ patients, and a pattern intermediate between patients and controls in the CHR sample. Conclusion: These preliminary results provide impetus for further study of resting state activity among CHR and psychotic adolescents, offering a glimpse into how the development of the brain's information processing infrastructure may be affected by psychosis.
ID: 986416

SOURCE LOCALIZATION OF SENSORY GATING: A COMBINED EEG AND FRMI STUDY IN SCHIZOPHRENIA PATIENTS

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Background: Reduced sensory gating appears to be among the core features in schizophrenia. The sources of sensory gating however are largely unknown. The aim of the current study was to identify the brain structures causing the deficits in sensory gating we see in schizophrenia patients. Methods: Twenty healthy male volunteers and 24 schizophrenia patients were tested with identical P50 suppression paradigms in two separate sessions: once in an EEG setting, and once in an EEG concurrent with fMRI setting. The stimuli in the P50 paradigm consisted of weak electrical stimulation of the left median nerve. The stimuli were presented in pairs with either 500 ms or 1000 ms interstimulus intervals (ISI). Results: In healthy controls: No difference was found between the EEG setting and the concurrent EEG and fMRI setting. P50 suppression was, in both settings, found only in the 500 ms trials, not in the 1000 ms trials. EEG-dipole modeling resulted in 4 sources located in the medial frontal gyrus, the insula, the hippocampus, and primary somatosensory cortex. These sources corresponded to significant fMRI clusters located in the medial frontal gyrus, the insula, the claustrum, and the hippocampus. All data from the schizophrenia patients have been assessed and are currently being processed. We expect to present the results at the conference. Conclusion: In healthy controls: Activity in parts of the hippocampus and the claustrum was higher in the trials with suppression, suggesting that these brain areas are involved in the inhibitory processes of P50 suppression. The opposite was found for activity in the medial frontal gyrus and the insula, suggesting that these brain areas are involved in the generation of the P50 amplitude. When

the data from the patients has been analyzed we will hopefully be able to draw conclusions on which sources are affected in schizophrenia.
ID: 978225

PREPULSE INHIBITION IN PRODROMAL AND EARLY PSYCHOSIS: EFFECTS OF CANNABIS AND TOBACCO IN A VULNERABLE POPULATION

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Background: A better understanding of the prodrome and first episode of psychosis can lead to improved prediction of illness risk and the development of targeted treatments in the early course of illness. Startle reactivity and prepulse inhibition (PPI) are important behavioral markers for understanding neuropathological changes across a range of neuropsychiatric disorders including the schizophrenia spectrum. Methods: Startle reactivity and PPI were assessed in 75 early episode psychosis (EP) patients, 89 at risk (AR) for psychosis (putatively prodromal) and 85 comparison subjects (CS). Group effects as well as the effects of sex, age, antipsychotic treatment, tobacco and cannabis were assessed in this population. Results: There were no group differences in startle reactivity, but cannabis users ($N = 125$) had greater startle magnitude than non-users ($N = 124$). EP subjects had reduced PPI relative to AR and CS and this effect was most evident in those who smoked tobacco. In contrast, EP and AR subjects with a history of cannabis use and antipsychotic treatment had the largest PPI. PPI was stable across repeated assessment, suggesting its utility as a trait marker in understanding neurodevelopment abnormalities and response to treatment in early psychosis. Conclusion: Detailed analyses of startle measures demonstrate not only interesting cannabis and group effects but a complex interaction between age, sex, antipsychotic treatment and exposure to environmental risk factors for psychosis. These novel findings, in a relatively large sample of subjects in the early stages of psychosis, provide new insights that need replication and further exploration in collaborative and translational studies.
ID: 979630

AUDITORY ERPS FOR DISCERNING PSYCHOSIS RISK AMONG BIPOLAR AND SCHIZOPHRENIA FAMILIES

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Background: Paired-stimuli (or P50 gating) and oddball (or P300) paradigms have been of interest for probing the neurophysiological and genetic correlates of psychosis. This project addressed whether auditory ERP variables were associated with psychosis generally (schizophrenia and bipolar disorder), differentiated between these psychotic disorders, and/or discerned risk for specific psychotic disorders. Methods: Auditory paired stimuli (P50 gating) and oddball (P300) paradigms were administered to 150 schizophrenia patients and 200 of their relatives, 150 bipolar disorder patients and 200 of their relatives, and 200 healthy subjects. Data were recorded from 68 EEG sensors with a left mastoid reference. One hundred fifty paired-stimuli (P50) paradigm (500 ms ISI, 9.5 seconds ITI) and 667 auditory oddball paradigm (1 second ITI, 15% targets to which subjects responded with a button press) were administered. After data pre-processing using standard procedures and transformation to an average reference, data analyses compared traditional (latencies and amplitudes at sensors that captured the highest voltage responses) and modified (using voltage information over the whole head) ERP peak measurements and time-frequency decomposition (Morlet wavelets) methods for discriminating between groups. Results: Some salient results were: (i) schizophrenia and bipolar patients had lower than normal N100 amplitudes to S1 when using ERP peaks; this effect was more specific to schizophrenia in the time-frequency analyses (both low and high frequencies); (ii) between S1 and S2 schizophrenia patients had less theta, beta, and gamma power than the other groups; (iii) schizophrenia patients had modestly lower N100 amplitudes to S2 than the other groups, an effect accentuated in the time-frequency analyses especially in the beta range; (iv) compared to healthy subjects, the other groups had reduced amplitude N200 responses to target stimuli in the oddball paradigm; and (v) lower P300 amplitudes were evident among schizophrenia patients and their relatives Conclusion: There were important similarities and differences in auditory ERP responses between groups. Some measures were associated with psychosis generally, some were associated with schizophrenia, but no measures were peculiar to bipolar disorder or putative risk for this illness. Frequency domain analyses were superior in many respects to ERP analysis approaches (both traditional and modified) for characterizing group differences.
ID: 979359

AN ERP STUDY OF EMPATHY IN SCHIZOPHRENIA

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Background: Empathy is an important component of normal social function, but studies of empathy in schizophrenia are limited. This study used ERP recordings to compare neural aspects of automatic (bottom-up) and executive (top-down) empathic responses to seeing others in pain in patients with schizophrenia (Sz) and healthy subjects (Hc). Methods: Eleven patients meeting DSM-IV criteria for Sz and seven Hc, matched for gender, age and parental education, were tested; 20 are expected in each group by the time of presentation. ERPs, reaction times (RT) and accuracy following presentation of pictures of hands in either painful or neutral situations were recorded during two task conditions; the Pain Judgment Condition (PC) in which participants decided whether the hands were receiving pain and the Counting Hands Condition (CC) in which participants counted the number of hands (one vs. two hands). Results: Accuracy in the Hc group was high and similar in both the PC and CC. Sz performed non-significantly better than Hc in the CC but significantly more poorly in the PC than the Hc, (group × condition $P = .01$). Sz tended to be slower in RT than Hc in both tasks ($P = .06$). Participants responded more accurately and rapidly to the neutral stimuli than the painful stimuli in the CC and to the pain stimuli in the PC (condition × stimuli $P = .04$ and $P < .01$). ERP analysis revealed the expected temporal dynamic responses in both groups (N110, P180, N240, N340, P3). In addition, a main effect of condition was found in both groups in N340 (at FZ, $P < .001$), and P3 (at C3, $P = .01$; at CZ, $P = .009$; at P3, $P = .002$; and at PZ, $P = .003$) with a positive shift of ERP amplitudes in the PC. The effect of condition was not found in the early automatic components possibly due to limited sample size. Patients also showed diminished amplitude of major ERPs compared with healthy controls (P180, $P = .04$; N240, $P = .03$; N340, $P = .04$; P3, $P = .01$). Conclusion: These preliminary results provide physiological evidence of a preserved late-controlled empathy response in patients with schizophrenia despite evidence in this study of impaired behavioral discrimination of painful stimuli and evidence in the literature of impaired social, emotional and empathic function in patients with Sz. If substantiated in the full study sample, this dissociation between brain and behavioral responses could suggest new directions in efforts to understand social dysfunction in Sz.
ID: 976969

ELECTROPHYSIOLOGICAL ANALYSES OF LEARNED IRRELEVANCE IN SUBJECTS AT CLINICAL HIGH RISK FOR SCHIZOPHRENIA

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Background: One of the key deficits described in schizophrenia is the inability to ignore or filter out irrelevant stimuli, and it has been argued that the major abnormalities in schizophrenia can be derived from this single underlying deficit. A powerful behavioral task paradigm to study an organisms' capacity to ignore irrelevant stimuli is the learned irrelevance (LIrr) task paradigm. In the current study, we combined a modified LIrr paradigm with event-related potential (ERP) measurements to investigate the LIrr effect in a group of subjects at clinical high risk for schizophrenia and a carefully matched comparison group. Methods: Electrophysiological recordings were obtained from 66 channels while participants performed a fast-pace version of a visual LIrr task. The task required participants to learn associations between cue shapes and target shapes in three alternating task conditions: random (R), pre-exposed (PE), and non pre-exposed (NPE). The critical difference between the R, PE and NPE conditions was determined by the predictability of the target by the pre-target shape. Results: The behavioral results demonstrated successful implementation of the LIrr paradigm in that both healthy control subjects and high risk subjects showed a significant LIrr effect. Surprisingly, the LIrr effect in the high risk group was similar in size to the effect observed in the healthy comparison group. In spite of the absence of a difference in behavioral LIrr effects between groups, the ERP results did show clear differences between groups. High risk subjects showed (1) reduced early sensory (P1, N1) components to the pre-target shapes during the R and PE condition, (2) reduced later cognitive (N2, P3) components to the target shapes during the R and PE condition, and (3) a reduced LIrr effect as measured by the difference wave between the ERP to the PE and the ERP to the NPE target shapes. Conclusion: Inefficient cortical information processing during the LIrr task paradigm may be an indicator of altered brain function in individuals at clinical risk for schizophrenia. The observed ERP effects may aid in the development of early intervention strategies designed to prevent or delay the onset of schizophrenia. Longitudinal assessments will further inform about their predictive value for illness onset in populations at high risk for psychotic illness.
ID: 979928

AGE EFFECTS ON MISMATCH NEGATIVITY IN HEALTHY MALE VOLUNTEERS

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Background: Cognitive disturbances, including attention deficits, form core features in schizophrenia. Mismatch negativity (MMN) is an event related potential paradigm, which is thought to reflect the earliest stages of information processing free of attentional and motivational artifacts. Patients suffering from schizophrenia have in a large number of studies shown robust deficits in MMN. Furthermore it has been shown that MMN correlates with daily psychosocial functioning estimates both in psychiatric patients and in healthy individuals. Most studies concerned with the analysis of MMN deficits, use age as a covariate in the early statistical analysis yet discard it in a later stage of the analysis, since it does not covariate significantly. The subject population of these clinical studies are however relative small, age homogenous and prone to gender- and medication effects. The current study reports on the effect of age on MMN as observed in large group of healthy males evenly distributed over a wide age span. Methods: Fifty-eight healthy male volunteers evenly distributed in age from 18 to 80 years, were tested in a MMN paradigm. Stimuli were presented binaurally, and consisted of to different types: A 1000 Hz standard stimulus ($P = .9$) and a 1200 Hz deviant stimulus ($P = .1$). Intensity of all stimuli was 75 dB and they were 50 ms in duration. A total of 1750 stimuli were presented with an inter stimuli interval randomized between 300 ms and 500 ms. Both MMN latency and amplitude were measured at electrode Fz. Results: All subjects showed significant MMN amplitudes, however, no age effect was found on MMN latency nor on MMN amplitude. Conclusion: To our knowledge, this is the first study with a primary focus on effects of age on MMN. The results suggest that age has no influence on MMN, However, future research should focus on the effects of age on MMN in a longitudinal design.
ID: 979215

NEURAL CORRELATES OF LOCAL CONTEXTUAL PROCESSING DEFICITS IN PATIENTS WITH SCHIZOPHRENIA

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Background: Deficits in processing contextual information are one of the main features of cognitive dysfunction in schizophrenia, but the neurophysiologic substrate underlying this dysfunction is poorly understood. Methods: Using EEG with event related potentials (ERPs), in the current study we aimed to investigate the neural correlates of local contextual processing in 30 schizophrenic patients. Local context was defined as the occurrence of a short predictive series of visual stimuli occurring before delivery of a target event. Peak P3b amplitude and latency were evaluated for targets after predictive and non-predictive sequences. Results: Behavioral and neurophysiological measures showed that patients were impaired in their ability to use local contextual information. We found that reaction times were shorter for predictable targets than for non-predicted targets in controls but not in patients. ERP analysis showed that schizophrenia patients did not show the P3b latency shift between predicted and non-predictive targets that was observed in controls, indicating that there was no differential processing of predicted vs random targets in the patients, while controls utilized predictive local context to reduce the duration of stimulus evaluation. Patients also demonstrated a prominent reduction of the peak of an early latency context dependent positivity compared to controls. Finally, unlike controls, schizophrenia patients failed to generate a robust P3b to the predictive sequence. Conclusion: The current study provides evidence of contextual processing impairments in schizophrenia patients, by demonstrating alteration in the behavioral and neural correlates of local contextual processing.
ID: 984753

ALPHA FREQUENCY ALTERATIONS IN SCHIZOPHRENIA DURING HIGH WORKING MEMORY LOAD CONDITIONS

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Background: Working memory (WM) alterations in schizophrenia have been associated with alterations in high- frequency rhythms (Gamma

and beta bands). Nonetheless, it has been suggested that lower frequencies (ranging from 4 to 13 Hz) might regulate these higher rhythms (Schroeder and Lakatos 2009), thus the dysfunctions observed in schizophrenia may be part of wider alterations at different ranges of frequencies. The aim of the present study was to evaluate if schizophrenia patients show power spectral alterations at low frequencies during different working memory loads. Methods: Twenty-six subjects (13 patients, 13 matched controls) performed an implicit verbal type of N-back task which varies the amount of items stored in memory (0-, 1- and 2- back conditions). While the subjects were performing this task, we registered the neuronal surface activity with a continuous scalp 80 channel electroencephalogram (Sampling rate: 1000 Hz, band pass filter: .1–100 Hz.). Time-frequency representations, estimating the temporal course in power, were computed using a Fourier approach, applying a sliding tapered window (Hanning taper, fixed time window of .5 seconds, spectral smoothing of 3 Hz). Statistical significance was tested trial by trial and across subjects using a non parametric permutation tests across clusters of sensors. Results: Posterior alpha (9–13 Hz) and frontal theta (4–8 Hz) power spectral activities were elicited in all the conditions studied (0-, 1-, and 2- back), however, only alpha power activity showed modulation as a function of WM load. As WM load was increased (from 0- to 2- back conditions) an increment in posterior alpha power activity was observed in healthy subjects. However, in the schizophrenia group, differences in WM load did not elicit variations in alpha power between conditions. Significant between-group (controls and schizophrenia patients) statistical differences were obtained over parieto-occipital scalp sites in the alpha band range during the highest WM condition (P = .021) Conclusion: We hypothesize that this effect of patients' failure to modulate alpha activity at high WM load conditions may represent a failure to suppress brain regions not involved in the ongoing task . This hypothesis is consistent with the proposal that alpha band activity subserves WM resource allocation by disengaging task-irrelevant brain regions during normal conditions (Jensen, et al 2002).
ID: 979556

LOSS OF LTP IN α7 NEURONAL NICOTINIC RECEPTOR (α7*) KNOCKOUT MICE IS STRAIN DEPENDENT

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Background: Cognitive deficits are a core feature of schizophrenia, a neurodevelopmental disorder that affects approximately 1% of the population. People with schizophrenia have demonstrated deficits in multiple domains of cognition which have proven refractory to treatment with antipsychotic agents used to treat positive symptoms of the disorder. The α7 neuronal nicotinic receptor (α7*) is known to play a role in the development of schizophrenia multiple studies. The receptor is a homopentameric ligand-gated ion channel expressed in neuronal and non-neuronal cell types, with both a presynaptic and postsynaptic localization. Activation of the α7* receptor on neurons leads to an influx of calcium and increased neurotransmitter release. Postsynaptically, it is associated with regulation of gene expression. The α7 subunit is encoded by the CHRNA7 gene in humans and by the Chrna7 gene in mice. C3H and C57BL/6J wild-type mice have similar levels of the high-affinity α4β2* receptor, while C3H mice have significantly elevated levels of the low-affinity α7* receptor compared to C57BL/6J. Chrna7 knockout animals have been shown to have cognitive deficits by the 5-choice serial reaction test. Methods: Long-term potentiation (LTP) is a reflection of synaptic plasticity and a model for learning and memory. LTP was examined in the hippocampal CA1 region of C3H and C57BL/6J (C57) Chrna7 wild-type and homozygous knockout mice. Results: Wild-type C3H animals demonstrated robust LTP, while homozygous knockout animals had minimal levels of LTP. Both wild-type and Chrna7 knockout C57 mice had reduced levels of LTP compared to C3H wild-types, but did not significantly vary from each other. Paired-pulse ratios did not differ, indicating no difference in probability of glutamate release. Conclusion: We hypothesize that the differences in LTP levels observed between strains and genotypes is a reflection of α7* receptor levels interacting with strain-specific genetic differences, resulting in altered downstream gene expression and protein profiles. There may be a simple, direct effect of α7* activity on calcium flux and either neurotransmitter release or postsynaptic changes in calcium-dependent processes, the results of which are directly transmitted downstream, ultimately to the ability to establish or maintain LTP. Alternatively, reduced α7* receptor activity during development may lead to alterations in structural and functional capacity of the hippocampus which restricts its overall neuroplasticity.
ID: 979542

HIGH GAMMA (>60HZ) ABNORMALITIES IN SCHIZOPHRENIA PATIENTS DURING AUDITORY STEADY-STATE STIMULATION

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Background: Event related high frequency neural oscillations in the upper gamma range (60–200 Hz) correlate with a range of cognitive and perceptual processes, are characteristic of focal cortical network activity synchronized by GABA-ergic interneurons, and correlate with the Blood Oxygen Level Dependent Signal measured by fMRI. Interestingly, such neural activity has not been specifically examined in schizophrenia patients during auditory stimulation. Methods: Dense-array (256 channel) EEG was recorded while 17 schizophrenia patients (SZ) and 16 non-psychiatric subjects (NP) were binaurally presented 1500 ms duration noise bursts amplitude modulated at frequencies from 16 to 44 Hz, in 2 Hz steps. Based on a principal components analysis of evoked steady-state amplitudes and topographies at the driving frequency, trials were grouped into low (16–24 Hz) and mid (26–44 Hz) stimulus frequency conditions. Results: Consistent with previous studies, early (0–400 ms) event-related low frequency activity (1–4 Hz) amplitude and intertrial phase-locking (IPL) were reduced in SZ to all stimuli types, and ERP reductions were present in the 30–120 ms range (p50–n100). For all stimuli, SZ also showed a dramatic decrease from baseline activity in the amplitude of high frequency oscillations (60–90 Hz) in the 0–400 ms time range that was not present among NP. Conversely, event-related amplitudes and IPL at the driving frequencies were significantly increased in SZ, an effect that was most dramatic to mid gamma stimulation rates. Conclusion: Past auditory steady-state studies have consistently identified reductions in SZ auditory steady-state responses to 40Hz stimuli, but they used shorter durations of stimulation (500–1000 ms), the current results suggest that aurally dense and prolonged (>500 ms) steady-state stimulation drive SZ auditory cortical networks above NP levels at the cost of interfering with ongoing high-frequency oscillations. This could index, and represent a consequence of, abnormal gating mechanisms in thalamo-cortical networks. Furthermore, ERP abnormalities localized (L2 minimum norm) to left superior temporal lobe and right temporal-parietal junction. The former is consistent with left-hemisphere pathophysiology commonly associated with schizophrenia; the latter converges with a number of E/MEG studies and may be an index of suboptimal signal propagation in extended cortical networks.
ID: 979805

GAMMA SYNCHRONY IN FIRST EPISODE SCHIZOPHRENIA: ASSOCIATION WITH SYMPTOMATOLOGY AND NEUROCOGNITIVE DEFICITS

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Background: Dysconnectivity of the brain have been suggested as the basis for the clinical phenomenology of schizophrenia. Gamma synchrony, a measure of cortical connectivity, is altered in schizophrenia. However the relationship of altered levels of cortical connectivity and the phenomenology of schizophrenia is less well established. In this study we examine the association of the phenomenology and neurocognitive deficits of schizophrenia with measures of cortical connectivity in a cohort of subjects aged between 14 and 25 years of age, all with recent onset schizophrenia. Methods: Seventy three subjects recruited from community and hospital services in Western Sydney were assessed using a computerized battery of neurocognitive and social cognitive measures and ratings of symptomatology (PANSS). Gamma synchrony was measured during an auditory oddball paradigm. Synchrony was examined within the frontal, central and temporal regions and fronto-temporally. Results: Raised gamma synchrony was observed in the subjects with first episode schizophrenia both frontally (P = .006) and fronto-temporally (P = .002). These results were consistent over a number of windows of measurement. However the correlation with neurocognitive measures though observed over a number of cognitive domains was weak for both control subjects and for those subjects with schizophrenia. Similarly a trend towards a negative correlation with negative symptoms in subjects with schizophrenia was seen however this did not survive correction for multiple comparisons. Conclusion: Gamma synchrony abnormalities are present from early in the course of the schizophrenia. However the association of this measure of cortical connectivity with cognition and symptomatology is far less strong. Caution is required when trying to associate complex behaviors, with broad averaged measures of regional connectivity.
ID: 979269

EVALUATION OF A NORMAL-PREDICTED CHANGE INDEX FOR ASSESSMENT OF P50 SUPPRESSION IN SCHIZOPHRENIA

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Background: Auditory P50 event-related potential (ERP) suppression is assessed using a paired-stimulus paradigm and quantified as an index of change in P50 amplitudes from the first (S1) to the second (S2) stimuli. This measure has been extensively studied in schizophrenia, but is criticized on theoretical and psychometric grounds due to a tendency for smaller S1 responses in patients and unacceptable reliability of the conventional suppression score (S2/S1). Furthermore, although schizophrenia samples generally evidence less suppression than healthy samples in group-wise contrasts, the lack of normal parameters for determining impairment make this measure impractical for individual assessment. The present study evaluated an alternative, regression-based, P50 suppression index as a method of accommodating variability at S1 and identifying impairment at the individual level. Methods: The regression of P50 S1 on S2 was modeled in healthy normal subjects (HN; N = 75) and resulting coefficients were applied to a schizophrenia (SZ; n = 69) sample. Individual differences in P50 suppression were quantified as the residual of obtained S2 values and normal-predicted values (S2–S2'), with positive residuals indicating below-normal suppression status. Results: A cubic spline function explained 40% of the variance in S2 by S1. Regression residuals were highly dependent on S2 amplitude (r = .81) and independent of S1 (r = .01). HN and SZ samples did not differ in conventional P50 amplitude or suppression measures and were proportionately equivalent (44 vs. 43%) with respect to subjects classified as having below-normal suppression. Within SZ, subjects with below-normal suppression produced smaller amplitude P300 than above-normal subjects in a separate auditory target-detection task (P <.05), but equivalent N100 to non-target stimuli. Repeating this analysis in groups classified according to a S2/S1 ratio cut-point (.5) revealed no difference in N100 or P300 despite high classification agreement with groupings based on regression residuals (Phi = .72). Symptom severity, medication, and smoking status did not differ with suppression-status in SZ. Conclusion: Quantification of P50 suppression in reference to normal-predicted values provides an index that is independent of variance in S1 amplitude, represents deviation from normal at the individual level, and is more sensitive to down-stream auditory processing deficits in schizophrenia than the traditional S2/S1 suppression score.
ID: 985197

DISTRACTIBILITY IN SCHIZOPHRENIA AND ITS MODULATION BY ACUTE NICOTINE ADMINISTRATION

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Background: Elevated rates of tobacco smoking in schizophrenia when compared to the normal population may reflect an attempt to self-medicate cognitive deficits associated with this disorder. Attentional impairments are a core feature of schizophrenia that have been transiently corrected by acute nicotine but it is unclear as to whether nicotine's ameliorative effects involve selective attention or attentional control under conditions of distraction. The main objective of the present study was to employ a combination of behavioral performance and brain event-related potentials (ERP) to examine responses to small and large auditory deviants in minimally tobacco-deprived (3 hours) patients and matched tobacco deprived smoking controls and to assess the effects of acute nicotine on distractibility in patients. Methods: Twelve smokers with schizophrenia and twelve control smokers were instructed to ignore task-irrelevant auditory stimuli while they performed a visual discrimination task, with the patients being tested during two double-blinded sessions with either nicotine gum (6 mg) or placebo while the controls were tested in one non-drug session. Results: Reaction times were longer in the presence of large deviant sounds for both controls and patients with placebo, but not for patients with nicotine. Pre-attentive detection of small deviant sounds was greater in controls (vs placebo treated patients) as evidenced by a larger mismatch negativity (MMN) and involuntary attentional orienting to large deviant sounds was reduced in patients with nicotine as shown by diminished P3a amplitudes. Conclusion: These preliminary findings demonstrate deficits in the early detection and involuntary attentional orienting to auditory distracters in schizophrenia and document for the first time that acute nicotine can alter these neural processes and reduce behavioral distraction.
ID: 978451

SHORT-TERM TROPISETRON TREATMENTS IMPROVE DEFICITS IN AUDITORY P50 SUPPRESSION IN SCHIZOPHRENIA: DOSE-RESPONSE RELATIONSHIP

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Background: Deficient inhibitory processing of the P50 auditory evoked potential is a pathophysiological feature of schizophrenia. Several lines of evidence suggest that alpha 7 nicotinic receptors play a critical role in this phenomenon. Nicotine has ameliorating effects on sensorimotor gating deficits in schizophrenia, but its toxicity and marked tachyphylaxis make it an ineffective therapeutic. Tropisetron, a drug already approved for clinical use outside the United States as an anti-emetic, is a partial agonist at alpha-7 nicotinic receptors and an antagonist at 5-HT3 receptors. A previous study showed that a single administration of tropisetron (10 mg) significantly improves P50 inhibition in Japanese schizophrenics. This study examined the dose effects of short-term tropisetron treatment on the P50 inhibition in Chinese schizophrenic patients. Methods: 40 patients who had been taking a fixed dosage of risperidone were randomly assigned to receive a dose of tropisetron (placebo, 5 mg-, 10 mg- or 20 mg) for 10 days. P50 auditory evoked potentials were recorded at baseline and post-treatment. Results: The placebo group showed no statistically significant difference in P50 S2/S1 ratio between pre- and post-treatment (1.3 ± .6 vs 1.4 ± .6). All tropisetron groups showed a significant improvement in P50 inhibition at post-treatment compared to pre-treatment (5 mg group: 1.6 ± .7 vs .7 ± .5; 10 mg group: 1.6 ± .5 vs .5 ± .6; 20 mg group: 1.5 ± .6 vs .7 ± .5) (all $P < .01$). Furthermore, at post-treatment, all tropisetron groups showed a better P50 inhibition than the placebo group (all $P < .01$). However, no significant difference was noted between three tropisetron groups. No side effects were observed in the 5 mg and 10 mg groups. Two cases in the 20 mg group showed lower limb edema. Conclusion: Our results suggest that short-term tropisetron treatment improves the deficient inhibitory processing of the P50 auditory evoked potential in schizophrenia, but it is not dosage dependent.
ID: 978830

N1M AND MMNM IN ULTRA-HIGH-RISK FOR SCHIZOPHRENIA AND PATIENTS WITH SCHIZOPHRENIA: AN MEG STUDY

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Background: The N1 and mismatch negativity (MMN) responses observed in electro- and magnetoencephalographic recordings, reflect sensory processing, sensory memory, and adaptation and are usually affected in schizophrenia, but their differential sensitivity to ultra-high-risk (UHR) status and schizophrenia is controversial. The current study evaluated the sensitivity of N1m, N1m adaptation, and MMNm in UHR for schizophrenia and patients with schizophrenia. Methods: Using a 306-channel magnetoencephalographic system, we measured brain responses from 16 UHR subjects, 10 patients with schizophrenia and 18 healthy controls during a passive auditory oddball task. The adaptation was assessed using the difference in N1m dipole moment between the first and last standard tones in a standard stimulus sequence. Results: N1m latency to the first standard tone was delayed in the left hemisphere compared with the right in both the UHR and patient groups. N1m adaptation occurred in healthy controls, whereas neither the UHR group nor the schizophrenia group showed adaptation to the standard tone on repeated presentations. The UHR group had values between those for the healthy control and patient groups. Additionally, MMNm dipole moment was reduced in both the UHR and patient groups compared with healthy control group, whereas the UHR and schizophrenia groups did not differ from each other. Conclusion: These findings indicated that both N1m and MMNm were altered in the UHR subjects and in patients with schizophrenia. Moreover, both UHR subjects and patients with schizophrenia failed to show adaptation of the N1m to repeated standard tones. This failure in adaptation was more severe in schizophrenia patients than in UHR subjects, suggesting that adaptation may be sensitive to the progression of the illness and be an early biomarker of UHR for psychosis. Deficits in auditory sensory memory, on the other hand, may be similarly impaired in both groups.
ID: 977625

DYSFUNCTIONAL SOURCE ACTIVITY OF EVENT-RELATED POTENTIALS FOR AFFECTIVE FACIAL PICTURES IN SCHIZOPHRENIA PATIENTS

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Background: The ability to recognize facial affect is impaired in schizophrenia patients. This study compared the source activities of the event-related potentials (ERPs) for affective facial pictures between schizophrenia patients and normal controls. Methods: Twenty-five schizophrenia patients (13 females) and 25 normal controls (13 females) were recruited. The standardized low-resolution brain electromagnetic tomography (sLORETA) source activities of four ERP components (P100, N170, N250, and P300) were compared between schizophrenia patients and normal controls for three types of affective facial pictures: fearful, neutral, and happy faces. Results: Group differences of sLORETA source activities were found only for the N170 component, and only for the fearful face. Source activities in the insular area were lower in schizophrenia patients than in normal controls ($P < .05$, one-tailed). Source activities in the precuneus, superior temporal gyrus, insula, and inferior frontal gyrus areas were lower in male than in female schizophrenia patients ($P < .05$, two-tailed). However, the ERP source activities did not differ significantly with gender among the normal controls. Conclusion: These results support the hypothesis that the N170 component of facial affect processing is dysfunctional in schizophrenia. They suggest that the dysfunctional source activity of the N170 component for fearful faces is localized to the insular areas, and that gender differences exist during this processing in schizophrenia patients but not in normal controls.
ID: 976146

A STUDY OF THE RELATIONSHIPS BETWEEN THE RATIO OF 2ND–4TH DIGIT LENGTH AND CEREBRAL LATERALITY

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Background: Cerebral laterality is thought to be an important marker for neurodevelopment. Prenatal testosterone could influence both cerebral laterality and the ratio of 2nd–4th digit length (2D:4D). High prenatal testosterone exposure is known to make 2D:4D small ("masculine digit type"). Low prenatal testosterone exposure is known to make 2D:4D great (''feminine digit type''). We studied EEG coherence and 2D:4D of healthy subjects to investigate the relationships between prenatal testosterone exposure and cerebral laterality as a preliminary study for aberrant neurodevelopment in schizophrenia. Methods: EEG was recorded in 24 healthy subjects (11 males and 13 females) using 16 electrodes in the eyes-closed resting state. The length of 2nd (index finger) and 4th digit (ring finger) was measured using a vernier caliper. Differences in 2D:4D were used to discriminate between "masculine digit type" and "feminine digit type" groups. The 2D:4D ratio was less than one in masculine digit type group and greater than one in feminine digit type group, respectively. We used coherence analysis to estimate the cortical functional connectivity of EEG data. Statistical analyses such as Mann-Whitney test and Spearman correlation analysis were performed to examine the effects of both sex and 2D:4D on EEG coherence. Results: There were statistically meaningful relationships among sex, 2D:4D and cortical functional connectivity. Men and masculine digit type group showed higher intra-hemispheric coherence than women and feminine digit type group, which were prominent in the right cerebral hemisphere. Women and feminine digit type group showed higher inter-hemispheric coherence than men and masculine digit type group. In the correlational analysis between 2D:4D and EEG coherence, low 2D:4D correlated with high intra-hemispheric coherence and low inter-hemispheric coherence. These relationships were prominent, especially in the beta band. Conclusion: These results imply that prenatal testosterone exposure might act as important determinants of cerebral laterality. Further studies of the relationships between 2D:4D and EEG coherence in schizophrenia could give some clues for elucidating the neurodevelopmental hypothesis of schizophrenia genesis.
ID: 979076

SYNAPTIC AND CIRCUITRY MECHANISMS UNDERLYING COGNITIVE ABERRATIONS IN MICE DEFICIENT IN GENES LINKED TO SCHIZOPHRENIA

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Background: Findings from human genetic studies have provided unprecedented opportunities for research employing genetic manipulations to create animal models of various diseases. It has been challenging, however, to model mental disorders such as schizophrenia in animals. Schizophrenia is a complex disorder that is manifested by a wide spectrum of behavioral symptoms and involves dysfunction in multiple brain systems. It will be of great value to determine the causal links in mouse models between a particular genetic deficit, synaptic and circuitry abnormality, and a specific behavioral trait related to schizophrenia. Methods: To this end, we are using the Cre/Lox system and RNAi, combined with in vivo viral delivery to manipulate schizophrenia candidate genes, including ErbB4 and DISC1, in discrete neuronal populations within different brain regions. We focus on brain systems subserving cognitive processes that are impaired in schizophrenia, such as attention and behavioral flexibility. Results: Our preliminary data suggest that this approach is feasible. Conclusion: Our research will shed light onto the synaptic and circuitry mechanisms underlying the specific cognitive deficits, which are symptoms of schizophrenia that suffer from ineffective medications.
ID: 978932

ATTENTIONAL BLINK IN SCHIZOPHRENIA: PERFORMANCE AND ERP EVIDENCE FOR ABNORMALITY

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Background: Previous work has demonstrated that several aspects of early visual processing are impaired in schizophrenia, yet whether these impairments extend beyond the earliest stages of visual perception remains unclear. The current research examined the integrity of visual short-term memory, which is involved in later stages of visual processing, in schizophrenia using the attentional blink (AB) paradigm. Methods: In the AB paradigm, two target stimuli (T1 and T2) are presented at varying positions or ''lags'' within a rapid sequential stream of stimuli (appearing every 100 ms) that also includes eight distractor stimuli. In healthy subjects, when T2 lags T1 by 200–500 ms, identification of T2 is diminished due to the ongoing allocation of cognitive resources to processing T1, which is referred to as the AB effect. To evaluate the AB effect in schizophrenia, we conducted two studies that used complementary behavioral performance and Event-Related Potential versions of the AB paradigm in patients and matched controls. In Study 1, 145 patients and 84 controls completed a standard behavioral version of the AB task. In this version, participants verbally identified the target stimuli. In Study 2, a subset of 79 patients and 62 controls completed a modified version of modified AB task to assess ERPs to the target stimuli. In this version, the P300 component of the ERP elicited by target stimuli was evaluated. Results: In Study 1, controls showed the expected AB effect: their ability to detect T2 was reduced when it followed T1 by lags of 200–500 ms. Patients showed an exaggerated AB effect: the reduction in detection of T2 was significantly greater relative to the controls, even after correcting for deficits in basic perceptual processing. In Study 2, controls showed a reduced P300 to T2 during the same 200 period of the attentional blink that corresponded to reduced detection of T2. Patients showed the expected reduction in P300 amplitude at all lags. However, they also showed abnormal modulation of amplitude across the lags (ie, P300 amplitude had not recovered after 500 ms). Conclusion: The behavioral performance on the AB task indicates that patients with schizophrenia exhibit a deficit in visual processing that extends beyond basic perception, and the P300 results suggest that impaired visual short-term memory consolidation may underlie this abnormality.
ID: 979881

ELECTROPHYSIOLOGICAL AND STRUCTURAL MRI BIOMARKERS FOR PROGRESSION IN SCHIZOPHRENIA

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Background: In the search for biomarkers for schizophrenia (SZ) and for progression of this disorder, event-related potentials (ERP) & structural MRI (sMRI) need to be evaluated. Methods: ERPs & sMRI. Results: Our previous first episode SZ (FE) samples have indicated cross-sectional abnormalities for pitch mismatch negativity (MMN) and auditory P300, as well as progressive reduction in pitch MMN over the 1.5 years following baseline. In the current CIDAR FE sample we obtained baseline ERP data on 22 FE and 22 healthy controls (HC), all right-handed and group matched on age and gender. At baseline, pitch MMN was reduced at Fz in SZ ($P = .016$, 1.2 kHz 10% deviants, 1 kHz standards); on a 1 year later retest in a small subset of these patients (12 FE SZ), there was no clear evidence of further reduction. In the current sample, FE and HC did not differ on baseline duration mismatch (50 ms standards, 100 ms deviants, both 1 kHz). Auditory P300 consisted of silently counted targets (15%, 1.5 kHz) and standards (1 kHz); compared with the HC, the FE at baseline showed highly significant reductions at Cz & Pz. Moreover, the 10 FE SZ thus far retested 1 year later showed a further progression of P300 amplitude reduction at central electrodes. Our previous manual ROI MRI longitudinal data analysis showed progressive reduction of gray matter (GM) volume in superior temporal gyrus (STG), cingulate, and in overall temporal and frontal cortex. In addition to ROI, we are now analyzing longitudinal data using a new, high resolution VBM algorithm (DARTEL) on scans from 21 FE SZ & 23 matched HC. Unpublished results indicate its congruence with our ROI findings. Gray Matter (GM) loss over 1.5 years was observed in frontal, temporal and parietal gyri. Correlation analyses were conducted between changes in regional GM volumes in FE and positive and negative symptoms derived from the BPRS, as well as cognitive function as assessed by the Mini-Mental State Examination. Progressive GM loss in different regions showed distinct clinical correlations, the more loss, the worse the symptoms. Examples: Heschl gyrus/STG loss & Thinking disturbance/hallucinations; Inferior Frontal gyrus/insula and negative symptoms. Worse cognition on retest was associated with more widespread GM loss in both temporal and frontal cortex. ERP associations with GM loss are currently being analyzed. Both ERP and sMRI results were unrelated to medication dosage. Conclusion: Both ERPs and sMRI show great promise as biomarkers for progression of SZ.
ID: 978048

MULTISENSORY INTEGRATION IN SCHIZOPHRENIA AND CLINICALLY-HIGH-RISK INDIVIDUALS: A BEHAVIORAL AND ELECTROPHYSIOLOGICAL STUDY

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Background: Over recent years, findings suggestive of decreased neural connectivity have become the cornerstone of several models of schizophrenia. Consistent with this notion is a small body of research pointing to reduced multisensory integration in schizophrenia (SZ). Given that efficient multisensory integration requires precisely timed and directed neural coordination, it follows that SZ patients ought to exhibit reduced susceptibility to audio-visual illusions that result from automatic multisensory integration, such as the sound-induced flash illusion (Shams, Kamitani, & Shimojo, 2000). Here, we report preliminary results of a study examining sound-induced flash illusion in recent-onset SZ patients, age-matched individuals determined to be at clinical high risk for development of the disorder, and healthy controls. Methods: Both behavioral responses and event-related EEG were recorded. In the illusion conditions, participants were exposed to either one or two rapid flashes of a small white disk presented in silence or coupled with either one or two brief auditory tones (or ''beeps''). Previous research has documented altered perception of the number of flashes when participants are presented with an incongruent number of beeps (ie, they often perceive two flashes when one flash is presented with two beeps, or they frequently perceive one flash when two flashes are presented with one beep), even though task instructions ask participants to attend only to the visual stimuli. Results: Here we find that SZ patients exhibit a trend towards increased accuracy (ie, less illusion susceptibility) in the detection of visual stimuli in the presence of incongruent auditory stimuli, relative to healthy control subjects. Additionally, SZ patients exhibiting lower levels of gamma frequency band (30–50 Hz) EEG activity over occipital sites showed highest accuracy during incongruent conditions. On a group level, preliminary analyses of the clinical high-risk participants showed results intermediate between patients with established illness and controls. Conclusion: These findings suggest a reduction in multisensory integration among schizophrenia patients, consistent with impaired binding of multisensory information and abnormal functional connectivity among localized neural assemblies supporting audio-visual integration.
ID: 979073

ERROR MONITORING AND RESPONSE INHIBITION IN ADOLESCENTS WITH SUB-CLINICAL PSYCHOTIC SYMPTOMS ON A SIMPLE GO/NO-GO TASK

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Background: Executive functions such as error monitoring and response inhibition are impaired in patients with schizophrenia. The error-related negativity (ERN) observed following an erroneous response is attenuated in schizophrenia and may reflect deficient internal monitoring of behaviour (Bates et al, 2002). A reduction in P300 amplitude is also evident on tasks of response inhibition, which may be due to difficulties with inhibitory control (Strandburg et al, 1999). This study sought to examine whether the patterns of ERP abnormalities exhibited by patients with schizophrenia on response inhibition tasks are common to adolescents with sub-clinical psychotic symptoms. Methods: Twenty-four adolescents with psychotic-like experiences and twenty-three controls aged 11–13 years old completed a visual Go/NoGo task. Participants were presented with the letters ''X'' (Go trials) and ''K'' (NoGo trials) and were instructed to make a button press response to a Go trial and to withhold their response to a NoGo trial. Group differences were examined in the amplitude and latency of six event-related potential components: the P300 and N2 elicited by response inhibition processes following presentation of a stimulus, error-related negativity (ERN) and later error-positivity (Pe) elicited on false-alarm responses to NoGo trials, and the correct response negativity (CRN) and later correct response positivity (Pc) elicited during processing of correct responses to Go trials. Results: Adolescents with sub-clinical psychotic symptoms displayed reduced P300 amplitude when compared to controls. However, the error-related negativity to correct and incorrect responses remained unaffected, as did the positivity associated with correct and incorrect responses. Conclusion: The reduction in P300 amplitude is indicative of impaired inhibitory control, which is similar to that of patients with schizophrenia. The results of this study suggest that adolescents at-risk for psychosis are characterized by deficits of inhibitory control rather than impaired monitoring of internal behaviour. Thus, the unaffected ERN component in this group further supports the findings that the ERN may be modulated by clinical state in schizophrenia (Bates et al, 2004).
ID: 976951

NEUROPHYSIOLOGICAL PARADIGMS IN PATIENTS AT ULTRA HIGH RISK FOR DEVELOPING PSYCHOSIS

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Background: Subjects at ultra high risk (UHR) for psychosis show dysfunctions in several neurophysiological paradigms. To our knowledge, studies reporting on several neurophysiological paradigms in the same UHR subjects are scarce. Methods: Eye movements (antisaccades, smooth pursuit eye movements) and event-related potentials (N100, N200 N200b, P200, and P300 amplitudes) were assessed in 61 UHR subjects, of whom 18 subjects (30%) made a transition to psychosis over a 3-year follow-up period (UHR+T) and 43 did not (UHR+NT) and 28 age- and intelligence matched healthy control subjects. Results: The UHR subjects showed increased antisaccadic errorrate and higher corrective ($t = 2.62$, $P = .011$) and non-corrective saccadic rates ($t = 2.19$, $P = .023$) during smooth pursuit eye movements compared to controls. In addition, UHR+T subjects showed smaller parietal P300 amplitudes, compared with control ($t = 6.73$, $P < .0001$) and UHR+NT subjects ($t = 4.16$, $P < .001$). N2b difference was larger in controls compared with both UHR+T ($t = 2.32$, $P = .025$) and UHR+NT ($t = 2.44$, $P = .017$) subjects. We found no differences in N100 or P200 components between the groups. Reduced P300 amplitudes were the best predictor for subsequent psychosis in the UHR group (Wald = 10.4, $P = .001$, HR = 1.37). Conclusion: UHR subjects showed reduced antisaccade and smooth pursuit eye movement performance indicating prefrontal lobe dysfunction. In addition, P300 amplitude was reduced in UHR+T. Reduced P300 amplitude was the best predictor of transition to psychosis. Earlier event-related potential components (N100 and P200) showed no deficits in our UHR group. Our results can be used to create a neurophysiological profile for subjects most at risk for transition to psychosis.
ID: 977511

THE EFFECT OF INTRAVENOUS SYNTHETIC THC ON RESTING STATE EEG BELOW AND ABOVE 20HZ

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Background: Electroencephalogram (EEG) oscillations have been shown to be altered in schizophrenia and it has been hypothesized that changes in the gamma band may be involved in the disease process. Δ9-tetrahydrocannabinol (THC) intoxication can trigger psychotic symptoms, and regular cannabis use is a risk factor for development of schizophrenia. Whilst the effects of THC on frequencies below 20 Hz have been previously reported, results for frequencies above 20 Hz have been confounded by artifacts caused by the contraction of the extra-ocular muscles during saccades and scalp and neck muscle tension. Methods: A randomized, double-blind, within subject, design was used with 14 healthy adults. THC intravenous (1.25 mg), or placebo, was administered prior to recording EEG during rest with 30 second periods of eyes open and eyes closed. EEG was recorded using a 64 channel electrode cap based on the 10–20 system. The amplitude was quantified using a Fast Fourier Transform with 2.048 second epochs for frequencies below 20 Hz and 256 ms above 20 Hz. To obtain the high beta and gamma values novel artifact reduction algorithms were used to reduce the gamma band noise arising from the power line noise, micro-saccades and tonic scalp and neck muscle activity. Results: THC produced significant reductions in the magnitude of high alpha ($P = .007$). A preliminary analysis also suggests that the low gamma band magnitude (30–45 Hz) may be increased by THC. Conclusion: Neural oscillations, which have been linked to changes in attention, consciousness and psychosis are altered by intravenous THC.
ID: 979096

GAMMA (40 HZ) AUDITORY STEADY-STATE RESPONSES IN SCHIZOPHRENIA AND MONKEY

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Background: Gamma (40 Hz) oscillations are disrupted in schizophrenia, but the question of how and where 40 Hz oscillations are generated is still being disputed. Methods: We assessed 40 Hz oscillations in schizophrenia patients, controls, and 1 monkey with clicks at a rate of 40 Hz to produce steady-state responses (SSR). All subjects were presented with 2 types of auditory stimuli: a standard stimulus at a rate of 40 Hz for 500 milliseconds (20 clicks), and an aperiodic (AP) click embedded in 40 Hz stimuli. Results: A change in the series of clicks during AP stim disrupted the 40 Hz evoked power and 40 Hz phase-locking factor (PLF) of gamma SSR in the EEG of controls and schizophrenia patients. A significant group x condition interaction ($F(1, 55) = 11.520$, $P = .001$) was identified for 40 Hz evoked power at frontal and central electrodes, suggesting that for the time-stationary results, AP stim drives the power of interneuron-pyramidal gamma networks of schizophrenia subjects ($N = 30$) to a different extent than controls ($N = 25$). Current source density analysis of intracranial recordings from A1 of Macaq revealed that AP stim led to an increase of sinks and sources in the supragranular layers (L2/3) of cortex, and a disruption in the periodicity of sinks in L4 associated with thalamic input. Supragranular activation due to AP stim resembled the pattern of laminar activation during the first 50–80 ms of standard gamma SSR, though sink/source activity to AP stim lasted for as long as 300 ms after the onset of AP stim. Conclusion: The results provide the first profile of gamma oscillatory activity in monkey and target the supragranular layers as a site of gamma abnormalities in schizophrenia.
ID: 980003

QUETIAPINE NORMALIZES MISMATCH NEGATIVITY IN INITIALLY ANTIPSYCHOTIC NAÏVE, FIRST-EPISODE PATIENTS WITH SCHIZOPHRENIA

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Background: Scientists and clinicians become increasingly aware that cognitive deficits form core features in schizophrenia. It has been suggested that treatment with atypical antipsychotics can ameliorate these deficits. However, studies have often been confounded by patients either being medicated or chronically ill, making it hard to differentiate between medication effects and course of the disease. Mismatch negativity amplitude represents one of the most basic forms of information processing, and is usually found to be decreased in schizophrenia. The present study investigated the influence of a six months treatment period with quetiapine (atypical antipsychotic) on MMN in a large group of antipsychotic naïve, first episode schizophrenia patients and age and gender matched healthy controls. Methods: Thirty-three antipsychotic naïve patients with first-episode schizophrenia and 33 age and gender matched healthy controls were tested both in

a standard MMN paradigm as well as in a selective attention paradigm. After a period of 6 months both patients and controls were retested. During that period the patients were treated with quetiapine while the controls received no treatment. Seventeen patients and controls completed the study. Both paradigms made use of 1000 Hz standards and 1200 Hz deviant stimuli, ie frequency deviants. Results: At baseline the patients showed significantly lower MMN amplitude compared to healthy controls, in both paradigms. At follow-up however, this difference had disappeared. In fact, the patients showed significantly larger MMN amplitudes at follow-up compared to baseline in the selective attention paradigm. Conclusion: The results indicate that reduced frequency-based MMN amplitude is present already at an early stage in the development of schizophrenia, in the absence of antipsychotic treatment. Furthermore, the results suggest that a 6 months treatment period with quetiapine normalizes this deficit. The results are consistent with the idea that a relatively long treatment period with atypical antipsychotics is able to normalize at least some of the basic information processing deficits in schizophrenia.
ID: 978334

GAMMA-BAND ASYNCHRONY ACROSS THE ILLNESS COURSE OF SCHIZOPHRENIA

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Background: Oscillations in the gamma-band (30–80 Hz) have been posited as a mechanism for cortical coordination by inducing synchronous neural firing. Disruptions in cortico-limbic GABAergic and glutamatergic cells that entrain the firing of target neurons contribute to a reduction in the synchronized neuronal activity that is likely related to perceptual and cognitive deficits in schizophrenia. Previous studies reported that patients with chronic schizophrenia, and individuals with a genetic liability (but without treatment-seeking clinical precursors) for schizophrenia express gamma-band asynchrony. Here, we asked if reductions in gamma-band synchronization found in chronic patients and their probands extend to patients in early phases of the illness, and whether these abnormalities are evident before psychosis onset in a clinically prodromal sample, especially in those who ultimately convert to psychosis. Methods: We recorded EEG activity during an auditory target detection task in 3 groups: schizophrenia patients early in their illness ($n = 42$), prodromal patients ($n = 55$), and healthy controls ($n = 88$). Time frequency analysis was done with a Morlet wavelet decomposition of single trial data to estimate inter-trial phase coherence (ITPC) of gamma activity time-locked to stimulus onset. To account for possible effects of normal brain maturation in the current sample (12–38 years), we assessed and removed the effects of normal aging from ITPC values prior to comparing the patient groups using Glesjer's estimate of the standard error of regression for a given age. Results: Reductions in ITPC in the gamma-band to target stimuli were found in fronto-central sites in early illness schizophrenia patients and in prodromal patients ($P < .02$). Additionally, prodrome subjects who later converted to psychosis ($n = 18$) showed a greater degree of gamma abnormality when compared to non-converters ($n = 37$) in response to target stimuli ($P = .05$). Conclusion: Putative auditory gamma-band asynchrony is evident in the early stages of schizophrenia, and even before psychosis onset. Moreover, prodromal patients who go on to convert to psychosis display exaggerated asynchrony of gamma band response compared to nonconverters. Thus, gamma-band asynchrony is evident across the illness course of schizophrenia. Asynchronous neuronal activity may represent an elemental deficit in the illness, and may be a window into the pathophysiology of schizophrenia.
ID: 978041

EVENT-RELATED POTENTIALS ELICITED USING AND AUDITORY ODDBALL PARADIGM IN ADOLESCENTS WITH SUB-CLINICAL PSYCHOTIC SYMPTOMS AND CONTROLS

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Background: van Os et al (2000) suggest that psychosis may exist as a continuous phenotype in nature. Recent research suggests that psychotic symptoms/psychotic-like experiences (PLEs) are often reported by a substantial proportion of the healthy general population (Kelleher & Cannon, 2010). The presence of psychotic symptoms/PLEs in adolescence has been identified as a potential risk marker for the development of schizophrenia in adulthood. Reduced amplitude of the P300 auditory event-related potential has been consistently reported in schizophrenics, their first-degree relative and persons with schizotypal personality and also in prodromal groups (Frangou et al, 1997; Bramon et al, 2005; Gassab et al, 2006; Özgürdal et al, 2008). The aim of the present study was to explore whether a decrease in P300 amplitude is present in a group of adolescents who reported PLEs compared to a group of control participants. Methods: Participants were recruited from 8 primary schools in north Co. Dublin. Participants were initially screened for psychotic symptoms in schools using a 7-item Adolescent Psychotic-Like Experience Screener (Kelleher et al, 2009). Further screening was carried out via clinical interview. 26 participants took part in the study (age range 11–13 years), 10 participants who reported PLEs (at-risk group; 7 male; mean age 11.6 years) and 16 controls (control group; 11 male; mean age 11.6 years). Behavioural and electroencephalographic (EEG) data (62 channels) were collected as participants completed an auditory oddball task. The task included 2 blocks. Each block contained 100 test trials in which participants made a button press response to infrequent target tones (20% of trials). Results: Grand average waveforms showed a common pattern of ERP components for both groups, including N1, P2 and P300 components. Subtraction waveforms were generated for target minus non-target stimuli, which revealed larger frontal amplitude for controls at approximately 270 ms post-stimulus. Larger amplitude for the at-risk group was observed frontally at approximately 500 ms. Conclusion: These differences may reflect qualitative differences in the way cases and controls execute the task on a cognitive level and may provide valuable insight into the usefulness of including groups who have reported PLEs in future research. These results are discussed in relation to previous studies using auditory oddball tasks with schizophrenic groups, groups considered genetically at-risk and prodromal group.
ID: 976180

DEFICITS IN THE SYNERGISTIC ENHANCEMENT OF AUTOMATIC SENSORY PROCESSING ON CONTROLLED PROCESSES IN SCHIZOPHRENIA

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Background: Previous studies employing ERP paradigms have reported deficits of information processing in schizophrenia across automatic processes including: (1) automatic change detection (MMN); (2) the orienting or covert shift in attention (P3a); (3) allocation of attention processes to task relevant target stimuli (P3b). Recently our group has begun to examine (4) the reorienting of attention (RON) back to the ongoing task. The goal of the current study was to employ novel "Attentional Component Enhancement" (ACE) oddball paradigm which was designed to separately measure

the contribution of (1) automatic processes, (2) controlled processes and most importantly (3) the synergistic enhancement of automatic sensory processing on subsequent attention dependent processes in schizophrenia patients and healthy matched controls. Methods: Schizophrenia Patients ($n = 34$) and Normal Comparison Subjects ($n = 41$) were tested with a novel ACE paradigm. Stimuli were 80 dB tones, with a 1 s SOA. 85% of the tones were (1000 Hz) 50 ms in duration (standard), 5% were (1000 Hz) 125 ms in duration (duration deviant), 5% were (1100 Hz) 50 ms in duration (pitch distracter) 5% were (1100 Hz) 125 ms in duration (pitch/duration deviant). Details of the physiologic and behavioral task parameters will be discussed. Results: Schizophrenia patients exhibited deficits in automatic and controlled processes as well in the extent to which automatic processes triggered and enhancement of subsequent controlled processes. ACE waveform ERP components indexing the enhancement (Normal controls) or the disruption (Schizophrenia patients) of automatic processes on attention dependent processes were correlated with downstream behavioral performance. Conclusion: The novel ACE wave implicated the peaks within the latency range of the MMN/P3a/RON response complex as the basis of the observed behavioral enhancement (Controls) and disruption (patients) and suggests the schizophrenia patients show substantial deficits in the info-processing cascades initiated at the level of automatic processes. This initial study is the first to date that directly tests the enhancing effects of automatic processes on subsequent controlled attention dependent processes in schizophrenia patients and that automatic processes may be separately and conjointly measured to parse the effect of automatic processes on controlled attention dependent processes both on a physiological and behavioral level. Supported by MH079777
ID: 979971

DO ADOLESCENTS WITH PSYCHOTIC SYMPTOMS SHOW EARLY INDICATORS OF SCHIZOPHRENIA?

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Background: Young adolescents with psychosis form a group of patients at high risk of developing schizophrenia. There is a great need to identify early indicators of schizophrenia in this population. The current project investigates whether a subgroup can be identified among adolescents with a first episode of psychotic disorder that show psychophysiological and/or neurocognitive deficits similar to what has previously been found in our study on first-episode, antipsychotic naïve schizophrenia patients. It will be determined if the presence of these deficits, with a special focus on deficits in prepulse inhibition of the startle reflex (PPI), can predict which patients will develop schizophrenia within a period of 5 years. Methods: Thirty-five children/adolescents aged 12–17 years, suffering a first episode of psychosis, and 35 age and gender matched healthy controls will be tested in the Copenhagen Psychophysiological Test battery (CPTB) in which, besides PPI, also eg P50 suppression, P300 amplitude, mismatch negativity (MMN) and processing negativity (PN) are assessed. Intelligence, working memory, attention, executive function, learning and memory, problem solving and reaction time are assessed in a battery of neurocognitive tests (eg WISC/WAIS, CANTAB, BACS, BRIEF). All subjects are interviewed with diagnostic schedules (Kiddie-Sads-PL, SCAN), and severity of symptoms in patients are rated (PANSS). After 3 months and 5 years, patients will be re-diagnosed in order to examine who have made the transition to schizophrenia. Results: We are currently recruiting the subjects for this project, and expect to present preliminary results at the ICOSR meeting. Conclusion: We expect to identify a subgroup among young patients who experience a first episode of psychotic disorder with similar psychophysiological and neurocognitive deficits as earlier found in antipsychotic naïve first-episode schizophrenia patients. We hypothesize that this subgroup are more prone to develop schizophrenia within a period of 5 years. In addition we expect the total first episode psychosis group to show intermediate levels of psychophysiological and neurocognitive function, between healthy controls and first-episode patients.
ID: 975777

ABNORMAL PHASE-AMPLITUDE CROSS FREQUENCY COUPLING DURING INFORMATION PROCESSING IN SCHIZOPHRENIA

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Background: Schizophrenia is associated with deficits including information processing, which may reflect a core abnormality of diminished recruitment of distributed neural networks. Accumulating evidence reveals that oscillations play an important role in the recruitment of distributed networks. In schizophrenia, reductions in event-related oscillations in low and high frequency ranges are observed. In animals and healthy control humans, interactions between oscillations at different frequencies such as the sinusoidal modulation of the recruitment of higher frequencies by the phase of low frequencies appears to play an important role. These observations suggest that impaired low frequency modulation of the recruitment of high frequencies contribute to the reduction in magnitude of event related oscillations in schizophrenia. This study investigates event related delta (1–4 Hz) phase modulation of theta (4–8 Hz) amplitude and theta phase modulation of gamma (30–80 Hz) amplitude. Methods: EEG data were recorded whilst 34 male schizophrenia patients (mean age = 25.22, SD = 5.46) and 34 male healthy subjects (mean age = 26.33, SD = 5.65) completed an auditory oddball task. Couplings between theta phase and gamma amplitude, and delta phase and theta amplitude were analysed in four time windows relative to stimulus onset; −600–−400 ms, 0–200 ms, 200–400 ms and 400–600 ms for both targets and non-targets. The modulation of amplitudes of higher frequencies by the phase of lower frequencies was approximately sinusoidal in many instances. The degree of sinusoidal modulation of higher frequency amplitude by lower frequency phase was quantified by assessing goodness of fit of a sinusoid to the relationship between phase and amplitude. The goodness of fit of these sinusoids were compared between groups. Results: Modulation of theta amplitude by delta phase during target trials in the 0–200 ms and 200–400 ms windows was significantly reduced in patients relative to controls (after correction for multiple comparisons). Differences in delta phase theta amplitude modulation during non-target trials, and theta phase gamma amplitude modulation did not survive correction for multiple comparisons. Conclusion: These results confirm the hypothesis that low frequency modulation of the amplitude of high frequency oscillations, in particular the modulation of theta amplitude by delta phase, is impaired in schizophrenia and might contribute to the deficits in information processing demonstrated by patients.
ID: 979275

THE TIMING OF HIGH-LEVEL AND LOW-LEVEL INFLUENCES DURING OBJECT PERCEPTION IN SCHIZOPHRENIA: USE OF MEG AND FMRI DATA TO EXAMINE THE BASIS OF PERCEPTUAL DEFICITS

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Background: Recent advances have allowed researchers to describe with high spatial and temporal resolution the neural underpinnings of visual anomalies in schizophrenia. This work has yielded evidence that interactions of high-level brain regions (eg, prefrontal cortex) with areas supporting more elemental visual functions may contribute to misperception of objects (eg, Sehatpour et al 2010). It appears that high-level brain regions exert early influence on percept formation that may mold object perception based on contextual factors (eg, the immediate environment or past experience). Synchronization of neural activity across separable brain regions is thought to reflect the influence of high-level top-down processes on object perception. At least one study has shown that increased synchronization between prefrontal cortex and occipital cortex occurs between 100 and 150 ms during object perception suggesting a mechanism supporting early high-level influences on object identification (Bar et al 2006). Nevertheless, neural abnormalities are also apparent over visual cortex as early as 100 ms after stimulus onset, and thus may provoke subsequent errors at higher levels of visual processing. Clarification of the timing of abnormal neural synchronization would help determine whether a unique low-level visual perceptual deficit in occipital cortex or a general high-level deficit, perhaps in prefrontal cortex, accounts for errant object perception in schizophrenia. Methods: Thirteen schizophrenia subjects and thirteen controls of similar age and gender composition completed a task requiring identification of target objects within a sequence of visually degraded stimuli. Magneto-encephalography (MEG) and functional magnetic resonance imaging (fMRI) data were gathered during the task to precisely characterize temporal and spatial aspects of the neural response. Results: Analysis of fMRI data revealed that perception of degraded targets activated lateral occipital cortex, inferior occipital cortex, and middle prefrontal cortex as compared to a perceptual noise condition. For degraded target objects schizophrenia patients exhibited diminished neural activation compared to controls in these cortical regions, but not when object contours were explicitly outlined. Conclusion: To reveal the timing of aberrant neural responses during object perception a new time-varying phase synchrony index (Aviyente et al, 2010) will be applied to MEG data for cortical sources identified through fMRI.
ID: 979291

SOURCE LOCALIZATION ANALYSES OF HIERARCHICAL EARLY INFORMATION PROCESSING DEFICITS IN A LARGE COHORT OF SCHIZOPHRENIA PATIENTS

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Background: Schizophrenia patients (SZ) have deficits in the processing and/or hierarchical organization of sensory and higher-order cognitive information processing. EEG measures of mismatch negativity (MMN), P3a and the reorienting negativity (RON) are event-related potential (ERP) measures of sensory discrimination, orienting of attention, and the reorienting of attention following stimulus changes. While previous studies have reported robust deficits in these ERP components in schizophrenia patients, whether these responses reflect a single-response complex vs. spatially and functionally dissociable neural responses is not well-understood. The aim of the present study was to examine the neural sources contributing to MMN, P3a, and RON in a large cohort of SZ and nonpsychiatric comparison subjects (NCS). Methods: 403 SZ and 192 NCS underwent EEG testing using a passive duration-deviant auditory oddball paradigm (1-kHz tones, 500 m/sec SOA; standard $P = .90$, 50-ms duration; deviant tones $P = .10$, 100-ms duration) while subjects watched a silent video. Standardized low-resolution brain electromagnetic tomography (sLORETA) was used to estimate sources of MMN, P3a, and RON, and, to perform voxel-by-voxel between-group comparisons. Results: SZ had robust deficits in MMN, P3a, and RON. These components were supported by neural sources broadly distributed across temporal, frontal, and parietal regions. Temporal and frontal generators were observed for MMN for both groups with reduced levels of activation of SZ. Compared to MMN, P3a was supported by relatively greater activation in frontal and parietal areas with lower levels of activation in temporal regions in both groups. ERP deficits in SZ corresponded to reduced activation frontal and parietal areas. In contrast to MMN and P3a, sources of RON were restricted to temporal regions in both groups with no differences in specific areas of activation despite substantial statistical power to detect small abnormalities. Conclusion: MMN, P3a, and RON are dissociable responses supported by complex and distributed neural networks. Abnormalities in the dynamic integration of sources rather than the sources themselves, account for the scalp-recorded ERP deficits in SZ. Future studies will examine the genomic and neural architecture supporting these distinct early information processing abnormalities as well as their relationships to higher-order cognitive and functional outcomes in SZ. Supported by MH079777.
ID: 982305

AUDITORY PROCESSING DEFICITS IN SCHIZOPHRENIA AND BIPOLAR DISORDER: DIAGNOSTIC SPECIFICITY, GENETIC CONTRIBUTION, AND BRAIN STRUCTURE CORRELATES

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Background: Early auditory processes as represented by the N1 and mismatch negativity (MMN) have been shown to be abnormal in schizophrenia, with the earlier N1 response being diminished in individuals with genetic liability for the disorder. Given recent evidence for early auditory deficits resulting in abnormalities in later high order auditory functions (eg, Leitman et al 2010) we sought to understand how biological relatives could exhibit deficient N1 responses but intact MMNs. Methods: In addition to schizophrenia patients, their biological relatives, and nonpsychiatric subjects, the study included bipolar patients and their biological relatives in order to test the specificity of early auditory processing abnormalities to the clinical syndrome of schizophrenia and genetic liability for the disorder. Electroencephalograms were gathered from subjects while they completed a dichotic listening task that required them direct their attention to infrequent frequency-deviant tones in one ear. Tones were also presented to the unattended ear. Results: The task allowed characterization of the N1 and MMN in attended and unattended ears, as well as high-level auditory responses such at the P300 component. Analyses revealed that schizophrenia patients exhibited deficits in both N1 and MMN components, biological relatives of schizophrenia patients showed only N1 decrements, while bipolar patients and their relatives failed to show decrements in either component. Thus, findings support early auditory processing deficits as being specific to schizophrenia. For a subset of nonpsychiatric subjects and schizophrenia patients with structural magnetic resonance imaging data, electrophysiological responses

will be tested for associations with the volume of temporal lobe structures thought to contain generators of the N1 and MMN Conclusion: Better characterization of early auditory processing abnormalities specific to schizophrenia may help elucidate aspects of the neural basis of schizophrenia and improve understanding of pathology in the frontal lobe.
ID: 980088

EVENT-RELATED POTENTIAL FACIAL PROCESSING DEFICITS IN SCHIZOPHRENIA

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Background: While facial affect processing has been extensively studied in schizophrenia (SZ) patients, it is not known exactly what stage of processing of faces is impaired. We explored facial affect and basic face processing in SZ using event-related potentials (ERPs) to explore whether SZ patients exhibit deficits in the structural encoding of faces or in the decoding of affective or gender information in faces. Methods: Data from 25 SZ patients and 18 healthy controls (HCS) were analyzed. Participants had their EEG recorded while performing two separate tasks: a gender identification task and a facial affect identification task. We examined two separate ERP waveforms that index separate stages of face processing: (1) the N170, to examine structural encoding of faces (measured in bilateral parieto-occipital regions); and (2) the N250, to examine activity associated with decoding of emotional or gender-identifying information in faces (measured in fronto-central regions). Both amplitude and latency were examined. Results: N170 amplitude and latency were comparable between SZ and HCS on both tasks, indicating that the structural encoding of faces is intact in schizophrenia patients. No N250 amplitude differences were seen between groups. However, N250 latency was significantly prolonged in SZ compared to HCS for both tasks (*P*'s $<.001$), indicating that schizophrenia patients have neurophysiological delays in decoding of facial information. Conclusion: These results show that schizophrenia is associated with neurophysiological delays in decoding of facial affect and gender information, whereas their structural encoding of faces is intact. While some studies find that the structural encoding (ie, N170) of faces is impaired in schizophrenia, this is the second, independent sample of SZ patients from our laboratory showing that the N170 is normal, but that the decoding of facial information for judgments (ie, N250) is impaired. These results imply that SZ patients may require longer face presentation time, compared to healthy controls, to effectively decode both basic (ie, gender) and complex (ie, affect) information contained in faces.
ID: 976722

EEG NETWORK ANALYSIS IN FIRST-EPISODE SCHIZOPHRENIA: INCREASED RANDOMNESS OF NETWORK ARCHITECTURE

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Background: Several studies have addressed the alterations of the architecture of brain networks using connectivity analyses of EEG or MRI data. Recently, such work has focused on resting state analyses employing various methods showing altered network architectures of functional brain networks in patients with schizophrenia. For larger scale studies, EEG has the advantage of easier availability and reduced costs as compared to MRI investigations. We aimed at combining information from MRI and EEG in order to investigate whether MRI-informed EEG-analyses would result in useful connectivity results in patients with schizophrenia. Methods: Controlled study assessing alterations of connectivity parameters in first-episode schizophrenia patients ($n = 73$) compared to healthy control persons ($n = 87$) using LORETA-based analyses of resting-state EEG signals based on regions of interest as defined by a metareview of resting-state MRI data in healthy persons (Toro et al, Cerebral Cortex 2008; 18:2553). Results: We used a total of 28 regions of interest comprising fronto-parietal and cingulo-parietal networks to guide LORETA-based connectivity analyses of resting-state EEG data. Network analyses showed an decreased internal strength of network architectures in first-episode schizophrenia patients within both networks in the EEG delta band (.5–4 Hz) and gamma band (35–45 Hz) and increased interregional connectivity in both bands. Conclusion: This study shows that grounding EEG-analyses in MRI-defined regions of interest in resting-state network analyses of EEG data from patients with schizophrenia is feasible and results in network analyses indicating an increased degree of randomness in first-episode schizophrenia patients. This corroborates other previous connectivity analyses and modularity analyses in resting-state studies of patients with schizophrenia using MRI or EEG. This novel methodological approach of combining LORETA-based EEG analyses with MRI-defined regions of interest provides a new way of performing network studies in schizophrenia patients employing easy to obtain EEG data. Further steps will need to address the simultaneous recording of both MRI and EEG data in order to confirm that both approaches yield similar results.
ID: 978080

5. Eye Movement Physiology

THE RELATIONSHIP BETWEEN TWO ENDOPHENOTYPES OF PSYCHOSIS IN VOLUNTEERS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER AND THEIR RELATIVES

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Background: Deficits in smooth pursuit eye movements are an established endophenotype for schizophrenia (SZ) and are being investigated as a potential biomarker for psychotic bipolar disorder (BDP). While the molecular determinant of the physiological deficit is still unclear, considerable research has shown deficits in the predictive mechanism of eye movements in SZ using target masking techniques, as well as with a more recent novel prediction eye movement task. The questions of whether this deficit is related to working memory alterations in SZ and extends to other psychotic disorders like BDP were a focus of this investigation. Methods: Volunteers with schizophrenia (SZ, $n = 38$), bipolar I disorder with psychotic features (BDP, $n = 31$), and healthy controls (HC, $n = 17$) performed a novel eye movement task to assess the predictive mechanism of smooth pursuit. Subjects also completed a battery of neuropsychological tasks that included measures of working memory. To examine the potential effects of psychiatric medication use on eye movement performance, a group of medication-free volunteers with psychosis also completed the eye tracking tasks ($n = 14$). Additionally, data from a sample of first degree family members of volunteers with schizophrenia (SZF, $n = 20$) and family members of volunteers with bipolar disorder (BPF, $n = 13$) will be presented. Results: Individuals with SZ and BDP performed similarly on both neuropsychological and eye tracking tasks. Both groups evidenced reduced predictive pursuit velocity and worse performance on the Wechsler Spatial Span task compared with healthy controls. Further, a small but significant correlation ($r = .27$, $P = .03$) between predictive pursuit gain and working memory performance on Spatial Span was obtained, without statistically significant correlations in other cognitive domains. Conclusion: Individuals with SZ and BDP showed similar deficits on the predictive pursuit eye movement task, suggesting that this alteration could be a characteristic of the psychosis domain. The a priori prediction that the predictive pursuit task is associated with working memory mechanisms was supported in part by its significant and selective correlation with a measure of working memory.
ID: 976618

REFINING THE SMOOTH PURSUIT ENDOPHENOTYPE: LONG RANGE FRONTAL/POSTERIOR PHASE SYNCHRONIZATION DURING EYE TRACKING

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Background: Smooth pursuit eye movement (SPEM) abnormality, arguably the first biological marker identified in schizophrenia, is a well recognized and valid schizophrenia/psychosis endophenotype. However, as traditionally measured, SPEM remains relatively a complex phenotype. Its successful application in genetic studies can be facilitated by refining the measurement so that it accurately reflects specific underlying physiological impairment. The SPEM endophenotype is served by a widely distributed neuronal system including the frontal eye fields (FEF), the mediotemporal (MT), and the medial superior temporal (MST) regions. Both motion perception and SPEM maintenance are abnormal in schizophrenia, and this could be a consequence of poor communication (or functional connectivity) between FEF and MT/MST regions. Methods: We examined phase synchronization in oscillatory activity within the EEG between frontal and posterior electrodes as a measure of functional connectivity while subjects were performing a remembered pursuit task. In this task, the same target velocity was presented in quick sequence within a trial. Participants were schizophrenia probands ($n = 21$), their relatives ($n = 25$) and healthy control ($n = 18$) subjects. Results: There was a significant improvement in the smooth pursuit response on repeated presentation, more so in the healthy subjects. Frontal/posterior phase synchronization increased in control subjects on repeated target presentation particularly in beta frequency range, but not in patients suggesting abnormal functional connectivity in schizophrenia. Correlations between the functional connectivity and eye velocity measures suggested that this relationship was inhibitory in the presence of maladaptive anticipatory SPEM (ie, before the target motion onset) and facilitatory after the onset of target motion. Higher synchronization predicted higher predictive pursuit and higher ratings of enduring psychosis and hallucinations. Data are being analyzed in the relative group. Conclusion: These findings suggest that poor communication between frontal (FEF) and posterior cortical (MT/MST) regions may underlie abnormal SPEM in schizophrenia. This refined measure of SPEM abnormality may better index the physiological deficit marking schizophrenia liability.
ID: 978368

6. Epidemiology

CAN SNP-VARIATION ACROSS THE WHOLE-GENOME AND ACROSS CANDIDATE GENES EXPLAIN THE EXCESS SCHIZOPHRENIA RISK IN OFFSPRING OF PARENTS WITH A SEVERE PSYCHIATRIC DISORDER?

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Background: Epidemiological family studies confirm that schizophrenia is a genetic disorder, and modern genome-wide association technologies are widely used to identify coding regions. To our knowledge, however, no study has combined the two approaches. The goal is to examine whether a single-nucleotide polymorphism(SNP), joint SNP-variation across the whole genome and across candidate genes can partly explain the excess schizophrenia risk in offspring of parents with a psychotic, bipolar affective or other psychiatric disorder. Methods: Design: Singletons with schizophrenia and gender-birthday matched controls. Setting: Danish national health registers and neonatal biobank. Participants: 739 cases and 800 controls. Parents and siblings. Main Outcome Measure: Schizophrenia rate ratios associated with SNP-based factors and familial psychopathology. Whole-genome amplified DNA from neonatal blood (547 071 analysable SNPs). Principal component analyses were used to capture whole-genome structure and variation in candidate genes (SzGene database). Results: Offspring schizophrenia risk was elevated in those whose mother, father or siblings had been diagnosed with schizophrenia or related psychosis, bipolar affective disorder or any other psychiatric disorder. The rate ratio was 9.31 (3.85; 22.44) in offspring whose 1st degree relative was diagnosed with schizophrenia. This rate ranged between 8.31 and 11.34 when adjusted for each SNP and shrank to 8.23 (3.13; 21.64) when adjusted for 25% of the SNP-variation in candidate genes. The percentage of the excess risk associated with familial schizophrenia mediated through genome-wide SNP variation ranged between −6.1% (−17.0%; 2.6%) and 4.1% (−3.9%; 15.2%). Analogous results were seen for each parent and for familial histories of bipolar affective and other psychiatric diagnoses. Conclusion: The excess risk of schizophrenia in offspring of parents who suffer from a psychotic, bipolar affective or other psychiatric disorder cannot be explained by variation across 547 071 SNPs.
ID: 976456

TAXOMETRIC EXPLORATIONS OF THE LATENT LEVEL ASSOCIATION BETWEEN ALCOHOL/DRUG USE PROBLEMS AND PSYCHOSIS

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Background: The reason for the high rates of co-occurrence of alcohol/drug use problems in psychotic disorders has been the subject of debate across explanatory models of dual-diagnosis (Gregg, Barrowclough, & Haddock, 2007). Some models suggest a meaningful relationship whereas others attribute co-occurrence to artifactual factors such as sampling bias or overlapping criteria. The distinction between latent and manifest levels of analysis is crucial to understanding the nature of diagnostic co-occurrence and distinguishing between types of co-occurrence (Meehl, 2001). The current study examines the latent structure of psychosis and alcohol/drug use problems and their latent level association in an epidemiological sample to test the viability of meaningful vs artifactual models of co-occurrence. Methods: A subset of the Collaborative Psychiatric Epidemiological Surveys sample (n = 1 1994) for whom data on alcohol and drug use problems and psychosis were available was included in the study. The MAMBAC (Mean Above Minus Below A Cut; Meehl & Yonce, 1994), MAXEIG (MAXimum EIGenvalue; Waller & Meehl, 1998), and L-Mode (Latent Mode Factor Analysis; Waller & Meehl, 1998) taxometric procedures were used to analyze indicators created from survey items. Indicators for psychosis were Hallucinations, Mind Control, Persecution, and Communication Attempts. Alcohol Use indicators were Dependence, Consequences, Frequency, and Duration. Drug use indicators were Dependence, Use, Consequences, Frequency, and Duration. Results: Taxometric analyses supported a taxonic structure for alcohol and drug use problems via visual inspection of taxometric plots and CCFI indices. For alcohol use problems, CCFIs ranged from .661 to .894. For drug use problems, CCFIs ranged from .621 to .755. Psychotic symptoms, however, demonstrated a dimensional structure. The graphical models were more consistent with a dimensional model. The CCFIs ranged from .257 to .434. The alcohol and drug use taxa were associated with an earlier age of onset of symptoms, family history of alchol/drug use problems, male sex, and treatment seeking. They also demonstrated significant latent level associations with the psychosis dimension, suggesting an etiologically meaningful co-occurrence between alcohol and drug use and psychotic symptoms. Conclusion: The co-occurrence of psychosis and alcohol/drug use problems reflects an etiological type of comorbidity rather than an artifact of chance co-occurrence, sampling bias, or other artifactual factors.
ID: 979362

STRATEGIES FOR EFFECTIVE RECRUITMENT OF INDIVIDUALS AT RISK FOR DEVELOPING PSYCHOSIS

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Background: Early identification of individuals in the prodrome and first episode of psychosis can lead to preemptive intervention and perhaps prevention of the significant functional decline that often accompanies a first psychotic episode. The development of an extensive community outreach and education campaign is essential for programs that aim to identify and treat individuals in the early stages of psychotic illness. Methods: Over the last decade, the Cognitive Assessment and Risk Evaluation (CARE) Program at the University of California San Diego has implemented a recruitment strategy to increase public awareness about early psychosis and establish community collaboration in San Diego County. Educational materials were distributed to community partners, local media and via the internet. The number and pattern of referrals were then analyzed to inform ongoing recruitment efforts. Results: Overall, 799 referrals were telephone screened. Of 313 who completed diagnostic interviews, 223 were enrolled including 122 in an ''At Risk'' state and 101 in an Early Psychotic episode. The majority who met inclusion criteria were referred by outpatient mental health practitioners (46.6%), while 16.1% came from inpatient facilities and 16.1% from internet sites. Other important referral sources were the public schools, community colleges and the National Alliance for the Mentally Ill. Conclusion: The successful recruitment efforts of the CARE program reflect not only the extensive educational outreach but the emphasis on enhancing professional relationships with community partners. The internet became an important source of information and

referrals and will likely be an essential component of any public education campaign.

Ethnicity of CARE Program Participants

	Number	CARE Program Percent	San Diego County Percent
Caucasian	115	51.6	50.9
Hispanic/Latino	45	20.2	30.9
Asian	14	6.3	10.3
African American	29	13.0	5.5
Other	13	5.8	3.1
American Indian/Alaska Native	5	2.2	1.0
Native Hawaiian/ Pacific Islander	1	.4	.5
Unknown	1	.4	n/a
Total	223	100.0	n/a

ID: 974938

A DRUG EPIDEMIOLOGIST'S PERSPECTIVE ON CANNABIS-PSYCHOSIS EVIDENCE

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Background: No longer an ''illegal'' drug in many parts of the world, cannabis ranks #1 in prevalence of use among the ''internationally regulated drugs''. Nevertheless, for many users, cannabis smoking remains illegal and carries some degree of social stigma. Seeking to ''get high'' from cannabis, these users must be willing to break the law, even where there is no social stigma. These facts create special challenges in the standard clinical and epidemiological research designs we ordinarily might use in post-marketing surveillance for adverse drug effects when there is ''confounding by indication'' or ''barriers'' that limit access to the drug. We must address these challenges if we seek to draw firm causal inferences about whether cannabis smoking might cause psychosis among individuals who otherwise would not develop a psychosis. Methods: Representative evidence on the cannabis-psychosis association is presented, with emphasis on epidemiological evidence, and with a special focus on whether and how the research teams have attempted to address the above-mentioned challenges, including ''confounding by indication'' and the illegal nature of cannabis smoking. Results: The results of this review help to clarify some important directions for future research on the cannabis-psychosis association, including: (1) research in parts of the world where cannabis use does not carry the stigma associated with an illegal behavior and where there is a strong tradition of schizophrenia research (eg, parts of South Asia), (2) use of the epidemiological case-crossover design with ''subject-as-own-control'' features to address uncontrolled confounding, (3) long term follow-up of large samples in randomized intervention trials where the interventions sought to prevent tobacco and cannabis smoking, and (4) ''cessation'' research designs of the type used to clarify that tobacco smoking-associated morbidity and mortality is reduced in the years after tobacco smokers have stopped smoking. Conclusion: Standard clinical and epidemiological research designs are not likely to produce definitive evidence about whether cannabis smoking accounts for psychosis among individuals who otherwise would not develop psychosis. If our goal is a firm causal inference about the observed cannabis-psychosis association, future research on this topic must face challenges associated with ''confounding by indication'' and with the illegal and sometimes stigmatized nature of cannabis use in society.

ID: 978660

PSYCHOTIC-LIKE EXPERIENCES IN GENERAL POPULATION: PREVALENCE AND CORRELATES IN AN IRANIAN URBAN AREA

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Background: Given the need for international multisite collaborations on attenuated psychotic symptoms in community[1], we decided to determine the prevalence of these symptoms in an urban general population in Iran and the associations of them. Methods: A total of 2158 subjects residing in Southern Tehran (capital of Iran) were interviewed by psychoticism and paranoia dimensions in Symptom Check List Revised version (SCL90-R) to assess prevalence and severity of psychotic like experiences (PLEs). Other dimensions in SCL90-R were used to examine the severity of non-psychotic symptoms. Paykel's Interview for Recent Life events was employed to assess stressful life events. Results: The prevalence rates of PLEs were in the range of 7.4%–50.3% when the cut-off of ''moderately'' distressful symptoms was used in SCL90-R. Severity of PLEs were higher in those with younger age, female gender, divorced or single marital status, unemployment, lower level of income, higher education, more stressful life events, and more severe non-psychotic symptoms. Multiple regression analysis confirmed the associations just for: (1)Non-psychotic symptoms and severity of both dimensions of psychosis ($P < .01$ for all correlations), (2)Stressful life events and psychoticism ($P < .05$), (3) Female gender and paranoid ideas ($P < .01$). Conclusion: In an under development setting, we found relatively high prevalence rates of PLEs[2]. Urban dwelling[3] beside some sociocultural factors could have contributed to the high prevalence. For example, one of the most commonly observed symptom in psychoticism dimension was belief in punishment for sins that is a religious belief and may have nothing to do with PLEs. The before mentioned associations of PLEs in western studies were proved for non-psychotic symptoms, and stressful life events[4] (regardless of the exact nature of these associations, due to our study being cross sectional), but for poor marital status, unemployment, lower income and lower age[3,5] they were rejected through secondary analysis. Regarding gender, the results for paranoid beliefs in our study was contrary to some previous research[4], with more paranoid ideas observed in females. This observation needs further replication in other studies.

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ID: 946369

VITAMIN D IN ADULTS WITH SCHIZOPHRENIA: DOES IT MATTER? A STATE HOSPITAL STUDY

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Background: Low vitamin D levels in the general population are associated with increased mortality, diabetes, higher body mass index (BMI), smoking, Parkinsonism, falls, incontinence, perhaps depression and poor cognitive functioning, all of which are features of the patients in the authors' hospital. Deficient vitamin D perinatally is a risk factor for schizophrenia and in adult rats it increases dopamine in the cortex and hypothalamus. Low vitamin D has been reported in severely mentally ill patients but there is no evidence yet of whether it affects their symptoms or outcome. This State Hospital survey examines the extent of low vitamin D and whether it is associated with poor health, psychiatric symptoms, outcome or movement disorders. Methods: All patients in the hospital are having their Vitamin D level measured. This is being correlated with demographics, clinical measures (including the monthly BPRS) and movement disorders. An open label 3 month intervention study of those with low vitamin D has started. Results: As of September 2010 143 subjects have been included in the survey, 104 with vitamin D levels. The mean level was 23.8 ng/mL (SD 14.7). 33 had a normal vitamin D level: 30–100 ng/ml. 20 had insufficient levels (20–29.9 ng/mL), 43 had deficient levels (<20 ng/ml) and eight were below 7 ng/ml. There were significant correlations of vitamin D level with prescription of vitamin D, age and years of illness (only the elderly were routinely prescribed vitamin D), race, BPRS activation, CGI, tardive dyskinesia, and negative correlations with GAF and HBA1C. There was a trend towards a correlation with BPRS total, months in hospital and negatively with diabetes. There was no correlation with skin color, age of onset, sex, BPRS positive, negative or depression/anxiety, BMI, cholesterol, triglycerides, calcium, phosphorous, uric acid, blood pressure, smoking status, Parkinsonism, akathisia, falls or psychiatric diagnosis. 12 subjects have entered the intervention study, 5 completed, with a slight improvement in the PANSS but this may be a time effect. Conclusion: There are hints that Vitamin D may matter for diabetes but the correlations with psychiatric measures are hard to explain. The study is half way through. The larger sample may show whether or not Vitamin D matters in adults with schizophrenia.
ID: 975845

RISK FACTORS OF AUDITORY HALLUCINATIONS IN CHILDHOOD: TRAUMA, ADVERSITY AND THE FORMATION OF PSYCHOTIC-LIKE IDEATION

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Background: In a baseline study among 7–8 year old children, auditory vocal hallucinations (AVH) in general had limited functional impact. However, transitory developmental expression of such psychotic symptoms may become more persistent (and clinically relevant), depending on the degree of exposure to environmental risk factors. Aim of this study, was to examine associations of (severity of) AVH with social adversity (traumatic experiences and stressful events) and the formation of delusional ideation in the five-year follow-up of a case-control sample. Methods: In total 337 children (mean age 13.1 years) were reassessed on AVH after a mean follow-up period of 5.1 years. Also delusions, traumatic experiences and stressful life events were assessed. From these children, 40 continued to hear voices (24%, persistent group), 15 had heard voices for the first time (9%, incident group), 130 children no longer reported voices in the past five years (remitted group) and 152 never reported AVH (referent group). To examine the impact of TE and SE on the occurrence of psychotic-like symptoms (PLS), four PLS groups were defined: (i) children with AVH only, (ii) children with delusions only, (iii) children with both AVH and delusions, and (iv) children without symptoms (the referent PLS group). Results: Measures of early social adversity predicted greater severity of AVH at follow-up, and were strongly associated with both incident and persistent AVH. Incident and persistent (severe) AVH were associated with more delusional ideation and more hallucinations in other modalities. Rates of exposure to trauma and stressful life events exposure were significantly higher in children with both AVH and delusions than in the groups with either AVH or delusions in isolation. Conclusion: Although hearing voices in 7–8 year olds is in most cases benign, experience of social adversity can predict persistence and onset of new AVH closer to puberty. Given evidence for the association with delusion formation, they do pose a significant clinical risk.
ID: 978308

CAN AUTOIMMUNE DISEASES COMBINED WITH THE EXPOSURES TO SEVERE INFECTIONS INCREASE THE RISK OF SCHIZOPHRENIA?

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Background: Autoimmune diseases have in previous research been associated with an increased risk of schizophrenia which is hypothesized to be induced by brain-reactive antibodies produced by the immune system. The blood-brain-barrier (BBB) normally protects the brain against agents in the blood, but increased permeability has been observed during periods with infections and inflammation, and when the protective BBB is compromised, an influx of brain-reactive antibodies or other immune components into the brain might occur. Therefore we investigate if autoimmune diseases combined with the exposures of severe infections can increase the risk of schizophrenia in the individual. Methods: We linked nationwide population-based registers including the Danish Psychiatric Central Register and the National Hospital Register. Data were analyzed as a cohort study using survival analysis techniques. We used incidence rate ratios (IRRs) and accompanying 95% confidence intervals (CIs) as measures of relative risk. Results: If a person only had an autoimmune disease the IRR of schizophrenia was increased by 1.30 (95% CI, 1.19–1.42) and if the person only had an infection the IRR of schizophrenia was increased by 1.59 (95% CI, 1.56–1.63). If the person had both an autoimmune disease and an infection, the IRR of schizophrenia was increased by 2.25 (95% CI, 2.05–2.46). When the person both had an autoimmune disease and three or more infections, the IRR of schizophrenia was increased by 3.42 (95% CI, 2.94–3.95). The risk of schizophrenia increased the closer the infections were to the schizophrenia diagnosis and the results remained significant after adjusting for substance use disorders. Conclusion: Autoimmune diseases and each severe infection are additive risk factors for the development of schizophrenia. The results are based on infections of any kind severe enough to have been treated at a hospital. The increased risk could partly be caused by increased BBB permeability with influx of brain-reactive antibodies or other immune components. Following up on this, results will also be presented from a population-based screening study on autoantibodies and the risk of psychiatric disorders.
ID: 976123

ASSOCIATION OF MATERNAL GENITAL AND REPRODUCTIVE INFECTIONS WITH VERBAL MEMORY AND MOTOR DEFICITS IN ADULT SCHIZOPHRENIA

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Background: Maternal exposure to genital and reproductive infections has been associated with schizophrenia in previous studies. Impairments in several neuropsychological functions, including verbal memory, working memory, executive function, and fine-motor coordination occur prominently in patients with schizophrenia. The etiologies of these deficits, however, remain largely unknown. We aimed to assess whether prospectively documented maternal exposure to genital/reproductive infections was related to these neuropsychological deficits in offspring with schizophrenia and other schizophrenia spectrum disorders. Methods: The cases were derived from a population-based birth cohort, the Child Health and Development Study in northern California; all cohort members belonged to a prepaid health plan. Cases ($N = 26$) exposed and unexposed to maternal genital-reproductive infection based on assays of archived prenatal sera for HSV2, and prospectively collected abstracted records on these infections, were assessed for verbal memory, working memory, executive function, and fine-motor coordination with a comprehensive neuropsychological battery. Results: Compared to unexposed cases, patients exposed to maternal genital/reproductive infection performed more poorly on verbal memory ($P = .007$), fine-motor coordination ($P = .02$), and working memory ($P = .051$). Stratification by race revealed associations between maternal G/R infection and verbal memory and fine-motor coordination for case offspring of African-American mothers, but not for case offspring of White mothers. Significant infection-by-race interactions were also observed. Conclusion: Although independent replications are warranted, maternal G/R infections may be responsible at least in part for verbal memory and motor function deficits in African-American patients with schizophrenia.
ID: 978773

MATERNAL INFLUENZA AND OTHER RESPIRATORY INFECTIONS: SPECIFICITY TO SCHIZOPHRENIA

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Background: Accumulating evidence from epidemiologic studies suggests that maternal respiratory infections, including influenza, are involved in the etiology of schizophrenia. To our knowledge, however, no studies have utilized prospective data from individual pregnancies to determine whether these infections increase the risk of bipolar disorder among offspring. Methods: In a follow-up of the Child Health and Development Study (CHDS), a large population-based birth cohort, we investigated the relationship between prospectively documented maternal exposure to respiratory infections and risk of bipolar disorder. Cases with bipolar disorder were identified by registry linkages between CHDS and Kaiser Permanente Medical Plan (KPMCP) data on bipolar disorder diagnoses and use of medications to treat bipolar disorder. Potential cases were interviewed with the SCID for DSM-IV-TR and consensus diagnoses were made by three psychiatrists; 60 cases were diagnosed and were compared to 8919 non-cases. Prospectively collected data on maternal respiratory infections from the CHDS database were utilized. Results: Maternal influenza infection during pregnancy was associated with a greater than fivefold increased risk of bipolar disorder among offspring (RR = 5.24, 95% CI = 1.87–14.67, $P < .01$). Maternal respiratory infection during the periconceptional period was related to a greater than twofold increased risk of bipolar disorder (RR = 2.69, 95% CI = 1.32–5.48, $P = .01$). The associations were not confounded by maternal age, race, education, smoking, and birth weight. Conclusion: These findings suggest that maternal influenza and other respiratory infections may not be specific to schizophrenia among major psychiatric disorders. However, there appear to be differences between schizophrenia and bipolar disorder with regard to the period of gestational vulnerability to maternal respiratory infections. These findings may have implications for preventive approaches for schizophrenia and bipolar disorder, and may further elucidate developmental pathogenic mechanisms that are shared and non-shared between these two disorders.
ID: 977153

ASSOCIATION OF MATERNAL GENITAL AND REPRODUCTIVE INFECTIONS WITH VERBAL MEMORY AND MOTOR DEFICITS IN ADULT SCHIZOPHRENIA

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Background: Maternal exposure to genital and reproductive infections has been associated with schizophrenia in previous studies. Impairments in several neuropsychological functions, including verbal memory, working memory, executive function, and fine-motor coordination occur prominently in patients with schizophrenia. The etiologies of these deficits, however, remain largely unknown. We aimed to assess whether prospectively documented maternal exposure to genital/reproductive infections was related to these neuropsychological deficits in offspring with schizophrenia and other schizophrenia spectrum disorders. Methods: The cases were derived from a population-based birth cohort, the Child Health and Development Study in northern California; all cohort members belonged to a prepaid health plan. Cases ($N = 26$) exposed and unexposed to maternal genital-reproductive infection based on assays of archived prenatal sera for HSV2, and prospectively collected abstracted records on these infections, were assessed for verbal memory, working memory, executive function, and fine-motor coordination with a comprehensive neuropsychological battery. Results: Compared to unexposed cases, patients exposed to maternal genital/reproductive infection performed more poorly on verbal memory ($P = .007$), fine-motor coordination ($P = .02$), and working memory ($P = .051$). Stratification by race revealed associations between maternal G/R infection and verbal memory and fine-motor coordination for case offspring of African-American mothers, but not for case offspring of White mothers. Significant infection-by-race interactions were also observed. Conclusion: Although independent replications are warranted, maternal G/R infections may be responsible at least in part for verbal memory and motor function deficits in African-American patients with schizophrenia.
ID: 978773

MATERNAL ANEMIA AS A RISK FACTOR FOR SCHIZOPHRENIA: A POPULATION-BASED, RECORD-LINKAGE STUDY AND META-ANALYSIS

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Background: Recent work has pointed to the importance of maternal anemia as a risk factor for schizophrenia in the offspring. We sought to replicate this finding in a large population based register linkage study in Finland. Methods: The study population comprised all individuals born in Helsinki, Finland between 1951 and 1960. Case ascertainment was from three national health care registers: 928 cases were identified. Controls were taken as the next child born in the same year listed in alphabetical order after each case in the child health clinic archives. Obstetric records were obtained for 636 individuals with schizophrenia and 203 controls. Hemoglobin during the last trimester of pregnancy was recorded on the birth records and categorized as normal, moderate or severe anemia according to WHO guidelines. Results: Odds ratios and 95% confidence intervals were calculated for schizophrenia in later life in relation to maternal anemia category (moderate or severe vs no anemia: OR 1.7 (95% CI: 1.2–2.5); P = .006). Both moderate anemia (OR 1.6 (95% CI: 1.1–2.3) P = .02) and severe anemia (OR 2.9 (95% CI: 1.3–6.6) P = .002) were associated with an increased risk of later schizophrenia in a linear fashion (test for trend z = 3.2; P = .002) and persisted following adjustment for socioeconomic status. When hemoglobin was analysed as a continuous measure, increasing concentrations of hemoglobin were associated with a decreased risk of schizophrenia (OR = .8 (95% CI: .7–.9) P = .02). The other obstetric variable significantly associated with risk for later schizophrenia in this sample was ponderal index (kg/m^3). Babies in the lowest quartile of ponderal index were at two-fold increased risk of later schizophrenia (OR 2.2 (95% CI: 1.4–3.7) P = .001). This association persisted following adjustment for socioeconomic group and prematurity. Both anemia and low ponderal index remained significant when adjusted for each other in a regression model indicating independent effects. We pooled our results with those of 6 other studies examining anemia as a risk factor for schizophrenia. The pooled odds ratio from 7 studies was 1.7 (95% CI: 1.3–2.1) with no significant heterogeneity (I^2 = 33%). Conclusion: These findings add to the evidence that maternal anemia is a robust risk factor for schizophrenia and operates in an independent pathway from fetal growth retardation. Neuroscientific investigation into the role of iron in brain development could provide clues to etiological mechanisms in schizophrenia.
ID: 978264

THE PREVALENCE OF PSYCHOSIS IN EPILEPSY: A SYSTEMATIC REVIEW

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Background: Epilepsy has long been considered to be a risk factor for psychosis. However there is a lack of consistency in findings across studies on the effect size of the risk. This reflects methodological differences in studies and changing diagnostic classifications within neurology and psychiatry. Estimates of prevalence rates of psychosis vary from 3.8% to 35.7% of patients with epilepsy. To date, no systematic review on the prevalence of psychosis in epilepsy has been carried out. Methods: We systematically reviewed all the published literature pertaining to prevalence rates of psychosis in epilepsy using electronic databases PUBMED, OVIDMEDLINE, psycINFO and Embase from their inception until July 2010 with the following search terms: prevalence, incidence, rate, rates, psychosis, schizophrenia, schizophreniform illness, epilepsy, seizures, temporal lobe epilepsy. Data was analysed using SPSS and STATA. Results: The literature search and search of reference lists yielded 215 papers. Of these, 58 (27%) had data relevant to the review and 157 were excluded following a more detailed assessment. The pooled estimate of prevalence of psychosis in epilepsy was found to be 5.6% (95% CI: 4.8–6.4). There was a high level of heterogeneity. The prevalence of psychosis in temporal lobe epilepsy was 7% (95% CI: 4.9–9.1). The prevalence of schizophrenia in epilepsy was 1.3% (95% CI: .8–1.8). The prevalence rate of interictal psychosis in epilepsy was 5.2% (95% CI: 3.3–7.2). The prevalence of postictal psychosis in epilepsy was 2% (95% CI: 1.2–2.8). Conclusion: Our systematic review found that approximately one in twenty patients with epilepsy have a co-morbid psychotic illness. The prevalence rate is higher in temporal lobe epilepsy. Although suggestive of a causal relationship, temporal information is lacking in these studies and there is a need for larger studies with control groups in order to provide risk estimates. Nevertheless, we suggest that epilepsy should be considered a risk factor for psychosis. Further investigation of this association could give clues to the etiology of psychosis. Prompt recognition and effective treatment of psychosis is important among patients with epilepsy to reduce the burden of morbidity and improve quality of life.
ID: 978311

EVIDENCE FOR A SHARED VULNERABILITY TO EPILEPSY AND SCHIZOPHRENIA

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Background: There is emerging evidence of an etiological overlap between a range of neurodevelopmental disorders including schizophrenia, epilepsy and autism. Here we investigate shared genetic vulnerability to schizophrenia and epilepsy in a family-based study. Methods: The study population consisted of parents and their children born in Helsinki between 1947 and 1990. The Finnish Hospital Discharge Register was used to determine psychiatric and neurological outcomes in adulthood for all offspring. Parental history of psychotic disorder and epilepsy was determined by linking the Hospital Discharge Register and the Finnish Population Register. Results: Our total sample comprised 9653 families and 2 3404 offspring. 232 offspring had an ICD diagnosis of broadly defined psychotic disorder, 71 had a diagnosis of schizophrenia, and 208 had a diagnosis of epilepsy. 11 offspring had epilepsy and broadly defined psychosis and 5 had epilepsy and schizophrenia. Individuals with epilepsy had an almost 5-fold increase in the odds of having broadly defined psychotic disorder and a greater than 8-fold increase in the odds of having schizophrenia (OR 8.6, 95% CI 3.4–21.7). The temporality of this association remains to be investigated. Among offspring with a family history of psychotic disorder, there was a 2.7 fold increase in the odds of generalized epilepsy among those with co-morbid psychotic disorder (OR 2.7, 95% CI 1.2–6.1) and a 2.4 increase among those without co-morbid schizophrenia or psychotic disorder (OR 2.4, 95% CI 1.1–5.8). Reciprocally, among offspring with a family history of epilepsy, there was a 2-fold increase in the odds of psychotic disorder among those with a co-morbid diagnosis of epilepsy (OR 2.1, 95% CI 1.1–4.1) and also a 2-fold increase among those without co-morbid epilepsy (OR 2.0, 95% CI 1.0–4.0). Conclusion: These findings support recent evidence of overlapping etiological factors between epilepsy and schizophrenia especially recent evidence of genetic overlap. Investigating commonalities in the pathways to epilepsy and schizophrenia has the potential to pinpoint abnormalities in neurodevelopment that are etiologically relevant for both disorders.
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ID: 979172

MODELING THE EXPRESSION AND COURSE OF DEVELOPMENTAL ABNORMALITIES PRECEDING ADULT SCHIZOPHRENIA: CHARACTERIZATION OF A NEW DEVELOPMENTAL ULTRA-HIGH-RISK GROUP IN 2 BIRTH COHORTS

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Background: Early detection of individuals who will develop schizophrenia is critical for efforts to identify mechanisms underlying psychosis onset and to the development of preventive interventions. Epidemiological studies have documented a large number of risk factors for schizophrenia, but these have provided only weak predictive accuracy. However, none of the previous studies incorporated longitudinal information in order to maximize positive predictive power. Methods: Two birth cohorts from Israel (Jerusalem Health and Development Study, $N = 14\,201$) and New Zealand (Dunedin Multidisciplinary Health and Development Study, $N = 1037$) assessed during multiple time points in childhood and adolescence were used. Family characteristics, obstetric conditions, cognitive and social development data were analyzed and compared in children in both birth cohorts who later developed schizophrenia or affective disorders, as well as in healthy comparison subjects. Recursive partitioning modeling was used to predict disease classification (ie, schizophrenia, affective disorders). Results: Children from both cohorts who developed adult schizophrenia exhibited deficits on the majority of measures. When only cross sectional information was used prediction models had 10%–30% sensitivity, and 97%–99% specificity, providing only low positive predictive values (<5%). When longitudinal information from the birth cohorts was included, prediction models had 20%–60% sensitivity, and more than 99% specificity, providing moderate to high positive predictive values (>30%). These patterns were not observed in children who developed affective disorders. Conclusion: These findings suggest that repeated prospective ascertainment of risk information in childhood and adolescence can result in dramatic increases in positive predictive power of schizophrenia. From a public health perspective, this could provide a benchmark for implementing current early detection and intervention programs (''podromal clinics'') to the population level.
ID: 978917

BIOLOGICAL AND SOCIAL PREDICTORS OF CLINICAL OUTCOME AFTER THE FIRST PSYCHOTIC PSYCHOTIC EPISODE: FINDINGS FROM THE AESOP 10-YEAR FOLLOW UP STUDY

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Background: AESOP is a large epidemiological study that evaluated a number of social and biological risk factors in individuals presenting to psychiatric services with a first psychotic episode. The study is now completing a 10-year follow up of the original cohort, and aims to evaluate clinical and functional outcome, and factors that can predict these outcomes. Methods: The original cohort comprised 357 patients, included when they first presented to psychiatric services in London. To date, we have attempted to follow up 327 of these. Approximately 88% of patients have been traced, and invited to undergo a second evaluation. Social deprivation, neurodevelopmental indeces (neurological function), and brain structure were evaluated at first presentation and again at follow up (7 years for MRI and 10 years for all other factors). At follow up we have assessed clinical and functional outcomes through subject interview, case-note review, and informant interview, and recorded them using the WHO Life Chart and the Global Assessment of Function (GAF). To assess functional outcomes we also included time spent in employment; independent accommodation; global function score; marital and parental status. Results: Preliminary analyses showed that by the end of the follow up, approximately 30% of the sample had developed a continuous illness course, 30% an episodic illness course, with periods of symptom remission of at least 6 months, and 40% had developed an illness course intermediate between the two. Most patients had been admitted to hospital at least once during follow up. In terms of biological predictors, patients who suffered more brain changes over time (graygray matter reduction, ventricular volume enlargement, $P < .001$), and more neurological dysfunction ($P < .001$), were more likely to have a poorer type of outcome. This was indicated by not having had periods of remission of at least 6 months duration, having spent more time in hospital and having had a higher exposure to antipsychotic medications. The role of social factors is also being investigated. Conclusion: There appears to be a large range of possible outcomes following a first psychotic episode, and it is possible that these can be predicted already at the time of illness onset by using a combination of social and biological factors.
ID: 978760

THE ROLE OF HIGH POTENCY CANNABIS USE AND PSYCHOSIS GENETIC LIABILITY IN MODERATING THE RISK FOR ONSET OF PSYCHOTIC DISORDERS

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Background: Epidemiological studies have reported that the risk of developing psychosis in cannabis users is dose related. Experimental research has shown that the active constituent of cannabis responsible for its psychotogenic effect is Delta-9-Tetrahydrocannabinol (THC). Recent evidence shows the potency (% TCH) of the cannabis seized in the UK is increasing. Hypothesis: We predicted that first episode psychosis patients would be more likely to have started using cannabis in early adolescence, to use higher potency cannabis and to use it more frequently than controls. We also predict that the effect of type of cannabis used is moderated by family history for psychosis. Methods: We collected information concerning sociodemographic and clinical characteristics, and cannabis use (age at first use, frequency, length of use, type of cannabis used) from 280 first-episode psychosis (FEP) patients and 174 matched healthy volunteers in South London. Results: There was no significant difference in the life-time prevalence of cannabis use or age at first use between cases and controls. Nevertheless, in the cases group age at first use was positively correlated with age of onset of psychosis: the earlier the age at first cannabis use, the earlier the onset of psychosis ($z = .49$; $P < .001$). After adjusting for age, gender, ethnicity, level of education, employment status other stimulants use, cases were more likely to be regular users (OR = 6.0; 95% CI 3.2–28.6) and to have smoked high potency cannabis (skunk), (OR = 6.8; 95% CI 2.6–25.4) than controls a positive family history for psychosis produced a further but not significant increase in the OR. Moreover, given a prevalence of 44% for skunk use among our cases and an OR = 2.6 for skunk use in cases vs controls, we calculated a population attributable fraction (PAF) for skunk use = 27%. Conclusion: Patients with first episode psychosis have smoked higher potency cannabis (skunk), for longer and with greater frequency, than healthy controls. We only found a trend of significance for the moderating effect on potency of cannabis use of positive family history for psychosis. Moreover, age at first cannabis use significantly moderates age of onset for psychosis. Our findings also suggest that if skunk use was abolished 27% of the psychosis cases in South East London would be prevented.
ID: 978354

AUTOIMMUNE DISEASES, SCHIZOPHRENIA, BIPOLAR DISORDER, AND NON-AFFECTIVE PSYCHOSIS

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Background: Clinic-based studies of immune function, as well as comorbidity of autoimmune diseases, bipolar disorder, and schizophrenia, suggest a possible autoimmune etiology. Studies of non-affective psychosis and schizophrenia suggest common etiologies. The objective was to determine the degree to which 30 different autoimmune diseases are antecedent risk factors for bipolar disorder, schizophrenia, and non-affective psychosis. Methods: A cohort of 3.57 million births in Denmark was linked to the Psychiatric Case Register and the National Hospital Register. There were 2 0317 cases of schizophrenia, 3 9076 cases of non-affective psychosis, and 9920 cases of bipolar disorder. Results: There were a range of autoimmune diseases which predicted raised risk of schizophrenia in individuals who had a history of autoimmune diseases, and also raised risk in persons whose first-degree relatives had an autoimmune disease prior to onset of schizophrenia in the case. These relationships also existed for the broader category of non-affective psychosis. Only pernicious anemia in the family was associated with raised risk for bipolar disorder (relative risk: 1.7), suggesting a small role for genetic linkage. A history of Guillain-Barré syndrome, Crohn's disease, and autoimmune hepatitis in the individual was associated with raised risk of bipolar disorder. Conclusion: The familial relationship of schizophrenia to a range of autoimmune diseases extends to non-affective psychosis, but not to bipolar disorder. The data suggest that autoimmune processes precede onset of schizophrenia, but also non-affective psychosis and bipolar disorder.
ID: 978154

DIFFERENTIAL INFLUENCES OF SEROLOGICALLY DOCUMENTED OBSTETRIC COMPLICATIONS ON BIRTH WEIGHT AMONG PRESCHIZOPHRENIA INFANTS COMPARED TO CONTROL INFANTS

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Background: Studies have repeatedly linked prenatal influenza exposure and fetal hypoxia (decreased oxygen to the fetus) to increased risk of schizophrenia in offspring. Further, there have been mixed results relating decreased birth weight (BW) to increased risk of schizophrenia. Both prenatal infection and fetal hypoxia have been associated with decreased birth weight; however no study has investigated whether the occurrence of these obstetric events accounts for the mixed BW findings in schizophrenia research. The purpose of this study was to determine whether influenza and fetal hypoxia contribute to decreases in BW among infant cases who later develop schizophrenia in adulthood compared to unexposed cases and control infants. Methods: Participants were 111 case infants diagnosed with psychoses in adulthood (70 with schizophrenia and 41 with affective psychoses) and 333 nonpsychiatric control infants. Participants were monitored prospectively during gestation as part of the Philadelphia, PA site of the Collaborative Perinatal Project. Psychiatric morbidity was determined in adulthood by medical records review and confirmed by validation study. Assays were conducted from archived maternal sera and umbilical cord sera collected at birth. IgG antibodies to influenza B and Erythropoiten (EPO; marker of hypoxia) were measured by solid-phase enzyme immunoassay. Infection and fetal hypoxia were positive if titers were >75th percentile. Fetal hypoxia was considered severe if >90th percentile. Analyses controlled for infant's sex, maternal race, maternal age, and gestational length. Results: Results indicated that there were significant decreases in BW among cases who were exposed prenatally to either influenza B or severe fetal hypoxia compared to cases who were unexposed. Similar decreases were observed among cases exposed to moderate fetal hypoxia, but these decreases failed to reach significance. There were no differences in BW among controls who were exposed to infection and hypoxia compared to those unexposed. Further, there were no significant differences in BW among unexposed cases and controls. Conclusion: Findings suggest that a genetic or an environmental factor associated with psychoses rendered the fetus particularly vulnerable to the effects of influenza and hypoxia, leading to disruptions in fetal growth.
ID: 975131

CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH PSYCHOSIS

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Background: Schizophrenia is associated with a significant excess mortality and morbidity from cardiovascular and metabolic causes. In order to assess the extent of excess cardiovascular risks, there is a need to investigate population-based schizophrenia patient samples. Methods: Patients and controls: During 2005–2008, 748 consecutive patients were recruited from psychosis outpatient clinics in Stockholm County. Controls were 5580 individuals from a population-based survey, also from Stockholm County. The controls were 10 years older and enriched for family history of diabetes (50%). Results: Results: Demographic data are presented in Table 1. Waist circumference was 10 cm longer for male and 12 cm for female patients compared to controls (P <.001), and fasting glucose was 5.7 vs 5.2 mmol/L for male and 5.7 vs 4.8 mmol/L for female patients compared to controls (P <.001), controlling for differences in age and family history of diabetes. Smoking was much more common among the patients with 44% compared to 18% in controls. Only 4% of the patients and 5% of the controls were treated with lipid lowering medication. Conclusion: Waist circumference, fasting glucose and smoking were substantially increased in psychosis patients compared to the population. Surprisingly few psychosis patients were treated with lipid lowering drugs.
ID: 980138

INTERACTION BETWEEN CHILDHOOD ADVERSITY AND THE COMT VAL158MET POLYMORPHISM IN FIRST-EPISODE PSYCHOSIS

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Background: Childhood adversity has frequently been associated with psychosis but not all exposed individuals develop this disorder suggesting that some may have a genetic vulnerability. The valine (Val) allele of the catechol-O-methyltransferase (COMT) Val158Met polymorphism has been linked to psychosis in those exposed to stress in adulthood. Therefore, we predicted this allele would also interact with childhood adversity in the development of clinically-relevant psychotic disorders. Methods: In a cross-sectional study, 161 first-presentation psychosis patients and 100 unaffected controls completed the Childhood Experience of Care and Abuse Questionnaire (CECA.Q) to determine experience of at least one

adverse event before 17 years of age (physical or sexual abuse, parental separation or death, taken into care, disrupted living arrangements). Blood samples were genotyped for the COMT Val158Met polymorphism using polymerase chain reaction. Results: Reported exposure to any adversity in childhood was significantly associated with being a psychosis case in this sample (unadjusted OR = 2.80, 95% CI 1.66–4.74, P <.001). No gene-environment correlations were found though between COMT genotype and childhood adversity. However, reported exposure to childhood adversity was associated with psychotic disorder amongst non-White British carriers of the COMT Val allele (OR = 6.20, 95% CI 2.86–13.45, P <.001), but not minority participants homozygous for the Met allele (likelihood ratio test for interaction X^2 = 4.15, P = .042). No interaction was found for White British participants (likelihood ratio test X^2 = .06, P = .809). Conclusion: This study provides preliminary evidence that the COMT Val158Met polymorphism moderates the association between childhood adversity and psychotic disorder in minority ethnic groups. Replication is required in larger samples from other geographical locations.
This work was supported by a postdoctoral fellowship awarded to Dr Fisher by the Medical Research Council and Economic and Social Research Council, UK.
ID: 979109

MATERNAL/FETAL BLOOD INCOMPATIBILITY AND STRUCTURAL BRAIN ANOMALIES IN SCHIZOPHRENIA

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Background: Prior research has shown that maternal-fetal Rh D and ABO blood incompatibility increase the risk for schizophrenia. In the present study, the relationship between blood incompatibility and volumes of brain structures previously implicated in schizophrenia was assessed in schizophrenia cases and controls from a large birth cohort. Methods: Cases and controls in the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) study were drawn from a schizophrenia follow-up investigation of the Child and Health Development Study (CHDS), a large birth cohort. Maternal-fetal incompatibility was assessed by analysis of blood samples in the CHDS birth cohort at the time of the maternal and umbilical blood draws. For the present study, maternal-fetal blood incompatibility was defined as either ABO or Rh incompatibility. Results: Cases exposed to ABO/Rh incompatibility, compared to unexposed cases, had significantly smaller total cortical gray matter volume (P = .016), as well as bilaterally diminished volumes of the dorsolateral prefrontal cortex (DLPFC; right P = .002; left P = .024) and inferior frontal cortex (right P = .044; left P = .027). Consistent with these findings, a statistical trend was also observed for increased sulcal CSF volume in exposed cases. In addition, there was a trend for diminished right thalamic volume in exposed cases. In comparison, the ABO/Rh incompatible exposed controls, compared to unexposed controls, did not have smaller total cortical gray matter (P = .47) and had reductions in the DLPFC that were not statistically significant; but, similar to cases, had reduced bilateral volume in the inferior frontal cortex (right P = .014; left P = .016). Exposed controls also had larger hippocampal volume than unexposed controls (total left hippocampus volume P <.0001; total right hippocampus volume P = .01) and enlarged right putamen volume (P = .016). Conclusion: These data suggest that maternal/fetal blood incompatibility may significantly increase the risk for both altered brain morphology and schizophrenia. The findings lend themselves to two main conclusions. First, it is possible that in utero exposure to blood incompatibility heightens the risk for structural brain changes which in turn increase the risk of developing schizophrenia. Second, these data suggest that the exposed controls' enlarged hippocampus may be protective against the development of disease by an adaptive resiliency.
ID: 977408

MIDLIFE PROGRESSION IN SCHIZOPHRENIA: A 45-YEAR FOLLOW-UP IN THE NORTHERN FINLAND 1966 BIRTH COHORT STUDY

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Background: Schizophrenia usually progresses in midlife from age 30 to 50 years in key areas, including brain morphometry, cognition, comorbidity, and functional outcomes. Methods: Population-based Northern Finland 1966 Birth Cohort members (N = 1 2058) were followed serially from mid-pregnancy until age 45, with detailed data on approximately 120 cases at age 35 and 200 cases at age 45 with diagnoses of schizophrenic psychoses. Repeated sMRI, cognitive and clinical analyses were performed at ages 35 and 45. Results: During the midlife period at ages 35 and 45, brain matter deficits, cognitive decline, somatic comorbidity and mortality were found in patients with schizophrenia. Gray and white matter deficits were associated with duration of illness, suggesting that either developmental brain deficits are associated with an earlier age of onset or brain abnormalities in schizophrenia are progressive in nature. Full or partial recovery was unusual and outcomes and medication adherence relatively poor. Conclusion: Midlife progression of illness may follow a variety of different trajectories. A deteriorating course and illness relapses/exacerbations are common but not necessary outcomes. In a minority of cases the course of illness may also be relatively benign, and frequently symptoms reach a plateau 5–10 years after disease onset. Mechanisms behind disease progression—and targeted interventions to address them—are largely unknown. For most patients with schizophrenia, substantial and enduring adverse consequences during midlife reduce potential adult maturity, well-being and creativity typical to this epoch. Our results will provide new insights into the etiology and care (antipsychotic drugs) of schizophrenia, as well as its developmental, diagnostic and treatment aspects, having increasing clinical relevance and translational research paradigms.
ID: 979163

GESTATIONAL EXPOSURES TO INFECTIOUS AGENTS AND RISK FOR NON-AFFECTIVE PSYCHOSES: ANALYSES OF SWEDISH DRIED BLOOD FILTER PAPERS

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Background: High levels of immunoglobulins directed at infectious agents in maternal blood have been associated with an increased risk for developing non-affective psychosis in the offspring. Previous studies conducted in the US (stored maternal sera) or in Denmark (stored dried blood spots obtained from the neonate) have reported increased risk associated with high levels of antibodies directed at Toxoplasma gondii. With regard to the potential risk associated with immunoglobulin levels directed at herpes simplex type 2, conflicting results have been reported. Methods: A case-control study, with a nested design was used to retrieve dried blood filters from 211 individuals with verified diagnoses of non-affective psychoses

(F20-29, ICD-10) and 553 comparison subjects matched for sex, DOB and birth parish following informed consent. These individuals were born in Sweden 1975–1985 and followed up in national registers 1987–2003. IgG levels (directed at T gondii, HSV-1, HSV-2 and cytomegalovirus) in filter-eluates were analyzed by commercially available ELISAs. Results: Levels of IgGs directed at T gondii corresponding to the upper quartile among the controls were significantly associated with schizophrenia (F20) risk, OR 2.0 (95% CI: 1.0–4.3), but not with other diagnoses. These results were not confounded by maternal age or immigrant status. No significant associations were observed between levels of IgGs directed at other agents and non-affective psychoses. Conclusion: We can confirm three previous studies reporting a schizophrenia-risk associated with high levels maternal of maternal antibodies directed at T gondii during pregnancy. The risk associated with maternal HSV-2 antibodies remains to be clarified. Further studies are needed to identify mechanisms underlying the association between maternal T gondii antibodies and schizophrenia risk in the offspring.
ID: 979097

CLINICAL PREDICTORS OF CARER BURDEN IN SCHIZOPHRENIA: A 5-YEAR FOLLOW-UP STUDY FROM RURAL ETHIOPIA

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Background: Burden among informal caregivers of patients with severe mental illness (SMI) may be more prominent in low- and middle-income countries, where caregivers constitute the sole support for people with SMI. In order to establish the longitudinal course of carer burden and factors predicting change, we assessed carer-burden and its predictors within a traditional rural Ethiopian community. Methods: Using a 5-year follow-up data from the ongoing Butajira outcome study on SMI, carer burden was assessed annually with the Family Interview Schedule (FIS). Multilevel modeling was used to identify clinical predictors of severity and rate of change of burden. Patients were treated with conventional antipsychotic medications during the 5-year follow-up period. Results: Scores in all domains of carer burden decreased over time, although the greatest reduction was seen in the first year. In univariate analyses, longitudinal reduction in burden score was predicted by longer period in remission during follow-up, while higher burden score was predicted by higher negative and positive symptom severity scores. In the fully adjusted model, poor social support predicted higher burden score (= .38, 95% CI .04, .72), and longer period in remission predicted lower level of carer-burden (= −.49, 95% CI = −.89, −.10). Reduction in positive symptoms was associated with the instantaneous rate of reduction of burden score (= −.03, 95% CI −.05, −.01). Conclusion: There is a significant reduction in carer-burden over the years in all burden domains. Providing accessible mental health care has the potential to alleviate carer burden, as positive symptoms are amenable to intervention. The study also indicates that remission is associated with reduction in carer-burden.
ID: 979210

PSYCHOSIS PRODROMES IN THE COMMUNITY: IDENTIFICATION AND CHARACTERIZATION OF PSYCHOSIS RISK SYNDROMES IN THE GENERAL ADOLESCENT POPULATION

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Background: Interest has grown rapidly in the identification of patients during the psychosis prodrome, prior to the onset of psychotic disorder, when early - ideally preventative - intervention might be achieved. Multiple centres around the world have now shown that it is possible to identify individuals at very high risk of psychosis (variously titled psychosis risk syndromes, at-risk mental states, clinical high risk) among help-seeking individuals who present to the clinic, based upon defined criteria involving attenuated psychotic symptoms or frankly psychotic symptoms of brief duration. However, no attempt to identify individuals with psychosis risk syndromes in the general population has been reported to date. Methods: In order to test whether it is possible to identify prodromal adolescents in the community, we administered two psychosis screening instruments - the Adolescent Psychotic Symptom Screener (APSS) and the PRIME clinic psychosis screener - to 210 adolescents from the general population, who subsequently received in-depth clinical interviews aimed at evaluating psychotic symptomatology. We also administered the MATRICS neurocognitive battery, as well as collecting information on a range of clinical and socio-demographic variables associated with psychosis risk. Results: Approximately 5% of the sample met criteria for a psychosis risk syndrome (APSP or BIPS). These individuals had significantly higher scores than controls on both the APSS and PRIME screeners. Our community-based prodromal group demonstrated a similar profile of neurocognitive deficits to previously-reported clinically-presenting prodromes (Seidman et al, 2010), with the greatest deficits occurring in speed of processing tasks. They also demonstrated an overlap with clinical populations in terms of multiple clinical and sociodemographic variables, further supporting etiologic continuity between the two groups. Conclusion: These findings suggest that it is possible to identify psychosis risk syndromes in the general population, prior to clinical referral, and point to the possibility of earlier identification in psychosis, an important goal for psychiatry and all other fields of medicine.
ID: 975110

PREMORBID IQ AND SOCIAL FUNCTIONING DEFICITS AND SCHIZOPHRENIA RISK: EVIDENCE FOR SHARED GENETIC INFLUENCES ON NEURODEVELOPMENT

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Background: Premorbid IQ and social deficits in schizophrenia are well documented and have been interpreted as supporting a neurodevelopmental hypothesis of the illness. However the aetiology of this association remains unknown. It could be caused by the influence of genetic factors and/or environmental exposures, but it might also be an artifact of the high heritability of IQ and social functioning. We present the first study to directly address this question using a twin modelling approach applied to a population based birth cohort. Methods: Building on the Israeli Conscripts Study (Davidson et al, 1999), we identified all twin pairs born over the period of a decade. The data consisted of premorbid IQ and social functioning measures from a total twin population of 3729 pairs. Linkage with the Israeli National Hospitalization Case Registry identified 35 individuals that were affected by schizophrenia (4 concordant pairs and 27 discordant pairs). A trivariate correlated factors approach was implemented using finite mixture modelling. Results: Genetic influences contributed substantially to each phenotype, schizophrenia (h^2 = .81) was the most highly heritable followed by IQ (h^2 = .67) and social functioning (h^2 = .51). The phenotypic correlations between schizophrenia and IQ and social functioning were modest (for IQ r = −.11 and for social functioning r = −.10) of which 33% and 45% was due to genetic effects respectively. For IQ and social functioning genetic effects accounted for 48% of the phenotypic correlation (r = .17). In each case the remaining covariance was accounted for

by common and unique environmental effects. Conclusion: Using a population based study we demonstrated that the association between schizophrenia and premorbid intellectual and social abnormalities is caused by shared genetic effects, providing strong support for the neurodevelopmental hypothesis of schizophrenia. However the genetic and phenotypic correlations between schizophrenia and premorbid social functioning and IQ do not suggest a complete overlap of genetic effects, rather they imply that there are other distinct influences that contribute to their association.
ID: 976809

GENE-ENVIRONMENT INTERACTION IN PSYCHOSIS: EFFECTS OF CANNABIS USE, CHILDHOOD TRAUMA AND GENETIC LIABILITY

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Background: Cannabis use and childhood trauma are risk factors for the development of psychotic disorder. General population studies have recently shown that cannabis and trauma may interact in increasing psychosis risk. To further examine this putative interaction, the effects of cannabis use and trauma on psychosis risk were studied in a genetically sensitive design to investigate whether the interaction between trauma and cannabis may be moderated by familial liability for psychosis. Methods: The present study was part of the Dutch GROUP study (Genetic Risk and Outcome in Psychosis) which was designed to study gene-environment interactions relevant for psychosis. The sample consisted of 270 patients with a diagnosis of non-affective psychotic disorder, 442 of their first-degree relatives, and 223 healthy control participants. Cannabis use was assessed with the G-section of the Composite International Diagnostic Interview (CIDI). The Childhood Trauma Questionnaire (CTQ) was used to assess early exposure to trauma. Psychotic experiences were measured using the Community Assessment of Psychic Experiences (CAPE). Data were analyzed using linear regression models retrieved from STATA version 11.1. Results: Analyses revealed a significant interaction between lifetime cannabis use and trauma with regard to risk of psychotic experiences. The effect of cannabis use on psychotic experiences was much stronger for those individuals who had been exposed to trauma (β = .36, 95% CI: .17, 0.55, P = .000) compared to individuals who had not been exposed to trauma (β = .22, 95% CI: .04, .40, P = .015). Post hoc analyses furthermore revealed a three-way interaction between cannabis use, trauma and patient-status. The joint effect of cannabis use and trauma was stronger in patients (β = .17, 95% CI: .02, .33, P = .027), compared to their relatives and controls (relatives β = −.03, 95% CI: −.23, .18, P = .8; controls β = −.12, 95% CI: −.44, .19, P = .5). Conclusion: The present study supports previous observations that cannabis and trauma co-participate in causing psychosis. The results furthermore suggest that genetic liability for psychosis moderates the degree of synergism between environmental risk factors in causing psychosis.
ID: 979255

SOMATIC COMORBIDITY IN YOUNGER PSYCHOTIC PATIENTS EVALUATED BY THE CHARLSON COMORBIDITY-INDEX

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Background: Premature death in persons with psychotic disorders (schizophrenia and bipolar disorder) is well documented. Suicide and death by accidents in persons with psychotic disorders are frequent, but excess mortality from somatic disease and medical conditions accounts for even more years of life lost. However, the impact of somatic comorbidity is often not duly considered in analyses and explanations of the excess mortality. The first aim of the study was to investigate the incidence rate ratios of the 19 somatic chronic diseases (weighted from 1 to 6 according to severity) included in the Charlson Index among persons with psychotic disorders, compared with persons never in contact with a psychiatric hospital. The second aim was to evaluate the impact of somatic diseases, as measured by the Index, on the estimates of the excess mortality from natural death in patients with psychotic disorders. Methods: All persons born in Denmark from January 1, 1955 to June 1, 1992 and residing in Denmark at some point during the follow-up period from 1995 to 2007 were identified in the Danish registers. Incidence/mortality rate ratios of admission/mortality were calculated using survival analysis and were adjusted or stratified by the Charlson Index. Results: Cohort members with psychotic disorders had higher incidence rates of hospital contacts with almost all of the 19 disorders included in the Index. The Index was twice as high compared to cohortees with no contact to a psychiatric hospital. Mortality rate ratios (MRR) of natural death was 6.06 (95% CI 5.19, 7.09) for schizophrenic women, but only 3.03 (2.60, 3.55) after adjustment for the Index. The same pattern was present for men and women, and for bipolar disorder. Among cohort members with an Index equaling zero, schizophrenic patients had a MRR of 12.71 (11.31, 14.28), with similar high rates in bipolar patients. Conclusion: Our results indicate a potential under-treatment of the chronic disorders included in the Charlson Index among patients with psychotic diseases, but may also point towards the particular role of acute severe diseases, which are common among persons with psychotic disease but not included in the Charlson Index. We suggest that the insufficiency of somatic health care for persons with psychotic disorders contributes to the excess mortality.
ID: 978236

THE AUSTRALIAN SCHIZOPHRENIA RESEARCH BANK (ASRB): THE FIRST 550 SCHIZOPHRENIA SAMPLE PROFILE.

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Background: The Australian Schizophrenia Research Bank (ASRB) was established in 2007 to collect linked clinical, cognitive, neuroimaging and genetic data in people with schizophrenia and matched controls. The ASRB is the first of its kind developed in Australia. Demographic, clinical and neurological data is presented for the first 550 participants with schizophrenia. Methods: Participants were assessed using a comprehensive assessment battery that consists of socio-demographic questions including medical and family history, neurological evaluation (NES), neuropsychological assessment and cognitive performance measures (WTAR, WASI, RBANS, LNS, COWAT), a diagnostic interview that includes drug and alcohol history (DIP, Castle et al, 2006) to confirm diagnosis, ratings for negative symptoms (SANS), general functioning (GAF), and questionnaires of childhood adversity, personality disorder (IPDE) and psychosis proneness (SPQ). Results: A sample of 550 people with schizophrenia (mean age = 39.66 years; SD = 10.98) and 250 healthy controls (mean

age = 37.37 years; SD = 13.14) were compared across measures. The schizophrenia sample had a higher proportion of males (cases 66.80%; controls 46.40%), fewer living in married or de facto relationships (cases 15.80%; controls 53.60%) and fewer years of education (cases 12.93, SD = 2.91; controls 15.13, SD = 3.14). Schizophrenia participants also had lower premorbid IQ (cases 103.17, SD = 13.17; controls 111.83, SD = 8.76), current IQ (cases 102.29, SD = 15.62; controls 118.24, SD = 10.20) and RBANS total score (cases 82.55, SD = 15.59; controls 96.24, SD = 15.88), consistent with performance reported previously for Australian samples (Loughland et al, 2007). Conclusion: These findings are consistent with those reported previously in the Australian Low Prevalence Disorders Study (Castle, 1999), suggesting the ASRB sample is broadly representative of people with schizophrenia living in Australia. The ASRB is a unique schizophrenia resource that is accessible to approved national and international researchers.
ID: 979026

WHEN DOES PREMORBID COGNITIVE DECLINE OCCUR IN SCHIZOPHRENIA? A PROSPECTIVE COHORT STUDY OF COGNITIVE PERFORMANCE AT AGES 13 AND 18 IN 14 079 SWEDISH SUBJECTS

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Background: There is now clear evidence from many prospective, population-based studies, that patients who later develop schizophrenia suffer from a variety of cognitive deficits during childhood and adolescence. However, there are no studies using identical tests of cognitive performance in the same individuals at multiple time points during childhood. It is therefore not clear whether premorbid cognitive deficits during childhood and adolescence are static or progressive. Methods: Using Cox proportional hazard models, we analysed cognitive test results in three domains (verbal ability (opposites), spatial ability (paper folding) and logical reasoning (identify missing number in a sequence)) at age 13 and age 18, in 14 079 males, and followed them to a mean age of 41 years using the Swedish Hospital Discharge Register. Results: 59 individuals had hospital admissions for schizophrenia over the follow-up period of 304 943 person-years. Combining the results of all three tests, subjects who developed schizophrenia scored .29 standard deviations (SD) below their peers at age 13 and had declined by a further .25 SD by age 18. Every 1SD of decline increased risk of schizophrenia by around 59% (HR = 1.59, 95% CI = 1.07, 2.36). When individual cognitive domains were examined, verbal IQ showed by far the greatest decline, from near-normal level at age 13–.38 SD below population mean at age 18. By contrast, spatial IQ was equally impaired at age 13 and 18. Logical reasoning followed an intermediate pattern, with some impairment at age 13 and further decline by age 18. Conclusion: IQ decline occurs during the course of adolescence in pre-schizophrenic individuals. Moreover, the course of this decline differs between cognitive domains. Pre-schizophrenic individuals fall behind their peers in verbal skills during adolescence, from near-normal ability at age 13 to marked impairment at age 18, suggesting an impairment of late neurodevelopment. By contrast, spatial ability is already impaired at age 13 and remains static during adolescence, suggesting that this is a marker of early developmental deficits. This has potential implications for the likely neurodevelopmental processes involved in schizophrenia risk.
ID: 978491

CHILDHOOD ADVERSITY IN SCHIZOPHRENIA: NEUROCOGNITIVE AND CLINICAL CORRELATES FROM THE AUSTRALIAN SCHIZOPHRENIA RESEARCH BANK (ASRB)

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Background: Childhood adversity is considered an environmental factor that has influence on the development and course of schizophrenia. Further, when controlling for family history of the disorder, there is evidence that rates of childhood adversity are greater for people with schizophrenia compared to controls and non-affected relatives. The aims of this study were to compare the rate of childhood adversity in schizophrenia relative to a healthy control group and to examine associations between adverse childhood experiences, illness course and current functioning. Methods: Data from the Australian Schizophrenia Research Bank (ASRB) were used to examine the rates of childhood adversity of individuals with a confirmed diagnosis of schizophrenia ($N = 408$; mean age = 40.72) and healthy controls ($N = 267$; mean age = 39.27). All volunteers completed the Childhood Adversity Questionnaire. In addition, socio-demographic, clinical and neuropsychological data was collected. Results: Schizophrenia participants were significantly more likely than controls to report experiencing any childhood adversity (86.8% vs 69.5%, OR 2.87, 95% CI 1.95, 4.23, $P < .001$). In addition, schizophrenia participants reported more childhood adversities compared to controls (mean 5.4 vs 2.3, $P < .001$). Compared to controls, schizophrenia participants were significantly more likely to report the experience of most types of childhood adversities assessed. The Child Adversity Questionnaire items were grouped using factor analysis. Schizophrenia participants (compared to controls) were significantly more likely to experience parental abuse, problematic rearing, and parental dysfunction. Premorbid and current IQ was found to be associated with distinct types of childhood adversity. Among schizophrenia participants higher positive symptom scores were associated with childhood adversity. Conclusion: Consistent with previous findings, people with schizophrenia reported the experience of more childhood adversities compared to a control group. Further, several measures of clinical and neurocognitive functioning were found to be associated with specific experiences of childhood adversity.
ID: 979098

EXPLAINING VARIANCE IN PREMORBID MARIJUANA CONSUMPTION IN SCHIZOPHRENIA PATIENTS AND CONTROLS

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Background: Cannabis use increases the risk for psychosis with a dose response relationship; the risk is particularly strong for cannabis use before age 15. However, it is unknown what factors are associated with the quantity of cannabis used premorbidly, before any psychiatric symptoms appear. It is likewise unknown whether the factors that explain variance in premorbid cannabis consumption differ between schizophrenia patients and community controls. Our objective was to determine the extent to which family history of schizophrenia and of substance misuse, childhood trauma, and pre-cannabis use externalizing problems explain variance in the amount of marijuana consumed premorbidly in schizophrenia patients

and controls. Methods: Data were gathered for more than 100 schizophrenia patients and 68 controls on estimated amounts of premorbid cannabis consumption, childhood abuse and neglect, family history of psychopathology, and premorbid adjustment; prodrome onset was carefully dated in patients. Results: In controls, more severe childhood trauma was associated with greater marijuana consumption, while in schizophrenia patients trauma was associated with less marijuana used premorbidly. In controls only, more severe trauma was associated with younger age at onset of marijuana use. Also in controls only, childhood externalizing problems were associated with greater amounts of marijuana use and earlier age at onset of use. Models explained approximately 16% of the variance in amounts of marijuana use, at 20%–30% in age at onset, in both groups. Conclusion: These results suggest that factors that explain variance in marijuana use may differ between those predisposed to developing schizophrenia and the general population before prodromal signs are present.
ID: 979217

DEVELOPMENTAL VITAMIN D DEFICIENCY AND RISK OF SCHIZOPHRENIA: A TEN-YEAR UPDATE

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Background: There is an urgent need to generate and test candidate risk factors that may explain gradients in the incidence of schizophrenia. Methods: Based on clues from epidemiology, we proposed that developmental vitamin D deficiency may contribute to the risk of developing schizophrenia. This hypothesis may explain diverse epidemiological findings including season of birth, the latitude gradients in incidence and prevalence, the increased risk in dark skinned migrants to certain countries, and the urban-rural gradient. Results: Animal experiments demonstrate that transient prenatal hypovitaminosis D is associated with persisting changes in brain structure and function, including convergent evidence of altered dopaminergic function. A recent case-control study based on neonatal blood samples identified a significant association between neonatal vitamin D status and risk of schizophrenia. Conclusion: This presentation will provide a concise summary of the epidemiological and animal experimental research that has explored this hypothesis.
ID: 978076

THE ASSOCIATION BETWEEN GENERAL PSYCHOLOGICAL DISTRESS AND DELUSIONAL-LIKE EXPERIENCES: A LARGE POPULATION-BASED STUDY

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Background: Previous population-based studies have found that delusional-like experiences (DLE) are prevalent in the community, and are associated with exposure to trauma, substance abuse and the presence of anxiety or depressive disorders. We wondered if the presence of general psychological distress may also be associated with DLE, even in the absence of traditional psychiatric diagnoses. We had the opportunity to explore these issues in a large population-based sample. Methods: Subjects were drawn from the Australian National Survey of Mental Health and Wellbeing 2007, a national face-to-face stratified, multistage probability sample household survey of 8841 community residents aged between 16 and 85 years. DLE were assessed using a modified World Mental Health Composite International Diagnostic Interview (CIDI) schedule. Psychological distress was measured using the Kessler-10 (K10) short questionnaire, which examine the frequency of various symptoms over the previous month (eg ''how often have you felt - nervous, restless, depressed, hopeless, worthless etc''). We examined the relationship between DLE and quartiles of total psychological distress scores using logistic regression models, with adjustments for mediating variables such as depression and anxiety disorders, and other potential confounding factors. Results: Of the 8771 participants, 776 (8.4%) endorsed one or more DLE. Individuals with moderate and severe distress were two to three times more likely to endorse DLE. The association remained significant after adjusting for depressive and anxiety disorders together with other confounding factors. The majority of the individual K10 items were independently associated with DLE endorsement. Conclusion: While DLE have traditionally been associated with psychotic disorders, recent studies indicate that they are associated with an unexpectedly wide range of common mental disorders and non-specific psychological distress.
ID: 979174

SIBLING-PAIR ANALYSIS CONFIRMS AN ASSOCIATION BETWEEN CANNABIS USE AND PSYCHOSIS-RELATED OUTCOMES IN A COHORT OF YOUNG ADULTS

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Background: Prospective cohort studies have identified an association between cannabis use and later psychosis-related outcomes, but concerns remain about unmeasured confounding variables. The use of sibling-pair analyses reduces the influence of unmeasured residual confounding. Methods: We examined a nested sibling pairs within a cohort of 3801 young adults born between 1981 and 1984. Cannabis use and three psychosis-related outcomes (non-affective psychosis, hallucinations and Peters Delusional Inventory; PDI) were assessed at 21 year follow-up. Associations between duration since first cannabis use and psychosis-related outcomes were examined using logistic regression adjusted for gender, age, parental mental illness and hallucinations at the 14 year follow-up. Results: Duration since first cannabis use was associated with all three psychosis-related outcomes. For those with duration since first cannabis use of six or more years, there was a significantly increased risk of: (a) non-affective psychosis (Adjusted Odds Ratio 2.2; 95% CI 1.1, 4.5), (b) being in the highest quartile of PDI score (AOR 4.2; 95% CI 4.2, 5.8), and (c) hallucinations (AOR 2.8; 95% CI 1.9, 4.1). Within sibling-pairs (n = 228 pairs), duration since first cannabis use and higher scores on the PDI remained significantly associated. Conclusion: The use of sibling-pairs reduces the likelihood that unmeasured confounding explains these findings. This study provides further support for the hypothesis that early cannabis use is a risk modifying factor for psychosis-related outcomes in young adults.
ID: 977330

META-ANALYSIS OF CYTOKINE ALTERATIONS IN SCHIZOPHRENIA: CLINICAL STATUS, SYMPTOMS, AND ANTIPSYCHOTIC EFFECTS

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Background: Schizophrenia is associated with increased inflammation, as measured by increased blood concentrations of cytokines and increased in vitro cytokine production in stimulated peripheral blood monocytes. We performed a meta-analysis of these associations, considering the effect of clinical status, antipsychotic treatment following an acute exacerbation of psychosis, and correlations with clinical features. Methods: We identified articles by searching Pub Med, PsychInfo, ISI, and EMBASE, and the reference lists of identified studies. Results: Forty-four studies met the inclusion criteria. Mean effect sizes were similar in direction and magnitude for studies of acutely relapsed inpatients (AR) and first-episode psychosis (FEP). Four cytokines were significantly increased (blood levels of IL-6, IFN-γ, TNF-α, and TGF-β; $P \leq .006$ for each), and two cytokines were significantly decreased (blood levels of IL-4 and in vitro IL-2 production) in both AR and FEP subjects. After antipsychotic treatment of an acute exacerbation of psychosis (either AR or FEP), the alterations in all six of these cytokines normalized to some extent, with a significant decrease in blood levels of IL-6 ($P = .003$) and TGF-β ($P = .005$), and a significant increase in in vitro IL-2 production ($P = .04$). There was no difference in blood levels of IL-6 between stable medicated outpatients with schizophrenia and controls ($P = .37$). Blood concentrations of the soluble interleukin-2 receptor (sIL-2R) were significantly increased in treatment-resistant psychosis (TR) ($P = .001$). Conclusion: Similar effect sizes in AR and FEP suggest an association between cytokine abnormalities and acute exacerbations of schizophrenia that is independent of antipsychotic medications. Blood levels of IL-6 may be a biomarker for acute exacerbations of psychosis, and levels of sIL-2R may be a biomarker for treatment-resistant psychosis. Our results point to potential abnormalities in specific immunocompetent cells and immune pathways in acute exacerbations of psychosis. Clinical trials of antipsychotic augmentation with anti-inflammatory agents, including celecoxib and aspirin, also support the association between cytokine abnormalities and schizophrenia.
ID: 978438

THE AUSTRALIAN NATIONAL SURVEY OF THE EPIDEMIOLOGY OF PSYCHOSIS: AIMS AND PRELIMINARY FINDINGS

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Background: In 2010, the second national epidemiological survey of psychosis in Australia (Survey of High Impact Psychosis - SHIP) collected representative data from seven catchments across five states on the prevalence and profile of psychosis. Methods: The survey used a two-phase design: a brief psychosis screener followed by a detailed diagnostic interview. We screened 10 662 people who met age and postcode criteria: 76.7% were screen-positive with 37% aged 18–34 and 63% aged 35–64. We randomly selected 2000 screen-positive people for interview, stratified by age group. Questions covered: functioning and socialization; physical health; psychopathology and cognition; and service utilization and need. Internationally novel components were: (i) brief assessment of cognitive function; (ii) clinical assessment of physical comorbidity and collection of metabolic measures; (iii) concurrent collection of blood for genetic analysis; and (iv) detailed assessment of social roles including role support. Replication of key questions in the first national psychosis survey in 1997 provided a measure of change. Alignment with the 2007 Australian general population mental health survey permitted benchmarking against population data. Results: By September 2010, 1026 interviews had been completed with 67% entered in the study database that includes 1500 variables. Two-thirds of the sample were male, one-half with an ICD-10 diagnosis of schizophrenia. Levels of smoking, drug and alcohol abuse/dependence had increased markedly since the 1997 survey. There was a noticeable difference in the percentage with a chronic and/or deteriorating course of illness (down to 30% from 43%); more work is needed to identify whether this is related to changes in service provision/treatment, sample characteristics or subtle changes in criteria for classifying course patterns. Among the main three challenges named by participants were financial difficulties (41%), unemployment (37%), loneliness (36%), poor physical health (28%) and uncontrolled symptoms of mental illness (24%). Enumeration will finish in December 2010 with analysis of the full dataset complete in early 2011. Conclusion: Novel strategies to quantify cognitive function, assess physical health, collect genetic data, capture social roles and map pathways to recovery within a national, epidemiological framework are of international interest. Data generated will support new models within mental health services to engage people with psychosis in a long-term recovery process.
ID: 977491

GENETIC AND ENVIRONMENTAL RISK FACTORS FOR SCHIZOPHRENIA: CAN WE DISTINGUISH THE ONE FROM THE OTHER?

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Background: Family, twin and adoption studies have documented a substantial genetic role in the etiology of schizophrenia, and several risk factors likely to represent environmental exposures are well documented. A prevailing paradigm is now that multiple genes interact with environmental factors in causing schizophrenia. However, since many relevant etiological factors are unknown, and several are likely to be correlated, this raises several methodological problems as to how to identify genetic and environmental risk factors and how to tease apart their effects. Methods: In the

presentation I will present results from different study designs including register-based follow-up studies of a total national population, combination with sibling controls, uses of twins and their offspring, and the combination of register data and genetic and environmental data obtained from neonatal blood samples from a total National birth cohort. I will highlight the effect both of factors that normally are perceived as environmental (eg, obstetric factors), and measures that often are assumed to represent genetic risk (eg, psychiatric family history. Results: The results suggest that some risk factors, that generally are perceived as environmental more likely may reflect shared familial factors, whereas psychiatric family history as a risk factor for schizophrenia may be less closely tied to genetic variation than previously assumed. Conclusion: The combination of different study designs and data sources challenge the traditional gene environment dichotomy in schizophrenia research. I will discuss how these results might inform the general field of studies of risk factors for schizophrenia.
ID: 978274

MATERNAL ANTIBODIES TO CYTOMEGALOVIRUS AND SCHIZOPHRENIA RISK

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Background: Several studies have linked maternal infections to the risk of schizophrenia in their offspring, and three recent studies have associated maternal antibodies against Herpes Simplex Virus 2 with schizophrenia risk. Another Herpes virus, Cytomegalovirus (CMV), has been associated with schizophrenia risk in studies comparing patients to controls and it has been suggested that CMV interacts with variation in the MICB gene. No studies have documented an effect of maternal CMV on schizophrenia risk. Methods: A case-control study nested within the national Danish birth cohort constituted by the PKU Biobank covering all children born in Denmark since 1981. 602 cases of schizophrenia (ICD-10 F20) were ascertained in the Danish Psychiatric Central Register, covering all in- and out-patient contacts in Denmark, and 602 controls were matched individually on gender, exact date of birth and living in Denmark on the date the case became a case. Incidence rate ratio for schizophrenia was estimated using conditional logistic regression. Main exposure was CMV IgG antibody levels. This dataset has now been expanded to include app 900 cases and 900 controls, and genome-wide markers from the Illumina 610-k chip have been added. Results: In the initial sample of 602 cases of schizophrenia and 602 population controls we find an elevated risk of schizophrenia in males (IRR 1.9 95% confidence limits 1.2–2.9) but not in females. There was no association in females(IRR .8 95% confidence limits .5–1.2). Conclusion: The preliminary data suggest that maternal CMV antibodies may indicate an increased for schizophrenia, and that this association is confined to males. In the presentation I will present the analysis of an extended cohort of 900 cases and 900 controls and further explore the interaction with gender, other known risk factors for schizophrenia and genome-wide snp data.
ID: 978250

DUP AND CANNABIS CONSUMPTION IN A SICILIAN FIRST EPISODE PSYCHOTIC (FEP) SAMPLE

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Background: Cannabis consumption in adolescence increases the risk of developing schizophrenia in adulthood and some studies suggest that illicit drug use can be associated to an earlier onset of the disorder in first episode psychotic patients. Recent studies underline an association between cannabis consumption and duration of untreated psychosis (DUP) (Barnes et al 2006). The Section of Psychiatry of Palermo University in collaboration with the Institute of Psychiatry, King's College of London is carrying out an incident and case-control study on psychotic patients at their first episode of psychosis. In this work we would like to investigate the interactions between DUP and cannabis consumption in our sample. Methods: Our sample is made of 74 patients (69% males), 97.3% Caucasians. Data on DUP have been collected by the Nottingham Onset Schedule (Singh et al, 2005) and cannabis consumption data by Cannabis Experience Questionnaire (Barkus et al, 2006) on 55 subjects. Results: The mean DUP is 40.4 weeks. Patients who currently smoke cannabis have a shorter DUP than non-smokers ($P = .023$) and a earlier age of onset with a trend towards significance ($P = .064$). No correlation between DUP and PANSS scores has been found. Conclusion: Our results support the evidence that cannabis consumption can be associated to an early onset of psychosis. Further, patients smoking cannabis who become psychotic are referred earlier to mental health services. This could be due to several reasons (symptoms severity, social factors), but according to our data there aren't any correlation between DUP and symptoms severity.
ID: 979360

CHILDHOOD TRAUMA AND PSYCHOSIS: A CASE-CONTROL AND CASE-SIBLING CONTROL COMPARISON ACROSS DIFFERENT LEVELS OF GENETIC LIABILITY, PSYCHOPATHOLOGY AND TYPE OF TRAUMA

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Background: The aim of this paper is to investigate the association between different types of childhood trauma (abuse and neglect) and different psychosis symptom domains across samples defined by (i) psychotic illness (n = 271 patients), (ii) high psychosis vulnerability (n = 259 siblings of patients) and (iii) average psychosis vulnerability (n = 227 controls). Methods: Childhood trauma was assessed with the Childhood Trauma Questionnaire. Symptoms were assessed with the Positive and Negative Syndrome Scale in the patient sample and with the Structured Interview for Schizotypy-Revised in the sibling and control samples. Results: Childhood trauma was associated with psychotic disorder in a dose-response fashion in the case-control comparison (adjusted OR = 4.53, 95% CI: 2.79, 7.35, $P < .001$). The sibling-control comparison suggested a degree of trauma shared with the patient relative (adjusted OR = 1.61, 95% CI: .95, 2.61, $P = .05$), but the case-sibling comparison indicated much higher level of exposure in patients compared to siblings (adjusted OR = 2.60, 95% CI: 1.78, 3.78, $P < .001$). Childhood abuse but not childhood neglect predicted positive but not negative symptoms in a dose-response fashion in all three groups. There was no evidence for moderation by sex. Conclusion: Discordance in psychotic illness across related individuals can be traced to differential exposure to trauma. The association between trauma and psychosis is apparent across different levels of illness and vulnerability associated with psychotic disorder, suggesting true association rather than reporting bias,

reverse causality or gene-environment correlation. Psychotic illness in vulnerable individuals may arise as a consequence of the level and frequency of exposure to abuse rather than neglect, suggesting symptom-specific and exposure-specific underlying mechanisms.
ID: 979206

6-YEAR FOLLOW UP OF THE MESIFOS INCIDENCE COHORT

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Background: From 2002 to 2004 128 first episode schizophrenic patients were assessed regarding their pathology, social functioning, DUP, medication use and many other areas. They were recruited for a clinical trial (MESIFOS) comparing two medication strategies (continuation vs discontinuation of antipsychotics after stable remission). Relapse rates were twice as high in the discontinuated patients, but general outcome did not differ. Discontinuated patients were more often medication free and were lower in total medication consumption over a two year period, as intended. In a new study the cohort was followed up 6 years after this trial. The aim of this study was to follow up the patients in both conditions to see whether they differ in relapse rates and remission and recovery after six years. Also the patterns of medication use were established for both groups. A group of 14 patients were successfully discontinued in the original study, without sustaining a relapse. The question is whether they managed to remain drug-free without sustaining a relapse. Methods: The original cohort was traced and asked to participate. The interviews comprised schedules about pathology (PANSS), social functioning (GSDS), use of care, medication use, relapse, hospitalizations (Life Chart Schedule), substance use and remission and recovery (Andreasen criteria). Data collection covered the entire 6-year period. Results: Out of the original 128 probands, 105 were interviewed, of 18 sufficient information was available to make reliable assessments about critical research measures. Data collection has just been completed. No definitive outcome is avaliable at this point. In this presentation outcome for both treatment groups will be presented regarding medication use, relapse, course and remission and recovery. Outcome of the entire group of $N = 123$ will be compared to relevant earlier studies. Conclusion: No conclusions are available at this time
ID: 978351

INVESTIGATION OF HOW KNOWN RISK FACTORS FOR SCHIZOPHRENIA INCIDENCE IMPART RISK FOR SPECIFIC SCHIZOPHRENIA SUBTYPES

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Background: Of great importance in the etiology of schizophrenia is the discovery of how certain factors (ie urban birth, obstetric complications) impart increased risk for the disorder. This study investigates that question by examining if certain factors, known to increase risk for the disorder broadly, impart risk for the whole group of schizophrenias, or rather one of the subtypes. Schizophrenia subtypes were generated based on symptom ratings at onset of the disorder. The goal of this analysis was to identify homogenous subgroups with distinct risk factors. Methods: The sample includes 578 persons with first episode psychosis that participated in the OPUS trial, a randomized clinical trial comparing two years of an intensive early intervention program with standard treatment (Jørgensen et al, 2000). Data on risk factors were drawn from the Danish Psychiatric Central Registry and other Danish social registries. First, latent classes of the clinical presentation of first episode psychosis were formed based on symptoms obtained from the Scale for Assessment of Positive Symptoms (SAPS) and Scale for Assessment of Negative Symptoms (SANS), which was completed at entry into the study (Andreasen, 1983; Andreasen, 1984). Then, established risk factors for incidence (ie birth month, place of birth, family history, obstetric complications, immigrant status, paternal age, and cannabis diagnoses) were examined in relation to symptom class using latent class regression. Results: The latent class model with 4 symptom classes (global severe, moderate-severe, moderate-severe with good attention, and hallucinations/delusions) provided the best fit to the data. Preliminary results suggest that place of birth, birth month and sex are associated with symptom class. Conclusion: Individual factors were found to increase risk for specific symptom classes, suggesting that these factors may impart risk differently across the group of schizophrenias. This suggests that the symptom subtypes may represent forms of the disorder with differing etiologies. This work was supported by the National Institute of Mental Health Psychiatric Epidemiology training grant 5T32MH01492.
ID: 979841

THE RELATIONSHIP OF SOCIAL CLASS OF ORIGIN TO THE DURATION OF UNTREATED PSYCHOSIS AND AGE AT PRESENTATION IN INDIVIDUALS PRESENTING WITH A FIRST EPISODE OF PSYCHOSIS

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Background: Individuals diagnosed with schizophrenia from a higher social class of origin have been found to present to the mental health services at a younger age. This effect may be mediated by a number of factors including DUP. We examined the effect of social class of origin on age at presentation in individuals with a first episode psychosis. We explored the relationship between social class of origin, DUP and age at presentation. Methods: The social class at birth of two prospective cohorts of individuals ($n = 513$) experiencing a FEP in Ireland were obtained from birth records and clinical interview. We classified social class according to the father's occupation at the time of the subjects birth and we coded social class according to the Census of Population Classification of Occupations. Results: Individuals with a FEP from a higher social class at origin presented at a younger age than individuals from a lower social class at birth. ($P < .01$) The mean age of presentation of individuals from the higher social classes was 28.8 years (sd = 9.6) and for individuals from the lower social classes, the mean age was 32.0 (sd 12.5). This finding was consistent within the subgroup of individuals who were diagnosed with schizophrenia or schizophreniform disorder. ($P = .05$) However, this difference in age at presentation was not explained by a shorter duration of untreated psychosis for individuals from higher social classes, with there being no difference in the duration of untreated psychosis according to social class. ($\chi^2 = .28$, $P = .60$). Again, this finding was consistent within the subgroup of individuals diagnosed with schizophrenia or schizophreniform disorder. ($\chi^2 = .68$, $P = .41$). Conclusion: Individuals from higher social classes experiencing a first

episode of psychosis present to the mental health services at a younger age, however this is not explained by a shorter DUP. Further exploration of this finding could reveal interesting insights into the social and biological etiologies of psychosis.
ID: 978732

VALIDATION OF SUICIDE AS CAUSE OF DEATH IN CASES OF UNDETERMINED MANNER OF DEATH IN SCHIZOPHRENIA IN SWEDEN

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Background: Around 5% of the patients suffering from schizophrenia will die from suicide. Research dealing with suicide is of great importance to improve the prognosis of schizophrenia. Most definitions of suicide include the intention or will of the patient who commits suicide. The epidemiological knowledge we have about suicide is based on register studies. The aim of this study is to validate the cause of death register in cases of undetermined manner of death for schizophrenic patients in Sweden. Methods: The patients have been selected using information from the Patient Register and the Cause of Death Register of the Swedish National Board of Health and Welfare. Patients from four different counties in Sweden, suffering from schizophrenia, who have died from suicide or where the cause of death has been uncertain have been selected. All cases with an undetermined manner of death were further investigated. The pathology records for these cases have been evaluated using a scoring system based on known risk factors for suicide and common sense. The scoring system arranges the cases with an undetermined cause of death into three categories. One where suicide is apparently the likely cause of death (group 1), one where suicide is possibly the cause of death (group 2) and one group where suicide is unlikely the cause of death (group 3). Results: A total number of 514 suicide cases have been identified. 285 cases with an undetermined manner of death have been examined. Using the created scoring system 56 of the 285 cases were classified as likely suicides (group 1), 127 as possible suicides (group 2) and in 102 cases the cause of death was classified as unlikely to be suicide. The ratio between certain suicides and cases with an undetermined manner of death in the different counties examined, was found to be 133/118 (Stockholm), 26/42 (Uppsala), 62/42 (Linköping), 293/83 (Skåne). Conclusion: If you include the group of cases with an undetermined manner of death when studying suicide you are likely to overestimate the cases with 13% (102/799). If you choose to only include certain cases of suicide from the cause of Death Register you are likely to dilute the results or underestimate the problem with 36% (183/514). The differences in ratios between certain suicides and cases with an undetermined manner of death in the counties studied, imply that there is a need for national guidelines in forensic medicine to determine what should be classified as a suicide.
ID: 978552

DURATION OF MARRIAGE AND RISK OF SCHIZOPHRENIA IN OFFSPRING

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Background: A significant relationship exists between risk of schizophrenia and advancing paternal age. Father's age is strongly associated with other demographic factors such as duration of marriage and paternal age at marriage. Marital status, as well as marriage duration has now been linked to a variety of outcomes, both in patients with schizophrenia as well as in population-based studies. In order to better understand the role of duration of marriage of parents as a risk factor for schizophrenia and to disentangle it from paternal age, we conducted a new analysis of data from the Jerusalem Perinatal Study (JPS). Methods: We examined the relationship of key variables (parents ages, duration of marriage) and covariates in the cross-linked databases of the Jerusalem cohort (born 1964–1976) and Israel's nationwide Psychiatric Registry. Effects of duration of marriage on risk of schizophrenia in offspring were estimated using Cox proportional hazards models, controlling for parents' ages. Results: Offspring with schizophrenia were identified from the cohort of 90 079 available for study. The duration of marriage was inversely related to the offspring's risk of schizophrenia. The adjusted relative risk for offspring of born <3, 3–4 and 5–9 years after their parents were married was 1.53 (1.11, 2.10), 1.38 (1.05, 1.81) and 1.11 (.87, 1.42), compared with parents married for 10+ years. This effect was in the opposing direction of the effect of advancing paternal age. In contrast, the father's age at marriage was unrelated to schizophrenia risk in the controlled analyses. In a stratified analysis, men with advanced paternal age and short duration of marriage conferred the highest to their offspring. Conclusion: Shorter duration of marriage and advanced paternal age were both independently associated with a greater risk of schizophrenia in the offspring. This suggests two potential pathways or mechanisms may be at work, one associated with marriage duration, possibly mediated by social factors, stress, or isolation and another associated with changes in male reproductive health. The effect of duration of marriage on schizophrenia risk in offspring should be further considered for other studies of schizophrenia and birth order, paternal age, and related factors.
ID: 979655

DO OLD CHICKENS MAKE GOOD SOUP? MATERNAL AGE, PARITY, AND SOCIOECONOMIC BACKGROUND AS PREDICTORS FOR PSYCHOSIS

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Background: Among the environmental risk factors for schizophrenia obstetric complications (OCs) are one of the most well-documented. The most common predictors of the occurrence of OCs in the general population are parity, maternal age (<20 and >34 years), and poor socioeconomic background (Cantor-Graae et al, 1997). As these parental attributes influence OCs, the present analyses serve as a preliminary exploration of whether these attributes constitute a risk for psychosis in themselves. Methods: We collected sociodemographic data (age, gender, self-rated ethnicity, level of education achieved and employment status) on 346 first episode psychotic cases and 258 controls. All participants were asked about their father's main job at time of birth. Data on parental age and parity were obtained from the Family Interview for Genetic Studies (FIGS). Logistic regression was used to analyze the relationships between demographic factors (parental age, parity, and socioeconomic background) and case- control status, and to test for interaction effects while controlling for potential confounders. Associations are expressed as odds ratios. Results: There was no significant difference in term of maternal parity at birth ($P = .17$). Regarding parental age there were no significant associations between psychosis and paternal age ($P = .6$). In contrast mothers of psychotic offspring were slightly younger than controls (Mean difference = 1.57 years; $P = .07$). Moreover the risk of becoming psychotic is increased 5 fold when the mother is younger than 20 years old (adjusted OR= 5.009; CI 2.41, 10.42). Finally there was no significant difference in term of socioeconomic

background(P = .28). Conclusion: The offspring of younger mothers are increased risk of developing psychosis possibly because such women are at greater risk for OCs such as low-birth weight, premature, and small-for-gestational-age infants (Fraser et al, 1995; Ip et al, 2010).
ID: 975768

EVIDENCE OF AN ASSOCIATION BETWEEN ASTHMA AND SCHIZOPHRENIA

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Background: Several studies have suggested that there is an association between atopic disorders and some psychiatric illnesses, bur only one study has investigated an association with schizophrenia. Methods: All people born in Denmark between 1977 and 1992 (N = 847 426) were followed for the development of schizophrenia (3809 cases) during 7 million person-years at risk. Information of schizophrenia and asthma on cohort members and their siblings and parents was established through linkage of the Danish Psychiatric Central Register and the Danish National Hospital Register. Data were analyzed using log-linear Poisson regression. Results: Schizophrenia was significantly associated (RR = 1.43 (1.19, 1.70), P <.001) with severe asthma, and this was confirmed when comparing to sibling controls. The risk of schizophrenia was most elevated the first 5 years after asthma was first diagnosed, but continued to be elevated. In addition a family history of asthma in at least two first degree relatives was a risk factor for schizophrenia (RR = 2.23 (1.28, 3.57), P = .002). Conclusion: Our results suggest that asthma and schizophrenia are associated in a way that could be explained by common etiologic pathways for both disorders.
ID: 977495

AN INVESTIGATION OF EMOTIONAL PROCESSING IN ADOLESCENTS WITH PSYCHOTIC-LIKE SYMPTOMS: A SCHOOL-BASED SAMPLE FROM THE GENERAL POPULATION

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Background: Individuals with schizophrenia appear to show deficits in the identification of facial affect at all stages of the illness. However, little is known about face processing among individuals with psychotic-like symptoms. The current study examined the recognition of emotional expressions in children and adolescents who reported experiencing psychotic-like symptoms and in a control sample of children. Methods: In total, 798 10–13 year olds completed the following pen and paper assessments in their classrooms: (1) a screening questionnaire with 7 items designed to assess psychotic-like experiences (APSS), (2) the Penn Emotion Recognition Test (PERT), and (3) the Strengths and Difficulties Questionnaire (SDQ). The PERT presents 40 pictures of faces with expressions representing happy, sad, scared, angry and no feeling. Results: Overall, participants were best at identifying happy faces (M = 7.59, SD = .91) and were worst at identifying sad faces (M = 4.9, SD = 1.46; P <.001). In total, 24.9% of the overall sample answered ''Yes, definitely'' to 2 or more questions on the psychosis screener and 8% of the overall sample was ''Abnormal'' based on the total difficulties score of the SDQ. Participants with Abnormal scores on the SDQ scored significantly lower than those with ''Borderline'' and ''Normal'', on the total scale score of the PERT (P = .019) and on the Happy faces subscale (P = .031). There were no significant differences on any of the PERT scores for participants who did and did not endorse psychotic-like symptoms with or without adjustment for SDQ scores. Conclusion: We conclude that deficits in emotional processing of persons with schizophrenia were not evident among a sample of 10–13 year olds who self-reported psychotic-like symptoms.
ID: 978277

AN ECOLOGICAL STUDY OF PSYCHOTIC SISORDERS IN GUAM: EXPLORING SOCIAL RISK FACTORS

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Background: Higher incidence rates of psychotic disorders have been reported for ethnic minority groups and immigrant populations. Many researchers have turned to environmental and social risk factors in understanding these higher rates. A scarcity of research in the U.S., however, continues in this area. This study examined the effects of social risk factors on the incidence of psychotic disorders in Guam, a U.S. territory in Micronesia. Guam's ethnically diverse population, its geographical location, its rapid development in the last half century, its strategic role in the U.S. militarism, and its socio-political status as an unincorporated territory of the U.S. created a tapestry of complex social variables that have yet to be examined in the onset of psychosis. Methods: All first onset cases of psychotic disorders (N = 423) in a three year cohort (2005–2007) that presented to the Guam Department of Mental Health and Substance Abuse (DMHSA) were examined. Both individual (age, gender, ethnicity) and neighborhood (urbanicity, crime, ethnic density, poverty, and voter turn-out) level risk factors were explored. Results: Results indicated that after controlling for individual risk factors, neighborhoods with high Micronesian ethnic density had higher incidences of psychotic disorders (OR = 4.63, P <.001). In addition, all Micronesian groups had higher incidence rates of psychotic disorders than either Whites or Asians. The Chamorros, Guam's indigenous group, had a rate of psychosis almost double that of Whites or Asians (Chamorro IRR = 1.06; Whites IRR = .63; Asian IRR = .59) while groups from the outer Micronesian islands had even higher rates of psychosis (Chuukese IRR = 2.62; Palauan IRR = 7.16; other Pacific Islander IRR = 1.98). Neighborhood crime was also indicative of higher psychoses incidence rates (OR = 14.67, P <.01). Conclusion: The results indicated that, as has been found in other studies, some ethnic groups that had immigrated to Guam (the Chuukese, Palauans, and other Pacific Islanders) had the highest rates of psychosis. Unlike other research, other immigrant groups (Whites and Asians) had lower rates of psychosis than the indigenous population. Rates of psychosis, however, correlated strongly with the group's marginalization from power using an index developed by Burns & Esterhuizan (2007). The results add to the literature which suggests that socially mediated factors such as marginalization and social defeat may play a role in the development of psychosis.
ID: 978556

PROSPECTIVE STUDIES OF AUDITORY HALLUCINATIONS IN CHILDREN: A SYSTEMATIC REVIEW

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Background: Auditory hallucinations (AH) out of a psychotic context have been reported to be frequent in individuals before the adult age. However, the clinical and theoretical significance of these symptoms is not yet clear. The primary question to review was the association between this phenomenon and its outcome concerning persistence or transition to psychosis. We also reviewed risk factors involved in either persistence or transition.

Methods: Bibliographical research was conducted introducing a query of 3 items (using several synonymous) in 5 search engines. Studies that fulfilled inclusion but not exclusion criteria were reviewed using a comprehensive battery of quality assessment questions as a reference. Several epidemiological measures were used. Results: Ten studies were included, which despite methodological differences showed persistence rates (7%–42%), discontinuation rates (53%–93%), debut after baseline (83%–74% and 12.5), ORs to transition to psychosis (OR = 16–0). Most agreement was found on higher score on general psychopathology measures and features of AH. Most of the remaining factors analyzed showed poor value or discrepancy. Disparity of results was explained upon critical appraisal of original works. Conclusion: Nonpsychotic AH is a relatively frequent phenomenon in children and adolescents that disappears most of the times. Special attention should be payed to cases reporting high levels of general psychopathology and features indicating severity of the AH, as these factors are more frequently associated to cases that play a transition to psychosis.
ID: 986623

CANNABIS USE IS ASSOCIATED WITH SUB-CLINICAL PSYCHOSIS SYMPTOMS IN NON-CLINICAL POPULATION: EVIDENCE FROM SNOW-BALL SAMPLE

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Background: The aim of the present study is to exploring the associations between pattern of cannabis use and the dimensions of psychosis measured with the of the Community Assessment of Psychic Experiences (CAPE) (34) in a nonclinical population from snow ball sample. Secondly we explore the interaction between COMT Val158Met genotype and cannabis use on psychosis. Methods: The cases were daily cannabis user in the last year for at least one month, and the control those who did not smoke cannabis diary in the last year . Both case and control was identified by snow ball sample. Lifetime drugs use was recorded using the L section of the Composite International Diagnostic Interview (CIDI). Psychometric psychosis liability in lifetime was assessed with the CAPE. We apply the four factor reported by Stefany et al 2004 Two hundred and two subjects were included. One hundred and one were daily cannabis user in the last year. The mean age was 27.1 ± 5.8 years. Results: Daily cannabis use compared with non-daily cannabis use increased significatively voices experiences [25(25%) vs 8(8%); OR (IC95%) = 3.8 (1.8–8.9); $P = .001$], mania experiences [56(55%) vs 39(39%); OR (IC95%) = 2.0 (1.1–3.5); $P = .01$], and first rank experiences[38(38%) vs 15(15%); OR (IC95%) = 3.4 (1.7–6.9); $P = .0001$],. After adjusting by sex, age, social exclusion and heavy non-cannabis drugs use, voices and first rank experiences remained significative (0R (IC95%) = 3.2 (1.2–8.6); $P = 0.02$ and OR (IC95%) = 5.3 (2.2–13); $P = .0001$ respectively.).However mania did not remained significative after adjusting by other drugs. Paranoid experiences did not show association with daily cannabis use. We explore dose-response effect between the fours dimensions of psychosis and three levels of frequency cannabis use: non-daily, daily and more than five cannabis cigarettes' a day. Voices and first rank experiences were consistent with a dose-response.($P = .004$ and $P = .0001$ respectively). We explore the interaction between cannabis use (daily vs no daily) and COMT Val158Met genotype for presence four dimension of psychosis.. We found not interaction between the COMT met 158 and the four dimension. Conclusion: In conclusion, in our study those who smoke cannabis showed more prevalence of voices and first rank experience, and this association showed a doses effect response. Finally we did not found evidence of interaction between cannabis use and Catechol-O-Methyltransferase Val158Met gen
ID: 978527

ARE PSYCHOTIC-LIKE EXPERIENCES A VALID ESTIMATE OF ATTENUATED AND FRANK POSITIVE PSYCHOTIC SYMPTOMS? THE ROLE OF SUBJECTIVE DISTRESS, PREOCCUPATION AND CONVICTION.

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Background: Epidemiological studies reported a high prevalence of psychotic-like experiences (PLEs) that were also argued a measure of attenuated psychotic symptoms (APS) in the general population. From this line of argument, it was cautioned against an inclusion of a "Attenuated Psychotic Symptoms Syndrome" into DSM-V, as APS might not sufficiently distinguish ill and non-ill persons in the general population. Yet, the applied assessments of PLEs had not been designed to assess APS. Therefore, the correlation between PLEs and APS was studied. Methods: PLEs were assessed with Peter's Delusion Inventory and the revised Launay-Slade Hallucination Scale, psychotic symptoms (PS) and APS with the Structured Interview for Prodromal Syndromes in 71 persons seeking help at an early recognition service, FETZ (59% without psychosis or at-risk status according to ultra-high risk according to the SIPS or basic symptom criteria according to the SPI-A). Results: In the clinical interviews conducted by professionals, at least any one APS and/or PS was found in 24 (33.8%) patients, while, in the questionnaires, 98.6% reported PLEs when simple agreement was rated, and still 51.4% when a certain level of agreement, distress, preoccupation and conviction was required. Even if these additional qualifiers were accounted for, the explained common variance of PLEs with PS and/or APS did not exceed 20%. Conclusion: PLEs cannot be considered as a valid approximation of PS or APS as defined in early detection research even if additional qualifiers are used. Thus, self-report scales of PLEs are no valid screening tool for an increased risk for psychosis in terms of APS in the general population. Additionally, the prevalence of APS in the general population cannot be deduced from epidemiological studies of PLEs but warrants dedicated studies, in which at-risk symptoms are assessed in a way that equals their clinical evaluation.
ID: 986648

IS CANNABIS USE ASSOCIATED WITH SOLITARY LIFE STYLE IN BOTH PATIENTS FIRST EPISODE OF PSYCHOSIS AND HEALTHY VOLUNTEERS?

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Background: Recreational use of cannabis is very common among both first episode psychosis patients and the general population. Substance misuse is often associated with disrupted life style as psychosis onset is associated with lack of social network. Our aim is to test if there is a differential association between cannabis use and life style when we compare cannabis users at their first episode of psychosis and healthy controls users. Methods: Using the Social Data Schedule and the Cannabis Experience Questionnaire (modified version) we collected detailed socio-demographic and cannabis data as part of the Genetic and Psychosis Study, GAP, from 210 first episode psychosis patients and 120 healthy controls. All our cases were recruited from the South London & Maudsley National Health Service

(NHS) Foundation Trust, and the control group of cannabis users from the local population. Results: First episode patients smoking cannabis are more likely to live alone than controls who smoke cannabis (35% vs 13%; P = .000). Those cases who did not live alone where more likely to be living with parents (35% vs 22%; P = .016) rather than with a partner (7% vs 27%; P = 0.000) or friends (22% vs 38%; P = .002). More interestingly cases who used cannabis are more likely to be single than controls (78% vs 56%; P = .000) and less likely to have been able to sustain a long-term relationship, one or more years, (73% vs 84%; P = .025). Conclusion: Cannabis use does not seem to affect the social network in healthy controls but our data suggest that perhaps cannabis use increases the vulnerability to social isolation in individuals suffering their first episode of psychosis.
ID: 979472

EVIDENCE THAT ONSET OF PSYCHOSIS IN THE POPULATION REFLECTS EARLY HALLUCINATORY EXPERIENCES THAT THROUGH ENVIRONMENTAL RISKS AND AFFECTIVE DYSREGULATION BECOME COMPLICATED BY DELUSIONS

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Background: The delusions and hallucinations observed in psychotic disorder are considered as symptoms that naturally pertain to the same a-theoretical "class" of positive symptoms, yet refer to very different phenomena. We examined the hypothesis that the "natural" combination of delusions and hallucinations observed in psychotic disorder in fact represents a selection of individuals with poor outcome of early perceptual alterations because of secondary delusional ideation associated with environmental exposures and affective dysregulation. Methods: In the Early Developmental Stages of Psychopathology, a prospective, 10-year cohort study of a population of adolescents and young adults in Munich, Germany (n = 2524), hallucinations and delusions were assessed with the Composite International Diagnostic Interview at two time points (T2 and T3). Analyses compared differences in psychopathology, familial liability for non-psychotic disorder, non-genetic risk factors, persistence and clinical outcome between groups: (i) absence of positive psychotic symptoms, (ii) presence of isolated hallucinations, (iii) isolated delusions and (iv)both hallucinations and delusions. Results: Delusions and hallucinations occurred together much more often (T2: 3.1%; T3: 2.0%) than predicted by chance (T2: 1.0%; T3: .4%; OR = 11.0; 95% CI: 8.1, 15.1). Content of delusions was contingent on presence of hallucinations but modality of hallucinations was not contingent on presence of delusions. The group with both hallucinations and delusions, compared to groups with either isolated delusions or hallucinations, displayed the strongest associations with familial affective liability and non-genetic risk factors, and with persistence of psychotic symptoms, comorbidity with negative symptoms, affective psychopathology and clinical need. Conclusion: The early stages of psychosis may involve hallucinatory experiences that, if complicated by delusional ideation under the influence of environmental risks and (liability for) affective dysregulation, give rise to a poor-prognosis hallucinatory-delusional syndrome.
ID: 978422

PREFERENCES, SATISFACTION AND GOALS FOR TREATMENT IN PSYCHOSIS PATIENTS

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Background: Insight in preferences, satisfaction and goals of patients is important for reaching treatment alliance and may increase the success of initiated treatment. This is particularly important for people suffering from severe mental illness, like schizophrenia and other psychotic disorders. Although indicated as an important focus for patients and relatives, research is sparse. The current study, investigates these aspects in a large sample of patients with psychotic disorders in The Netherlands. Methods: Participants from the whole of The Netherlands, with at least 1 psychotic episode, were asked to fill in a questionnaire on an especially for this study designed website. Participants were recruited through associations for patients and family members, by psychiatric nurses at various institutions and through the Dutch GROUP study. Participants were asked to rank their priorities in treatment, to state whether they were satisfied on these items and to rank a list of treatment goals. Results: 462 respondents ranked their treatment preferences (mean age: 40.3 years, SD 11.4; mean duration of illness: 13.5 years, SD 11.1). The four items ranked as most important were: "early help, preferably in own environment" (35% unsatisfied or very unsatisfied); "attention for medication" (33% unsatisfied or very unsatisfied); "appropriate attitude of the professional caregiver" (28% unsatisfied or very unsatisfied) and "supportive counseling" (35% unsatisfied or very unsatisfied). More than half of the respondents rated "unsatisfied" or "very unsatisfied" in the following items: "practical help in resocialization", "aid to acquire autonomy" and "help with physical health". 345 participants ranked a list of treatment goals (mean age: 40.4 years, SD 11.0; mean duration of illness: 13.7 years, SD 10.8). The four ranked as most important were: "reduction of apathy and lack of initiative"; "reduction of disturbing or unusual experiences, such as voices and paranoia"; "reduction of confusion and concentration problems"; "increase of sensible activities". Conclusion: This study represents a large sample of patients with a psychotic disorder in The Netherlands. The results suggest that psychiatric services should pay great attention to early outpatient intervention with supportive counseling and an appropriate attitude of the caregiver with attention for medication use. Improvement is warranted for practical help in resocialization, aid to acquire autonomy and help with physical health.
ID: 975603

PATHWAYS TO SCHIZOPHRENIA: THE IMPACT OF SOCIAL DISADVANTAGE IN CHILDHOOD

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Background: Accumulating evidence suggests that adverse social experiences in childhood and in adulthood can increase risk of psychosis. Separation from, or loss of, a parent during childhood have been associated with family conflict, socio-economic disadvantage and neglect and abuse. However, there have been only a few studies considering these variables in relation to psychosis. Using data from a case-control study of first-episode psychosis, we investigated the relationship between long term separation from, and

death of, a parent before the age of 17 and the risk of adult psychosis. Furthermore, for the first time, we looked at number of family arrangements in cases and controls. Methods: We collected data relating to separation from, and death of, one or both parents before the age of 17 from a sample of 255 individuals with their first episode of psychosis and 194 healthy control subjects from the local population. We defined long-term separation as a separation (not living in same household) from one or both parents for 6 months or more resulting from family breakdown (parental separation or divorce, parents abandoned subject) before the age of 17. Results: Compared with controls, cases were approximately two times more likely to have experienced a long-term separation from one or both parents before the age of 17 (OR 1.99, 95% CI 1.28, 3.07), and approximately three times more likely to have had a parent die before the age of 17 (OR 2.81, 95% CI 1.28, 6.16). Cases were 2.58 times (95% CI 1.70, 3.90) more likely than controls to have had 2 or more family arrangements before age 17. Conclusion: We found strong evidence that separation from, and death of, a parent before age of 17 were both associated with a two- to threefold increased risk of psychosis, independent of a number of potential confounders. When number of family arrangements was analysed, cases were more likely to report 2 or more arrangements, indicating that this variable may be considered an early marker for psychosis.
ID: 979160

BIRTH WEIGHT AND SCHIZOPHRENIA: A FAMILY STUDY

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Background: Longitudinal cohort studies have implicated an association between low birth weight and schizophrenia. It has been suggested that obstetric complications may only increase the risk of schizophrenia in the presence of genetic susceptibility to the disease. Based on this, we hypothesized that the effect of birth weight on the risk of schizophrenia is pronounced in families with high genetic loading for schizophrenia. Methods: We investigated the association between birth weight and schizophrenia in a large Finnish schizophrenia family study sample. We utilized the birth weight data of 1051 offspring from 315 Finnish families. The families had been recruited based on two criteria: (1) there were at least two affected siblings in the family, or (2) the family belonged to an internal isolate with an exceptionally high lifetime risk of schizophrenia. We used a multivariate COX frailty model, with family as the frailty term, to analyze the effect of birth weight on the risk of developing schizophrenia within the families. The analyses were adjusted for sex, birth cohort, study sample (isolate vs. all Finland), and maternal and paternal mental illness. Using information from the Medication Reimbursement Register and parent interviews we further investigated the association of maternal type 2 diabetes, a proxy for gestational diabetes, and the development of schizophrenia among offspring. Results: High birth weight (>4000 g) was associated with a 1.7-fold increase in the risk of developing schizophrenia compared with intermediate birth weight individuals. The association between low birth weight (<2500 g) and schizophrenia was not statistically significant. Maternal diabetes at the time of data collection was associated with a 1.7-fold increase in the risk of developing schizophrenia among offspring, independently of offspring's birth weight. Conclusion: The benefit of investigating the effect of birth weight within families is that the shared genetic and environmental effects influencing birth weight within families are adjusted for. We found that high birth weight increases the risk of schizophrenia in families with high genetic loading for schizophrenia. Our results also point to a potential, birth weight independent, association between maternal type 2 diabetes and schizophrenia among the offspring.
ID: 978191

PREDICTING PSYCHIATRIC HOSPITAL CARE AMONG ADOLESCENT OUTPATIENTS

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Background: Severe mental disorders usually develop gradually, and initial outpatient care is an excellent opportunity for detecting such a disease course. However, the applicability of current psychosis-risk criteria in this setting is currently unclear, as prospective studies typically focus on a highly selected population referred to specialized clinics. Methods: We administered the Structured Interview for Prodromal Syndromes (SIPS) to 174 first-admission adolescent psychiatric patients; 62 met criteria for one or more prodromal syndromes. Psychiatric hospital admission data were collected for 1–6 years from the Finnish National Hospital Discharge Register. Results: Besides the predictiveness of the psychosis-risk criteria, we examine the usefulness of four main latent symptom dimensions of the SIPS, as well as their interactions. Using a Cox proportional hazards model, we estimate their impact on psychiatric hospitalization risk. Conclusion: Current psychosis-risk criteria are shown to create a large number of false positives.
ID: 979419

EXPERIENCE OF CHILDHOOD TRAUMA AND TRANSITION TO PSYCHOSIS: ANALYSIS FROM A LARGE "AT RISK" FOR PSYCHOSIS COHORT

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Background: Studies indicate a high prevalence of childhood trauma, both in patients with psychotic disorders, and those "at risk" of developing psychosis. This has lead researchers to postulate a causal link between childhood trauma and onset of psychosis. We aimed to examine the association between previous experience of trauma and "conversion' to psychosis in a large "Ultra High Risk" (UHR) for psychosis cohort. Methods: All UHR patients recruited to research studies at the PACE clinic, Melbourne between 1994 and 2006 were systematically followed-up. The participants completed a comprehensive assessment battery, which included the Childhood Trauma Questionnaire (CTQ), a self-report questionnaire that assesses experience of childhood trauma. The Comprehensive Assessment of At Risk Mental State (CAARMS) was used to determine if, and when, psychosis threshold had occurred. The relationship between CTQ scores (total and sub-scores) and transition to psychosis was explored using cox regression. Results: 233/416 (56.0%) UHR individuals in the cohort completed the CTQ at follow-up. Data on transition status was available

for 411 (98.8%) subjects. The average score on the CTQ was 47.8 (SD, 18.4). Overall score on the CTQ was not associated with transition to psychosis. Of the trauma types, only sexual trauma was associated with transition to psychosis ($P = .02$). The risk for an individual reporting high rates of sexual trauma was more than 4 times that for those reporting low rates of trauma. Higher sexual trauma CTQ scores were reported for those individuals who developed an affective psychotic illness opposed to a non-affective psychotic disorder. Conclusion: Previous experience of sexual trauma was associated with transition to a psychotic disorder in our large UHR cohort. This is a similar finding to a previous smaller study in our clinic and suggests that sexual trauma in particular may be an important factor in development of psychosis for some individuals.
ID: 978289

USING LATENT CLASS ANALYSIS TO UNDERSTAND WHERE SCHIZOPHRENIA AND BIPOLAR DISORDER FIT IN DIMENSIONAL MODELS OF PSYCHOPATHOLOGY

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Background: Evidence from quantitative modeling and molecular and behavior genetic studies indicate high levels of overlap among internalizing and externalizing disorders, and bipolar disorder and schizophrenia. This "comorbidity" poses a major challenge to conventional methods of diagnostic classification. While factor analytic models have shed some light on this issue by modeling this co-occurrence as correlated dimensions of psychopathology, the reason for inter-relationship among these disorders is still unclear. The current study aimed to characterize patterns of comorbidity among these various forms of psychopathology by modeling them instead as latent classes - ie, projecting them as clusters or hotspots of activity along these dimensions of psychopathology. Methods: Latent class analyses (LCA) of DSM-based diagnoses from two separate nationally-representative epidemiological datasets - the National Comorbidity Survey (NCS; $N = 5877$) and National Comorbidity Survey - Replication (NCS-R; $N = 2980$) datasets were undertaken. Results: Within each dataset, LCA yielded five latent classes exhibiting distinctive profiles of diagnostic comorbidity: a fear class (all phobias and panic disorder); a distress class (major depression, dysthymia, generalized anxiety disorder); an externalizing class (alcohol and drug dependence, conduct disorder); a multimorbid class (highly elevated rates of all disorders); and a few disorders class (very low probabilities of all disorders). Diagnoses of bipolar I disorder and schizophrenia-spectrum disorders (which was available in the NCS alone) occurred almost exclusively in the multimorbid class in both samples. Profiles for these five classes were highly similar across the two samples. Furthermore, removing this multimorbid class decreased the intercorrelations between the internalizing and externalizing dimensions of psychopathology. Conclusion: This finding suggests that co-occurrence among different forms of psychopathology occurs in a finite number of patterns, and has important implications for understanding the reasons for overlap among bipolar disorder, schizophrenia, and internalizing and externalizing disorders.
ID: 979979

GENDER DIFFERENCE IN FIRST EPISODE PSYCHOSIS- THE EPO 500 STUDY.

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Background: Gender difference have been suggested in schizophrenia for prevalence, age of onset and symptomatology (with negative symptoms more dominant in males, and depressive symptoms more dominant in females). Thus, the younger age of onset in males has been called a hallmark of schizophrenia, although a recent Australian research project was unable to find an age of onset difference. Here we describe gender differences in a large representative cohort of patients diagnosed with a First Episode Psychosis. Methods: All patients (age 16–45) that were referred to the Psychosis Department of the UMCG between 1997 and 2009 were included, yielding a representative cohort for the province of Groningen. Assessments included DSM-IV-diagnosis according to DMS-IV criteria; PANSS-interviews, clinical characteristics, family history, live-events, cultural background and a comprehensive neuropsychological test battery. Results: A total of 541 patients were include: 396 males (73.2%) and 145 females (26.8%). Age on onset age at first diagnostic procedure for psychosis (mean male: 26.53, female: 30.62). Symptomatology The total PANSS scores revealed no significance. Three factor model showed that positive symptoms as a total score where experienced more by males ($P = 0.021$). ''Grandiosity'' was scored significantly higher on by males ($P = 0.000$). Negative symptoms as a total were experienced significantly more as more severe by males. The Depression PANSS item did not differ significantly between groups. Analyses of the MADRAS revealed no significant gender difference either. The one item that was significantly (.02) lower in females was the inability to feel. On the general PANSS items males had three items significantly higher: ''unusual thought content'', ''poor judgment and insight'' and ''preoccupation''. Conclusion: The major findings of this study were a higher prevalence in males (3:1) and an earlier onset of psychotic symptoms in males (26.5 vs 30.6). Males also experienced more severe positive and negative symptoms. Depressive symptoms were not found to have a higher prevalence in women. The findings of this study underline the validity of gender differences in the first episode psychosis.
ID: 979885

EVIDENCE THAT FAMILIAL LIABILITY FOR PSYCHOSIS IS EXPRESSED AS DIFFERENTIAL SENSITIVITY TO CANNABIS: AN ANALYSIS OF PATIENT-SIBLING AND SIBLING-CONTROL PAIRS

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Background: Context. Individual differences in cannabis sensitivity may be associated with genetic risk for psychotic disorder. Objectives. To demonstrate and replicate, using two conceptually different genetic epidemiological designs, that liability to psychosis is associated with sensitivity to cannabis. Methods: Design. Sibling-control and cross-sibling comparisons using samples of patients with a psychotic disorder ($n = 1120$), their siblings ($n = 1057$) and community controls ($n = 590$). Setting. The Netherlands and Flanders. Main outcome measures. Positive and negative schizotypy using the Schizotypy Interview Schedule - Revised (SIS-R; siblings, controls) and self-reported positive and negative psychotic experiences using the Community Assessment of Psychic Experiences (CAPE; siblings, patients). Cannabis use was assessed as current use (by urinalysis), and lifetime frequency of use (CIDI interview). Results: In the sibling-control, case-control comparison, siblings displayed more than 15 times greater sensitivity to the positive schizotypy-inducing effect of particularly current cannabis use by urinalysis (adjusted $B = .20$, $P < .001$) than controls (adjusted $B = .013$, $P = .86$; P interaction = .041), and a similar difference in sensitivity to its negative schizotypy-inducing effect (siblings: adjusted B = .12, $P < .001$; controls: $B = .008$, $P = .87$; P interaction = .026). Similarly, siblings exposed to cannabis resembled their patient relative nearly 10 times more closely in the positive psychotic dimension of the CAPE (adjusted $B = .28$, $P < .001$) compared to non-exposed siblings (adjusted $B = .025$, $P = .12$; P interaction $< .001$). No significant effect was apparent for the CAPE negative domain,

although the association was directionally similar (2 times more resemblance; P interaction = .17). Cross-sib, cross-trait analyses suggested the mechanism underlying these findings was moderation (familial risk increasing sensitivity to cannabis) rather than mediation (familial risk increasing use of cannabis). Conclusion: Genetic risk for psychotic disorder may be expressed in part as sensitivity to the psychotomimetic effect of cannabis. Cannabis use may synergistically combine with pre-existing psychosis liability to cause positive and negative symptoms of psychosis.
ID: 978307

IS GENETIC RISK FOR PSYCHOTIC DISORDER MEDIATED IN PART BY DIFFERENTIAL SENSITIVITY TO CHILDHOOD MALTREATMENT?

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Background: Childhood maltreatment may give rise to hallucinatory experiences that, if complicated by delusional ideation, give rise to a psychotic syndrome in individuals at higher than average genetic risk. Methods: We tested the hypothesis of differential sensitivity to childhood maltreatment, assessed with the CTQ, in a group of healthy controls (n = 223) and a group of healthy siblings of patients with a psychotic disorder (n = 258), at higher than average genetic risk for psychotic disorder. Lifetime presence of hallucinations and delusions was assessed by clinical interview with the CASH in both groups. Results: The lifetime rate of hallucinations in unexposed siblings (5.0%), was similar to the rate in unexposed controls (6.7%). However, the rate of hallucinations in exposed siblings (13.9%) was much higher than the rate in controls (5.9%), giving rise to significant interaction (P <.05). No such differences were apparent for delusions. Conclusion: The results suggest that exposure to childhood trauma may give rise to intrusions that particularly in the context of genetic risk for psychotic disorder may become associated with ''aberrant salience'', resulting in the formation of hallucinations.
ID: 979622

THE CASE OF THE MISSING EVIDENCE: DO PSYCHOTIC EXPERIENCES PREDICT CLINICAL OUTCOMES IN UNSELECTED POPULATION-BASED SAMPLES? A SYSTEMATIC REVIEW AND META-ANALYSIS, ENRICHED WITH NEW RESULTS

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Background: The reported 10%–20% yearly conversion rate from psychotic experience to clinical psychotic outcome forms the major rational for the practice of intervention in individuals at ultra high-risk, and the proposed DSM-5 Psychosis Risk Syndrome. However, the base rate of transition from subthreshold psychotic experience (the exposure) to clinical psychotic disorder (the outcome) in unselected representative population-based samples is unknown. Methods: A systematic review and meta-analysis was conducted of representative, longitudinal population-based cohorts with baseline assessment of subclinical psychotic experiences and follow-up assessment of psychotic and non-psychotic clinical outcomes. Results: Six cohorts were identified with 3–24 year follow-up of baseline psychotic experiences. The yearly risk of conversion to a clinical psychotic outcome in exposed individuals (.56%) was 3.5 times higher than for individuals without psychotic experiences (.16%). Conversion risk increased with the number, certainty, frequency, persistence and degree of affective dysregulation of psychotic experiences. There was also evidence of specificity, as psychotic experiences only weakly predicted non-psychotic clinical outcomes. Conclusion: Subclinical psychotic experiences index psychometric risk for psychotic disorder. However, the discrepancy between the 10% conversion rate in the high-risk literature and the .56% conversion base rate in unselected population-based samples points to the crucial influence of sample enrichment strategies through community awareness campaigns and other selective alterations of the permeability of filters on the pathway to mental health care that lie at the heart of all ultra high-risk studies. Standardized sample enrichment strategies, rather than clinical high-risk criteria per se, may be the critical factor determining the success of high-risk early intervention initiatives. Further development of these, and insight in how they operate, may support the important effort towards intervening earlier in severe mental illness.
ID: 985460

IS GENETIC RISK FOR PSYCHOTIC DISORDER MEDIATED IN PART BY DIFFERENTIAL SENSITIVITY TO CHILDHOOD MALTREATMENT?

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Background: Childhood maltreatment may give rise to hallucinatory experiences that, if complicated by delusional ideation, give rise to a psychotic syndrome in individuals at higher than average genetic risk. Methods: We tested the hypothesis of differential sensitivity to childhood maltreatment, assessed with the CTQ, in a group of healthy controls (n = 223) and a group of healthy siblings of patients with a psychotic disorder (n = 258), at higher than average genetic risk for psychotic disorder. Lifetime presence of hallucinations and delusions was assessed by clinical interview with the CASH in both groups. Results: The lifetime rate of hallucinations in unexposed siblings (5.0%), was similar to the rate in unexposed controls (6.7%). However, the rate of hallucinations in exposed siblings (13.9%) was much higher than the rate in controls (5.9%), giving rise to significant interaction (P <.05). No such differences were apparent for delusions. Conclusion: The results suggest that exposure to childhood trauma may give rise to intrusions that particularly in the context of genetic risk for psychotic disorder may become associated with ''aberrant salience'', resulting in the formation of hallucinations.
ID: 978296

AKT1 MODERATION OF CANNABIS-INDUCED COGNITIVE IMPAIRMENT

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Background: Genetic variation in AKT1 was recently found to be associated with genetic sensitivity to the psychotomimetic effects of cannabis as well as with increased risk for psychotic disorder following cannabis use (van Winkel & GROUP Investigators, Arch Gen Psychiatry 2010). Investigation of the effect of this interaction on relevant intermediate phenotypes for psychosis may help to unravel the underlying mechanism. Methods:

Verbal memory (Visual Verbal Learning Test, VVLT), sustained attention (Continuous Performance Test, CPT) and cannabis use history were examined in a cohort of 707 patients with psychotic disorder. Results: No evidence was found for an AKT X cannabis interaction on verbal memory. Cannabis use preceding onset of psychotic disorder did interact significantly with AKT1 rs2494732 genotype to affect CPT reaction times (p=.033) and percentage of correct positives (P = .008). This was most apparent at higher levels of use in the most intense period (weekly to daily use). Those carrying the C risk-allele performed worst. Results were similar in patients reporting no use in the last twelve months as reported in interview and confirmed by urinalysis (reaction time: P = .027 and correct positives: P = .010, respectively). Conclusion: Cannabis use prior to onset of psychosis may have long-lasting effects on measures of sustained attention, even in the absence of current use, but this is contingent on AKT1 rs2494732 genotype. These results suggest that long-lasting changes in cognition may mediate the risk-increasing effect of the AKT1 X cannabis interaction on psychotic disorder.
ID: 976852

IS IT POSSIBLE TO IDENTIFY IMPENDING PSYCHOSIS IN THE MONTHS PRECEDING THE FIRST HOSPITALIZATION?

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Background: Most studies of the prodrome are performed in highly selected high-risk clinics. This current study utilizes the results of clinical examinations of treatment-seeking adolescents in the Israeli military. The objective was to determine whether signs and symptoms observed in adolescents examined by mental health professionals at baseline and found not to have a psychotic disorder, can be useful in predicting future hospitalization for the first psychotic episode. Methods: Utilizing a population-based historical-prospective design, data on adolescents serving in the IDF who were examined by a mental health professional between 2000 and 2006 (N = 142 158) were linked with a psychiatric hospitalization registry in 2009. During the follow-up period, 1789 cases were hospitalized for a psychotic disorder. This analysis focused on the results of the mental health examinations of adolescents not assigned a diagnosis of a psychotic disorder when examined at baseline, but who were hospitalized with a diagnosis of a psychotic disorder up to 9 years after the baseline examination (cases). Cases were matched with 2 same-gender adolescent controls. Results: In 197 cases examined 15–111 days prior to hospitalization, perceptual abnormalities (OR = 34.24), thought disorder (OR = 20.08), impaired judgment (OR = 8.26), and disheveled appearance and abnormal behavior (OR = 2.57), were predictive of hospitalization. In cases (N = 184) examined 112–365 days prior to hospitalization, only thought disorder (OR = 7.73) was predictive. Although these odds ratios are quite large, the vast majority of adolescents with perceptual abnormalities (90.8%) or thought disorder (89.2%) were not later hospitalized. Conclusion: In a population-based setting of treatment-seeking adolescents without clinically diagnosed psychotic disorders at baseline, thought disorder and perceptual abnormalities were strongly associated with later hospitalization for a psychotic disorder. However, due to the relative rarity of hospitalization for psychosis in the population, even those symptoms are not clinically relevant in predicting impending psychosis. These results underscore the difficulty of identifying impending psychosis in the general population.
ID: 979180

THE BIDIRECTIONAL RELATIONSHIP BETWEEN (PERSISTENT) SUBCLINICAL POSITIVE PSYCHOTIC EXPERIENCES AND COPING IN ADOLESCENTS FROM THE GENERAL POPULATION

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Background: Persisting subclinical psychotic experiences during adolescence may represent liability for frank psychosis. Coping style may play a role in the progression to a clinical psychotic state, although little is known about the relationship between subtle psychotic experiences and coping styles at over time. Methods: First, path modeling was used to examine longitudinal relationships between subclinical positive psychotic experience (assessed with CAPE), and coping strategies (assessed with CISS) in an adolescent general population sample (N = 813), assessed three times in three years. Next, distinct developmental trajectories of these psychotic experiences were identified with latent growth modeling and use of different coping styles was compared for the each developmental trajectory of positive experiences. Results: Only Emotion-oriented coping was bidirectionally related to positive experiences at all time points, whereby both worsen the other. Females reported using more (different) coping styles than males, but no gender differences on the paths between coping and positive experiences were found. Four distinct developmental trajectories of psychotic experiences were identified: Low, Decreasing, Strong-Decreasing and Persistent groups. The Persistent group also reported the highest levels of depression, poor general mental health and impaired daily functioning at all time points. The four subgroups did not differ in Task-oriented or Avoidance-oriented coping, but the Persistent group scored significantly higher on Emotion-oriented coping at all time points and reported this as the most used coping style. Conclusion: This is the first study to assess the interrelationships between coping styles and (persisting) psychotic experiences over time in a general adolescent sample. Emotion-oriented coping is the most important coping style in relation to psychotic experiences, since (i) it forms a vicious circle with psychotic experiences and (ii) it is being applied in a dose-response fashion in relation to level of psychotic experiences and used the most in a subgroup with persisting psychotic experiences. Results suggest that there may already be opportunities for intervention at the level of subclinical psychosis.
ID: 979087

HIGH THROUGHPUT SEQUENCING IDENTIFIES VIRAL SEQUENCES IN THE BRAINS OF INDIVIDUALS WITH PSYCHIATRIC DISORDERS

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Background: Infections have been postulated to be contributing factors to some cases of schizophrenia. In the past, studies of infections in schizophrenia have been hindered by the difficulty in directly identifying infectious agents in the brain. The recent availability of high throughput sequencing techniques has provided a sensitive method for the identification of a wide range of microbial species in human tissues. We applied this technology for the identification of microbial sequences in the brains of individuals with psychiatric disorders and controls. Methods: RNA was extracted from the

mid-hippocampus (including the dentate gyrus, cornu ammonis subfields CA1-4, and subiculum) region of brains obtained postmortem as part of the Stanley Brain Collection. The sample set includes individuals with an antemortem diagnosis of schizophrenia, bipolar disorder, and non-psychotic depression as well as controls. Messenger RNA was purified by binding to oligo-dT, fragmented by acoustic shearing, and reverse transcribed. The resulting cDNA was used to construct cDNA libraries which were subjected to high throughput sequencing using an Illumina Analyzer, with the resulting generation of more than 65000 000 paired end nucleotide sequences per brain sample. The nucleotide sequences were matched to databases of known viral sequences at the nucleotide level using the BLASTN algorithm and at the level of translated amino acids using the BLASTX and TBLASTX algorithms. Results: A total of 26 brain samples have been analyzed. These include samples from 10 individuals with schizophrenia, 10 individuals with an affective diagnosis, and 6 controls. Overall, there is a significantly increased number of viral agents identified in the cases as compared to controls. Identified viruses include herpesviruses, phycodnaviruses, picornaviruses, paramyxoviruses, papilloma viruses, and other viral species. Some of these viruses have not been previously identified in humans and are likely to represent novel viral strains. Conclusion: These studies indicate that viral infection of the brain is a common phenomenon and that the level of infection is higher in the brains of individuals with schizophrenia and other psychiatric diseases as compared to controls. Furthermore, some of the viruses infecting human brains have not been previously identified in other organs. These studies may lead to new methods for the diagnoses and treatment of psychiatric disorders.
ID: 977383

7. Genetics, Basic

PRODH GENE POLYMORPHISMS AND RISK FOR SCHIZOPHRENIA

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Background: Multiple studies in human and mouse models suggest that PRODH polymorphisms are risk factors for schizophrenia, although their role in the pathogenesis is not clear. The PRODH gene, located in 22q11.2 region, encodes proline oxidase (POX) that degrades proline to Δ1-pirolina-5-carboxilato (P5C). POX is an inner mitochondrial membrane enzyme expressed in kidney, liver and brain. The aim of this study is to investigate the association between polymorphisms of PRODH gene and schizophrenia. Methods: We studied 188 schizophrenia patients, recruited from PROESQ (Schizophrenia Program of UNIFESP), and 155 healthy subjects, from LiNC (Interdisciplinary Laboratory of Clinical Neurosciences). DNA extraction from peripheral blood was performed using a Gentra Qiagen® kit. We studied 16 polymorphisms of the PRODH gene: rs4819756, rs450046 and rs372055 using Real Time PCR detection system with Taqman®, L289M using Restriction Fragment Length Polymorphism (RFLP) and rs2870987, rs2870986, rs2870985, rs34603845, rs16983466, rs2238731, rs2904552, rs2904551, rs3970559, rs1807467, rs2870984 and rs2870983 using gene sequencing. Chi-square test was used to verify Hardy-Weinberg equilibrium and to investigate the association between each gene polymorphism and the disease. Results: The minor alleles were not found in either group for rs2870987, rs2870986, rs2870985 polymorphisms and for the rs34603845 the minor allele was not found in the control group. The other polymorphisms were in Hardy-Weinberg equilibrium except for rs4819756. A significant association was observed between rs2904552 polymorphism and schizophrenia (P = .004), with the GG homozygotes being more frequent in the patient group. Conclusion: PRODH rs2904552 polymorphism is a functional polymorphism that changes an amino acid and modifies the protein structure. These data support an association between PRODH gene and schizophrenia pathogenesis.
ID: 978398

LARGE-SCALE SEQUENCING OF DISC1 IN SCHIZOPHRENIA AND BIPOLAR DISEASE YIELDS NOVEL VARIANTS

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Background: Since the original finding of a translocation disrupting the DISC1 gene in a large Scottish family pedigree with multiple mentally ill family members, numerous association studies focusing primarily on common DISC1 variation have been conducted with mixed results. Methods: In order to investigate the hypothesis that rare, highly penetrant coding variation in DISC1 is present and a significant risk factor for schizophrenia and/or bipolar disorder, we began the search for rare highly penetrant variants by sequencing coding and adjacent non-coding regions of DISC1 in 188 schizophrenia (SZ) cases and 165 population matched controls as well as 185 bipolar (BP) cases and 181 controls from the same sample. Results: Following validation through Sequenom genotyping, 43 novel SNPs were confirmed as polymorphic. Given the limited power of our sequencing sample to confirm associations with individual variants, our newly identified SNPs and previously known SNPs from dbSNP and published studies were prioritized by predicted functional consequence for larger scale genotyping. Sixty-six SNPs (24 known and 42 novel SNPs) were genotyped using Sequenom in 16 340 subjects (4757 SZ cases, 4890 SZ controls 3774 BP cases and 2919 BP controls). Conclusion: Analyses of SNPs individually as well as in aggregate using PLINK did not yield strong support for the involvement of DISC1 in schizophrenia, bipolar disease or the combined sample.
ID: 986978

DISC1 LEU607PHE AND SER704CYS SUBSTITUTIONS INFLUENCE CENTROSOMAL LOCALIZATION OF ITS BINDING PARTNER PCM1 IN C6 GLIOMA CELLS

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Background: Disrupted-in-schizophrenia 1 (DISC1) has been genetically associated with psychiatric illnesses, and with brain phenotypes including graygray matter volume. However, the molecular and cellular basis for these associations remains to be elucidated. One potential mechanism may be via an altered interaction of DISC1 with its binding partners. In this context, we recently observed in post mortem human brain that two DISC1 variants, Leu607Phe and Ser704Cys, influenced the centrosomal localization of the DISC1 binding partner, pericentriolar material 1 (PCM1), in glia. PCM1 immunoreactive area was smaller in Cys704 carriers and Phe607 homozygotes, and individuals who were Phe607 homozygotes and Cys704 carriers exhibited reduced PCM1 centrosomal immunoreactivity compared to those with only one of the two ''risk genotypes''. The data highlighted a role for DISC1 in glial function, and indicated a potential cumulative influence of the variants. To investigate these findings further, here we have utilized an in vitro model system, C6 glioma cells. Methods: Site directed mutagenesis was used to create four V5-tagged plasmids encoding neither, one or both risk variants. Undifferentiated C6 cells were grown on slides, and 24 hours after transient transfection with the plasmids, anti-V5 and PCM1 double immunofluorescence was performed. PCM1 centrosomal immunoreactive area in transfected cells was measured using computerized image analysis, and normalized to native PCM1 immunoreactive area quantified in untransfected cells. Results: An overall effect of genotype was detected (P <.001), with centrosomal PCM1 immunoreactive area being smaller in cells transfected with Cys704 or Phe607 DISC1 compared to those over-expressing a construct containing neither risk variants (both <.001). No difference was found between cells transfected with Phe607 compared to Cys704 DISC1. Of note, centrosomal PCM1 immunoreactive area was smaller in cells over-expressing both risk variants compared to those transfected with any of the 3 other plasmids (all <.006), and was ~20% smaller than that of cells transfected with only one risk variant. Conclusion: These findings confirm in vitro that the Leu607Phe and Ser704Cys DISC1 substitutions modulate glial centrosomal PCM1 localization, and provide additional evidence supportive of a cumulative effect of the risk variants. What potential downstream consequences the two DISC1 variants may have upon glial function remain to be determined, and are currently under investigation.
ID: 977637

A CAG REPEAT POLYMORPHISM OF KCNN3 PREDICTS SK3 CHANNEL FUNCTION AND COGNITIVE PERFORMANCE IN SCHIZOPHRENIA

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Background: KCNN3, encoding the small conductance calcium-activated potassium channel SK3, harbors a polymorphic CAG repeat in the N-terminal coding region with yet unproven functional significance. An association of genetic variations of KCNN3 with the risk of schizophrenia was metanalytically not confirmed. We hypothesized that KCNN3 is not a susceptibility gene but a disease modifier, and explored the contribution of the CAG repeat to specific schizophrenic phenotypes. Methods: (1) Using the GRAS data collection with >1000 comprehensively phenotyped schizophrenic patients, we performed a phenotype-based genetic association study (PGAS) of KCNN3. (2) Three different human SK3 isoforms, characterized by different repeat lengths and fused with eGFP, were expressed in HEK293 cells for analysis of channel conductance using whole-cell patch clamping. (3) A line of transgenic mice, in which the murine SK3 gene is overexpressed under control of its own regulatory elements, was employed for behavioral/cognitive testing. Results: We demonstrate that long CAG repeats in the schizophrenic sample are specifically associated with better performance in higher cognitive tasks, comprising the capacity to discriminate, select, and execute. Long repeats reduce SK3 channel function, as we show by patch-clamping of transfected cells. In contrast, Kcnn3 overexpression in mice leads to selective deficits in a specific set of higher brain functions comparable to those influenced by SK3 channel conductance in humans. Conclusion: KCNN3 genotypes modify cognition in schizophrenia. Reduction of SK3 function may constitute a novel pharmacological target to improve cognitive performance in schizophrenia and most likely also in other conditions characterized by cognitive impairment.
ID: 980889

GENOME WIDE ASSOCIATION STUDY (SCHIZOPHRENIA GROUP; PSYCHIATRIC GENETICS CONSORTIUM) IDENTIFIES FIVE NOVEL SUSCEPTIBILITY LOCI

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Background: Schizophrenia is a common, severe, and highly heritable psychotic disorder for which biological insight and effective therapeutics remain largely elusive. Previous studies have identified several common and rare genetic loci associated with schizophrenia; however, together these explain only a small fraction of the heritability. Methods: We performed a combined genome-wide association study (GWAS) of schizophrenia in samples of European ancestry comprised of a total of 21 856 individuals (9394 cases and 12 462 controls), and followed up the strongest signals in 30 273 independent samples - by far the largest schizophrenia sample investigated to date. Results: Strong experiment-wide evidence for replication of our initial findings supported a multigenic model for schizophrenia inheritance. By combining the initial meta-analysis and follow up results, we found a total of seven genome-wide significant loci, of which five are novel (1p21.3, 2q32.3, 8p23.2, 8q21.3, and 10q24.32) and two (6p21.3–22.1, and 18q21.2) are replicated from previous studies. Conclusion: We anticipate that our findings, by bridging clinical phenotypes to specific genomic locations, will accelerate the discovery of the biological mechanisms through which the many risk genes underlying the substantial heritability of schizophrenia contribute to illness.
ID: 986723

GENETICS AND THE IDENTIFICATION OF VALIDATED DRUG TARGETS FOR COGNITIVE ENHANCEMENT

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Background: Genome wide association studies have proven successful in identifying regions of the genome that contain gene variants that influence common diseases, including schizophrenia and drug responses. In most instances, however, it has not been possible to track these associations down to the causal variants that are responsible, and this greatly reduces the utility of these findings in drug development. Sequencing based strategies, on the other hand, offer the promise of identifying the precise mutations and the genes they influence that are responsible both for predisposition to schizophrenia and also that influence the degree of cognitive impairment suffered by patients and the degree of response to compounds that aim to ameliorate cognitive deficits. Methods: Next-generation sequencing techniques will be discussed with an emphasis on applications to schizophrenia research. Results: I first review a series of sequencing studies underway at Duke University and outline what I see as the most important opportunities for future studies. Specifically, I will report analyses Duke has performed of whole genome sequencing of more than 50 genomes of individuals with schizophrenia who are drawn from multiplex families, as well as whole exome sequence data of 75 individuals that have treatment resistant schizophrenia requiring treatment with clozapine. Conclusion: Sequencing based studies of both schizophrenia and treatment response offer what may prove the best hope for identifying validated new targets for cognitive enhancement in schizophrenia.
ID: 976897

MOLECULAR ORGANIZATION OF ENDOCANNABINOID SIGNALING NETWORKS IN THE DEVELOPING NERVOUS SYSTEM

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Background: Endocannabinoids (eCBs), synthesized and released ''on-demand'' from postsynaptic neurons, act as retrograde messengers by engaging CB1 cannabinoid receptors (CB1R) to control the plasticity of many excitatory and inhibitory synapses in the adult brain. However, recent findings establish a strikingly different molecular organization of eCB signaling networks, particularly those utilizing 2-arachidonoyl glycerol (2-AG), in the developing mammalian forebrain. Methods: Data will be presented through systematic analysis of cellular models, mouse transgenics, and fetal human brains. Focus will be directed towards identifying the molecular pathogenic imprint of maternal cannabis exposure on fetal cortex organization and functions. Thematically, an array of neuromorphology, expression profiling, cell biology/imaging and biochemical data will be discussed. Results: 2-AG signaling in neurogenic niches contributes to the generation of pyramidal cells and to propelling prospective pyramidal neurons along their radial migration paths. Upon final positioning of cortical neurons, 2-AG signaling impacts the directional turning and motility of their developing axons by activating CB1Rs residing in the growth cones. Since sn-1-diacylglycerol lipases (DAGLα/β) synthesize 2-AG in the motile axon segment we hypothesize that autocrine 2-AG signaling could facilitate axonal outgrowth. However, 2-AG synthesis by DAGLs alone is insufficient to account for the spatial specificity and dynamics of 2-AG signaling. We show that the subcellular recruitment of monoacylglycerol lipase (MGL), degrading 2-AG, is temporally and spatially restricted to establish

2-AG's signaling competence during axonal growth. MGL coexists with DAGLα and CB1Rs in corticofugal axons but undergoes differential axonal targeting and is excluded from the motile neurite tip. MGL's axonal polarity is maintained by its differential proteasomal degradation. Thus, spatially-confined MGL activity generates a 2-AG-sensing microdomain within the growth cone. Accordingly, MGL inactivation drives a CB1R-dependent axonal growth response. Once synaptogenesis commences, MGL disperses in stationary growth cones to mute 2-AG signaling and prevent neurite overgrowth. Conclusion: We recognize eCB signaling as a novel and powerful regulatory network to control axonal growth, postsynaptic target selection and synapse positioning in developing brain.
ID: 975767

USE OF NEXT-GENERATION SEQUENCING PLATFORMS TO IDENTIFY SCHIZOPHRENIA GENES

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Background: The SZgene Database (www.szgene.org) lists hundreds of genes that have been associated with schizophrenia in case/control analyses. Whole-genome association (GWAS), however has failed to validate most of these associations, giving rise to the theory that schizophrenia is truly polygenic, and that most causative loci have small effect sizes. This scenario represents a significant problem for the identification of genes that are truly involved in the etiology of schizophrenia, and the ultimate characterization of causative alleles. One approach to validate candidate genes is through the identification of rare functional variants of large effect size, thereby demonstrating its involvement in the etiology of the disorder/trait, and can be used to validate to sub-threshold GWAS peaks, and act as a primer for additional resequencing efforts to identify the more common low effect size variants at those loci. Methods: To validate this approach, we applied it to the identification of genes that influence impulsivity by sequencing 14 candidate genes in individuals who have displayed severe impulsive behavior leading to incarceration for violent crime. Genes involved in the serotonin and dopaminergic neurotransmission were selected based upon data implicating their roles in impulsive behavior in humans and animal models. Exonic and promoter regions (totaling 82kb of genomic sequence) were PCR amplified from pooled genomic DNA (12 samples/pool), the amplicons pooled, and sequenced at 80X coverage using the Illumina Genome Analyzer. Sequencing was performed in 96 highly impulsive cases and 96 unrelated controls. Results: We identified 26 novel non-synonymous cSNPs (including a nonsense variant in HTR2B, Q20*), 22 of which were confirmed by Sanger sequencing. The Q20* variant is restricted to the Finnish population and is significantly associated with the violent impulsive phenotype ($P = .007$) in a case/control analysis (228 cases, 295 controls). Additionally Q20* carriers showed a significantly earlier onset of schizophrenia (mean 20.9 years) compared to Q20/Q2 individuals (mean 24.5 years). Conclusion: Advances in sequencing technology allow us to now simultaneously sequence almost 100x that used in this pilot study, and the ability to accurately detect novel SNPs will allow rapid analysis of large numbers of the schizophrenia candidate genes, bridging the common variant, rare variant divide. This approach is currently being adopted in cohorts of 244 cases scanning 560 candidate genes.
ID: 979826

DEVELOPMENTAL CANNABIS EXPOSURE INDUCES EPIGENETIC MODULATION OF MESOLIMBIC NEURONAL SYSTEMS RELEVANT TO ADDICTION AND SCHIZOPHRENIA VULNERABILITY

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Background: Maladaptive processes during neurodevelopment have been linked with mental disorders. Exposure to environmental insults such as drugs can impact normal ontogenic processes. Marijuana (Cannabis sativa) is the illicit drug most commonly used by two vulnerable populations germane to neurodevelopment — pregnant women and teenagers. Clinical and epidemiological studies have documented a significant link between repeated early cannabis exposure and increased risk for the subsequent abuse of other illicit drugs and the development of schizoaffective disorders in adulthood. Neurobiological mechanisms underlying this long-term vulnerability are unknown. A key molecular target for psychiatric disorders as addiction and schizophrenia is the dopamine D2 receptor (D2R) and thus was a focus for our studies assessing the effects of developmental cannabis exposure. Methods: We measured D2R mRNA expression in the postmortem striatum of human midgestation fetuses (18–22 weeks) exposed in utero to cannabis. We also examined the effect of prenatal Δ9-tetrahydrocannabinol (THC; major psychoactive component of cannabis) on D2R in rodent models in which behavior could be studied and performed chromatin immunoprecipitation (ChiP) assay to examine epigenetic marks. Results: We observed a significant reduction of D2R mRNA levels in the nucleus accumbens, but not dorsal striatum, of drug-exposed human subjects and rats, impairments that persisted into adulthood. To investigate whether the protracted alterations on D2R was achieved via epigenetic regulatory processes, we performed ChiP in the adult rat accumbens to examine dimethylation of lysine 9 on histone H3 (2meH3K9), a chromatin modification with a well-known role in developmental gene silencing. The data revealed an increase in 2meH3K9 at specific evolutionarily conserved genomic regions of the Drd2 gene in THC-exposed rats. Other epigenetic marks examined failed to show the same selective pattern. Conclusion: Overall, the data suggests that maternal cannabis use specifically alters the developmental regulation of mesolimbic D2R in the offspring through epigenetic mechanisms that modulate repressive histone lysine methylation. Such epigenetic mechanisms may contribute to increased addiction vulnerability later in life since adult rats carried through the prenatal THC paradigm had enhanced heroin intake and reward sensitivity. Whether similar epigenetic disturbances also relate to the long-term vulnerability of adolescent cannabis exposure is being studied.
ID: 986362

CANNABINOIDS: RISK FACTORS FOR A NEUREGULIN 1 MOUSE MODEL OF SCHIZOPHRENIA?

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Background: Heavy cannabis consumption, particularly during adolescence, appears associated with an increased risk of developing schizophrenia in susceptible individuals. However, cannabis is a mixture of cannabinoids, including the psychotomimetic cannabinoid receptor 1 (CB1) agonist Δ9-tetrahydrocannabinol (THC) and the potentially antipsychotic-like cannabidiol (CBD). To clarify the role of different cannabinoids in the development of schizophrenia, we investigated the neurobehavioral effects of chronic CB1 stimulation (ie THC and CP 55 940 treatment) in adolescence and adulthood using a heterozygous mouse model for the schizophrenia susceptibility gene neuregulin 1 (ie Nrg1 HET mice). We also characterized the impact of CBD exposure during adulthood on this mouse model. Methods: Adolescent male Nrg1 HET mice and their wild type-like (WT) littermates received vehicle or THC (10 mg/kg i.p.) for 21 days, whereas adult cohorts were treated chronically with vehicle and either CP 55 940 (.4 mg/kg for 15 days) or CBD (1, 50, 100 mg/kg for 21 days). On the first day of treatment and throughout chronic

treatment, behavioral tests were performed to assess locomotion, anxiety, prepulse inhibition, cognition and memory as well as social interaction. Results: Nrg1 HET and WT mice were equally sensitive to the locomotor suppressant effects of adolescent THC. THC decreased the startle response, but there were no main effects of treatment or genotype on prepulse inhibition. THC had cognition-impairing and social interaction-suppressing effects only in WT mice. However, adult Nrg1 mutants developed behavioral tolerance to chronic CB1 stimulation more readily than WT mice. Chronic exposure to high dose CBD attenuated the hyperlocomotor activity and prepulse inhibition deficit observed in vehicle-treated Nrg1 HET mice. Conclusion: Male Nrg1 HET mice appear to be less sensitive to some of the behavioral effects of CB1 stimulation during adolescence but more susceptible than WT mice in adulthood. Importantly, chronic treatment with CBD could partially rescue some of the behavioral abnormalities observed in this mouse model for Nrg1.
ID: 979060

THE EFFECTS OF RUNS OF HOMOZYGOSITY ON RISK FOR SCHIZOPHRENIA: A REPORT FROM THE PSYCHIATRIC GWAS CONSORTIUM'S ROH SUB-GROUP

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Background: Inbreeding depression, which refers to reduced fitness among offspring of related parents, provides clues to the evolutionary genetics of traits. The risk alleles for traits showing inbreeding depression tend to have been under negative (purifying) selection ancestrally. Inbreeding has traditionally been studied using known pedigrees. In practice, pedigree information is difficult to obtain, potentially unreliable, and rarely assessed for inbreeding arising from common ancestors who lived more than 2 or 3 generations in the past. In previous studies, we have demonstrated that very distal inbreeding (eg, from a common ancestors up to ~50 generations in the past) can be reliably measured in ostensibly outbred samples using modern, dense SNP arrays Methods: Using dense (300k-1M) SNP data, we measured runs of homozygosity for each individual in a schizophrenia case-control dataset of ~22 000 individuals from the Psychiatric GWAS Consortium. Results: Runs of homozygosity are a significant risk factor for schizophrenia. Extrapolating from our results, cousin-cousin inbreeding should lead to a 2-3 fold increase in risk of schizophrenia. Conclusion: This study represents the largest and most powerful test to date on the effects of distal inbreeding on schizophrenia risk. These findings suggest that schizophrenia risk alleles have not been invisible to natural selection across evolutionary time.
ID: 986904

HIGHLY ACTIVE RETROTRANSPOSONS AND THEIR RELATIONSHIP TO SCHIZOPHRENIA

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Background: Nearly 45% of the human genome sequence is composed of transposable elements, compared to 3%–10% observed in the genomes of other organisms. Some of these elements retain the ability to retrotranspose. Thus, they can cause human diseases by a number of mechanisms, including promotion of unequal recombination (resulting in copy number variations, (CNVs))and direct insertion into gene regions and flanking promoter sequences. Such phenomena have important implications for the pathogenesis of common disorders. Several recent studies indicate that CNVs occur at a higher rate than expected among schizophrenia (SZ) cases. Methods: We genotyped three highly active retrotransposons (Aco210017, Al512428 and Aco2980) based on published in vitro studies (Seleme MC et al (2006). PNAS 103 (17) : 6611–6616) that are transposed on chromosomes 6, 17 and X, in a sample of schizophrenia (SZ) patients (n = 500) and controls (n = 500) using a three primer PCR assay. Results: The insertion frequency of these retrotransposons was not significantly different when SZ cases were compared with matched controls, except for AC02980. The insertion frequency for the X chromosome retrotransposon AC02980 in SZ (male and female cases, .54 and .51, respectively) is lower compared to controls (both genders at .63) (P = .01). Conclusion: We report here the differential frequency of a retrotransposon insertion event in controls compared to SZ cases on the X chromosome. The nearest genes that could be affected by the insertional event are Male-specific lethal 3-like1 isoform (MSL3) and FERM and PDZ domain containing 4 (FRMPD4). We are currently exploring novel de novo retrotransposon sites in SZ samples and controls.
ID: 979506

EPIGENOMIC APPROACHES TO THE ETIOLOGY OF SCHIZOPHRENIA

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Background: As with all complex neuropsychiatric phenotypes, traditional approaches to the etiology of schizophrenia have focused on the interplay between genetic (DNA sequence) and environmental risk factors. Recent evidence supports the notion that epigenetic processes are also likely to be important. Epigenetics is the study of mitotically heritable, but reversible, changes in gene expression that occur without a change in the genomic DNA sequence, brought about principally through alterations in DNA methylation and chromatin structure. Epigenetic processes are highly dynamic, responsive to a range of environmental stimuli, and provide a direct mechanistic interface between ''nature'' and ''nurture''. Recent advances in epigenomic profiling methodologies mean it is now feasible to examine the role of epigenetic processes in complex disease. Methods: We have undertaken a number of studies using cutting-edge methylomic approaches across a comprehensive set of post-mortem brain samples. Methods employed include high-resolution CpG island microarrays, MeDIP-sequencing, and bisulfite-mapping. Our studies aim to examine both normal variations in epigenetic patterns across the brain and schizophrenia-associated changes in DNA methylation. Results: Our data highlight key methylomic differences across the human brain. We have uncovered key region-specific profiles, examples of allele-specific DNA methylation, and several disease-associated epigenetic changes. Conclusion: Taken together, our data support a role for altered DNA methylation in mediating between-individual variation in neurobiological phenotype, with changes at several specific loci associated with schizophrenia.
ID: 979850

MICRORNA EXPRESSION PROFILING SUGGESTS A NEURODEVELOPMENTAL ROLE FOR MIR-132 IN SCHIZOPHRENIA

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Background: Schizophrenia is characterized by a complex combination of affective, cognitive, neuromorphological, and molecular abnormalities that are thought to have a neurodevelopmental origin. MicroRNAs (miRNAs) are small non-protein coding RNA sequences that play an important gene regulatory role in both neurodevelopment and adult neuronal processes by

coordinating the activity of multiple genes within biological networks. Methods: In the present work, we examined the expression of 854 miRNAs in dorsolateral prefrontal cortex tissue from a large sample of control, schizophrenic, and bipolar patients, and followed the results with an exploration of miRNA function in a mouse model. Results: We found that the brain-enriched miRNA miR-132 was significantly downregulated in both the discovery cohort of schizophrenic patients and in a second case/control population, indicating that miR-132 dysregulation is a common molecular characteristic of schizophrenia. Furthermore, a number of miR-132 protein-coding targets were up-regulated in brain tissue from schizophrenic patients. Notably, miR-132 expression is induced by CREB signaling and regulates NMDA signaling and activity-dependent neurite outgrowth. In prefrontal cortex from mice, we identified highly significant developmental regulation of both miR-132 expression and expression of several miR-132 targets, with the greatest changes occurring during the adolescent period. Postnatal disruption of NMDA signaling resulted in adult dysregulation of miR-132 expression, similar to that observed in human patients. Conclusion: As the adolescent period is a critical time for the final stages of neurodevelopment, and is also associated with the onset of schizophrenia in humans, our data suggest that miR-132 dysfunction and abnormal expression of miR-132 protein-coding targets may underlie a number of the neurodevelopmental and neuromorphological pathologies characteristic of schizophrenia.
ID: 978585

A HIERARCHICAL FINITE MIXTURE MODEL APPROACH FOR DETECTING SCHIZOPHRENIA LIABILITY

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Background: A number of traits associated with schizophrenia aggregate in relatives of schizophrenia patients at rates much higher than that of the clinical disorder. These traits, considered candidate endophenotypes, may be alternative, more penetrant manifestations of schizophrenia risk genes than schizophrenia itself. In order for an endophenotype to potentially increase the power of linkage analyses, the distribution of the quantitative trait should be consistent with a finite mixture distribution. The presence of such heterogeneity is a necessary condition for distinguishing between two groups of unaffected relatives, those who are non-penetrant gene carriers and those who are not gene carriers. Methods: We apply finite mixture models to one provisionally identified endophenotype - ''thought disorder with schizophrenic features'' - in samples of clinically unaffected first-degree relatives of schizophrenia patients and nonpsychiatric controls. Results: Using finite mixture modeling, we establish the existence of two classes of subjects, those at high risk for thought disorder and those at low risk, and confirm that clinically unaffected relatives are more likely to be at high risk for thought disorder than controls. Conclusion: We demonstrate the utility of this model, establishing that thought disorder qualifies as an endophenotype that could substantially enhance the power of linkage studies.
ID: 978951

MOLECULAR MECHANISMS BY WHICH DISC1 REGULATES GRANULE CELL MIGRATION IN THE DEVELOPING HIPPOCAMPUS

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Background: The hippocampus is a brain region that is frequently abnormal in schizophrenia, possibly due to altered hippocampal development. We determined that Disc1 is expressed in migrating granule cells and their precursors that form the dentate gyrus (DG) during embryonic development [1, 2]. The proper migration of these early-born granule cells is critical for their integration into local hippocampal networks and likely influences functional connectivity and establishment of a neurogenic niche in the subgranular zone in the adult. In this study, we are examining the molecular mechanism by which Disc1 regulates granule cell migration. Disc1 has numerous isoforms that are expressed in the developing hippocampus [3] and their role has yet to be ascertained. Our work examines the role of Disc1 isoforms in regulating granule cell migration. Methods: To determine the effects of Disc1 isoforms on the migration of granule cells, we used in utero electroporation to deliver various Disc1 shRNAs as well as Disc1 isoforms into the developing mouse hippocampus. In utero electroporation was performed at embryonic day 15 (E15), soon after the start of granule cell migration, and sacrificed four days later (E19). In order to assess the migration of the granule cells, we measured the distance from the primary dentate neuroepithelium (where migration begins) to the tip of the dentate gyrus for each individual section. Based on this distance, three equal zones of migration were measured and the number of cells in each zone were manually counted. Results: We previously determined that Disc1 positively regulates the migration of embryonic-born granule cells as they make their way toward the future DG [2]. Robust knockdown of Disc1 using RNA interference results in hindered granule cell migration, whereas overexpression of human DISC1 results in increased migration compared to the control. We have continued these studies to examine the molecular mechanism by which Disc1 regulates granule cell migration. Our preliminary studies indicate that the role of Disc1 in this migration is isoform-dependent. In addition, this mechanism of migration is unique to the hippocampus compared to that of cortical migration. Conclusion: Understanding the role of Disc1 during the critical period of neurodevelopment may lead to insights in schizophrenia pathogenesis.
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ID: 979806

IDENTIFICATION OF ALTERNATIVELY SPLICED GENE VARIANTS IN SCHIZOPHRENIA

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Background: The role of splice variants in disease has been thus far, poorly characterized yet their importance in disease development is considered to be significant. Schizophrenia is a disorder which appears to have a high degree of heritability, yet large genome wide analyses have identified genetic markers with small effect sizes associated with the disease. Small genomic alterations in non-coding DNA or epigenetic modifications not detectable with traditional methodologies can lead to de-regulation of normal gene expression and may account for a proportion of cases. The contribution of differential RNA splicing which adds another dimension to the complexity of the disease has thus far been overlooked as a potential molecular mechanism associated with disease. Methods: RNA samples extracted from blood from 240 patients were used, comprising 160 verified schizophrenic patients and 80 verified healthy controls that were assayed using

Affymetrix Human Exon Arrays. These arrays are capable of detecting individual exons from all transcribed genes within the genome at a resolution that allows for the accurate identification of all differentially spliced transcripts. Analysis of data was performed using Genespring GX 11 software. Results: The spliceosome profile defined by comparing the schizophrenic patients to the control data has revealed genes that are differentially spliced in the cases compared to the controls and that the genes identified map to reported genetic loci (such as those occurring within the MHC locus) identified by recent genome wide association studies. In addition, genes which have previously been reported to be implicated in schizophrenia were differentially spliced between the two groups. This includes exons that are both over and under-represented in the schizophrenia group, indicating variation exists between healthy controls and persons diagnosed with disease. Conclusion: Identification of a schizophrenia specific spliceosome profile would point towards specific genetic or epigenetic differences that may be exploited to better understand the mechanisms underlying this disease.
ID: 979089

EXTENSION OF GENOME-WIDE ASSOCIATION STUDIES INDICATING HLA ASSOCIATIONS IN SCHIZOPHRENIA

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Background: The study was motivated by recent schizophrenia (SZ) genome-wide association studies (GWAS), as well as our earlier published studies indicating risk factors in the HLA region. Our studies suggested interactions between host variation in the MICB gene and exposure to neurotropic herpes viruses in SZ risk. Methods: In phase I, we comprehensively genotyped 61 ''tag'' SNPs from a ~100 KB region around MICB among Caucasian SZ cases (n = 517), and screened adult controls (n = 314) . In Phase II, we integrated SNPs from Phase I showing significant associations, with selected SNPs from recent GWAS. These SNPs were genotyped among independent African-American SZ cases (n = 600) and controls (n = 404). Exposure to Herpes Simplex virus, type 1 (HSV1) and cytomegalovirus (CMV) was assessed simultaneously using specific antibody assays. Results: In Phase I, SNP-based tests yielded significant associations (P-value $\leq$.05, uncorrected) for 11 SNPs. Phase II analyses showed 8 SNPs with significant association (P-value $\leq$ .05). Of these, five SNPs were derived from the GWAS (rs12214031- BTN3A2_3UTR, P = .006; rs6932590-BTN3A2, P = .007; rs12199613- BTN3A2, P = .02413; rs9393709, P = .02471; rs926300, P = .05587). Phase II analyses also implicated two SNPs in the vicinity of MICB (rs6940467, P = .0343, OR 1.25 & rs6915833, P = .079, OR 1.93) that were associated in the Phase I samples. When exposure to HSV1 and CMV was explored in conjunction with the genotype data, significant interactions were observed at five SNPs. Conclusion: Variation in the HLA region may be associated with schizophrenia risk. Additional studies integrating neurotropic infectious agent exposure data are warranted.
ID: 979570

INTERACTION BETWEEN UFD1L AND ZDHHC8 GENE POLYMORPHISMS IS ASSOCIATED WITH AGE AT ONSET OF SCHIZOPHRENIA

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Background: Several studies have shown that age at onset has an impact on clinical manifestations and neuropsychological profile of schizophrenia. One known genetic risk for this disease is the 22q11.2 deletion, where UFD1L and ZDHHC8 genes are located. UFD1L gene encodes a protein that seems to be involved in the neurodevelopment process and its rs5992403 polymorphism was associated with schizophrenia. ZDHHC8 gene encodes a putative transmembrane palmitoyltransferase, regulating trafficking and signaling pathways. Several studies found association between rs175174 polymorphism and schizophrenia, although there are conflicting results. The aim of this study was to evaluate the association between UFD1L rs5992403 and ZDHHC8 rs175174 polymorphisms and their interaction with age at onset of schizophrenia. Methods: A total of 154 patients with schizophrenia were recruited from the PROESQ (Schizophrenia Program) of UNIFESP. Each patient was assessed and diagnosed by two psychiatrists according to DSM-IV and genotyped for rs5992403 and rs175174 polymorphisms by TaqMan probe-based real-time PCR assay. Association between these polymorphisms and their interaction was verified by General Linear Model (GLM). We used z-score normalization as the dependent variable, since the distribution of age at onset was not normal. Results: Our results showed that the interaction between rs5992403 and rs175174 polymorphisms was associated with schizophrenia age at onset (F(4, 145) = 4.198; P = .003; observed power = .916), although we did not find association between each single polymorphism and this variable. Furthermore, Tukey's post hoc test showed that age at onset of AA/GG (rs5992403/rs175174) patients was earlier than GG/AG patients (P = .039). Conclusion: Our results showed that the AA/GG (rs5992403/rs175174) patients presented the earliest mean age at onset. It is worth noting that rs5992403 A allele and rs175174 G allele have been associated with schizophrenia in several previous studies. These data suggest that interaction between these two genes involved in brain function and development may contribute to the age at onset of schizophrenia, which may reflect the severity of the disease.
ID: 978363

NEUROTROPIC VIRUS-SPECIFIC TREATMENT MAY ALLEVIATE COGNITIVE DEFICITS IN SCHIZOPHRENIA

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Background: Cognitive deficits contribute significantly to poor long term outcome of schizophrenia (SZ) and respond minimally to antipsychotics. A potentially treatable factor, exposure to neurotropic herpes simplex virus 1 (HSV1), has shown replicable association with cognitive deficits and prefrontal graygray matter (GM) loss among SZ subjects. HSV1+ SZ subjects showed longitudinal changes in cognitive deficits and progressive GM loss compared to the unexposed. These observations on subjects without a history/evidence of encephalitis suggest that ''asymptomatic'' HSV1 exposure is not necessarily benign. Here, we conducted a test of concept trial of Valacyclovir (VAV), an effective anti-HSV1 drug as an add-on treatment on early course SZ subjects. Methods: We randomized 24 HSV1+ SZ subjects (mean age: 29.74 ± 8.7 years; mean illness duration: 5.0 ± 3.34 years) to receive VAV+antipsychotics (VAV+AP, n = 12) or placebo (PL+AP, n = 12) for 18 weeks. Majority of the subjects completed the study. Subjects were on stable doses of atypical antipsychotics without switching or adding new medications during the study. Substance use and adherence to medications (study+prescribed) were monitored with periodic study follow ups. VAV was started at 1 g PO BID for 2 weeks and then increased to 1.5 g PO BID. At each visit, subjects were administered the Positive and Negative

Symptom Scale (PANSS). The Computerized Neurocognitive Battery (CNB) evaluated on 7 cognitive domains at baseline and follow up. Intent-to-treat analysis using linear mixed effects models including all randomized patients were used to examine differential changes in cognition and psychopathology over the study duration between VAV+AP or PL+AP groups, accounting for placebo response. For the CNB scores, we examined reaction time and accuracy separately. Results: Subjects in VAV+AP group showed a trend toward improvement in overall accuracy of n-back test (t = 2.19, P = .051); the differences primarily contributed by improved accuracy in 2-back test (t = 2.42, P = .034) but not by 0 = back (P = .12) or 1 = back (P = .52). In addition, reaction time for verbal working memory also showed improvement (t = 3.28, P = .007). Besides, delayed visual learning accuracy also showed a trend toward improvement in the VAV+AP group (t = 2.06, P = .06). Psychotic symptom severity did not change between the groups. Conclusion: These results suggest that supplemental VAV treatment may be beneficial in treating cognitive deficits but not psychopathology in early course SZ subjects.
ID: 979744

GENETIC EXPRESSION FOLLOWING NEUREGULIN 1 β DEFICIENCY IN A MOUSE MODEL OF SCHIZOPHRENIA BIOLOGY

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Background: Schizophrenia is a major neuropsychiatric disease in which the genetic basis is still being investigated. Neuregulin1 (NRG1) is a risk susceptibility gene of schizophrenia but nothing is known about how the modulation of genes associated with the expression of NRG1, contribute toward schizophrenia pathology. In this study our goal was to investigate the genetic profile of the NRG1/epidermal growth factor domain (EGF) heterozygous knock out mouse. Schizophrenic-like behavior has been observed in the EGF mouse but the genetic consequences of NRG1 deficiency in these mice have not been fully investigated. Methods: In this study, brains of EGF and wild type mice were dissected and RNA was extracted from the whole brain. The cRNA was then hybridized to Affymetrix 430b mouse microarray chips. Microsoft excel was used to identify genes which increased in expression 2-fold or more. Subsequent ingenuity pathway analysis (IPA) was performed to identify the major biological pathways associated with genes which were up-regulated in the microarray data. Results: From the microarray, we identified multiple genes which were up-regulated in response to NRG1 deficiency. Our data revealed an up-regulation of the schizophrenia associated cytokine genes such as interleukin-6 and interferon gamma. In addition, other cytokines not previously characterized in schizophrenia were revealed. IPA analysis revealed that the majority of genes up-regulated in the EGF mice microarray are involved with biological processes associated with the immune response and inflammation. Conclusion: This study may reveal putative genes which are associated with schizophrenic biology as a result of NRG1 deficiency. In addition, these data may yield new therapeutic targets for the treatment of schizophrenia. This work was supported by NIH grants U01NS 057993, R01 NS056446, U54 NS060659, C06 RR-07571, K12 GM 000680 and the W.M. Keck Foundation.
ID: 1008403

FAMILY-BASED EXOME SEQUENCING IN FAMILIES MULTIPLY-AFFECTED FOR SCHIZOPHRENIA

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Background: Schizophrenia is a highly heritable disease, yet recent genome-wide association studies have demonstrated that common polygenic alleles cannot fully account for the observed inheritance. Recently, the exomes (the entire gene-coding region of the genome) of individuals affected with a variety of Mendelian diseases have been sequenced to identify rare, highly penetrant mutations underlying the pathology of those particular cases. Since schizophrenia (like other complex disorders) is likely to have a subset of cases caused by rare protein-coding changes, exome sequencing may be a useful approach, particularly in multiply-affected families in which several individuals may share a single causative mutation. Methods: We have completely sequenced the exomes of two families that are multiply affected with schizophrenia. Each family consisted of two affected individuals and either two or four unaffected first degree relatives. The exome of each individual was captured using the Agilent SureSelect technique and then sequenced on a single lane of the Illumina HiSeq sequencer with 100 bp paired-end reads. The exomes were analyzed to determine many different kinds of variations including SNPs, rearrangements and copy-number variations (CNV). We utilized existing computational tools for the SNP detection, while the rearrangement and CNV detection were performed using our own newly created tools. Results: High-quality, high-depth reads were obtained on 75% of the exome, with a median of 80x depth. Initial analysis of the first family indicates that there were an average of 20 000 SNPs per individual. After filtering the variants, ~200 missense mutations and 3 nonsense mutations shared by cases and absent in unaffected family members. Results from all 10 individuals will be presented at the meeting. Conclusion: We have utilized exome sequencing to identify mutations underlying the schizophrenia in two families. The overall genetic similarity of family members enhances the ability to pinpoint the variations by eliminating family-specific mutations that are irrelevant to disease status. Candidate mutations will then be tested in a larger panel of cases and controls to eliminate false positives and determine frequency and penetrance of potentially causative mutations.
ID: 980969

THE NF-KAPPA B PATHWAY IN SCHIZOPHRENIA POSTMORTEM BRAIN TISSUE

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Background: The NF-kappa B pathways regulates growth, differentiation and adaptive response to extracellular signals. Neurons exhibit a constitutive level of NF-kappa B signaling and this pathway plays a significant role in neurite outgrowth, activity-dependent plasticity and cognitive function. The role of NF-kappa B signaling in schizophrenia has not been studied in postmortem tissue. Methods: Brain tissue specimens were derived from the Mount Sinai School of Medicine/J.J. Peters VA Medical Center Brain Bank. For exploratory studies, fifteen cerebral cortical regions were analyzed using our microarrays database. Hypothesis driven studies used qPCR to measure mRNA levels of NF-kappa B pathway genes in the superior temporal gyrus (BA 22) and primary visual cortex (BA 17) from an independent cohort. We conducted similar studies in rats chronically exposed to haloperidol or saline vehicle. NF-kappa B p65 activation was examined by protein assay of nuclear extracts from BA 22. Results: Microarray data showed an overall downregulation of the NF-kappa B pathway. In BA 22 of the independent cohort, the brains of persons with schizophrenia had significantly reduced RELA [p65] (P = .016), MAP3K7 (P = .007), KPNA4 (P = .018) and NFKB1 [p50] (P = .1) and KPNA3 (P = .08) at trend level. In BA 17, schizophrenia patients had increased NFKB1 (P = .042) and RELA at a trend level (P = .07). The p50/p65 ratio of mRNA levels was higher only in BA 22 of patients with schizophrenia (P = .025). NFKB1 and RELA mRNA levels were not altered in antipsychotic exposed rats. Transcription factor assay of p65 in BA 22 was

significantly higher in controls ($P = .009$) and correlated positively with the RELA expression levels in controls ($r = .67$, $P < .001$) but not in patients ($r = .09$, $P > .8$). Conclusion: Expression levels of NF-kappa B signaling genes are downregulated in BA22 of patients with schizophrenia. Neuroleptics do not alter the expression levels in rats. Nuclear transcriptional p65 activity is reduced in patients with schizophrenia, accompanied by lower KPNA3 and KNPA4 expression levels, which are the main importins responsible for p65 translocation into the nucleus. Reduced p65 mRNA expression levels and transcriptional activity might contribute to decreased expression of genes involved in cellular plasticity, neuronal survival/differentiation and neurite maintenance.
ID: 978318

THE NODE OF RANVIER IN SCHIZOPHRENIA POSTMORTEM BRAIN TISSUE

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Background: Glial signals, including glial soluble factors and paranodal axoglial junctions are required for the formation of the nodes of Ranvier. We tested the hypothesis that schizophrenia presents with alterations in the expression levels of oligodendroglial and neurons genes associated with the formation and maintenance of nodes of Ranvier. Methods: Brain tissue specimens were derived from the Brain Bank of the Department of Psychiatry of the Mount Sinai School of Medicine/J.J. Peters VA Medical Center. For exploratory studies, fifteen cerebral cortical regions were analyzed using our microarrays database. Hypothesis driven studies used qPCR to measure mRNA levels of nodes of Ranvier genes in the superior temporal gyrus (BA 22) and primary visual cortex (BA 17) from an independent cohort. We tested the effect of ANK3 risk polymorphisms on mRNA expression levels. Results: Microarray data showed an overall dysregulation of nodes of Ranvier genes. In BA 22 of the independent cohort, the brains of persons with schizophrenia had significantly reduced Ankyrin G [ANK3] ($P = .01$), Neurofascin [NFASC] ($P = .016$), Neuronal cell adhesion molecule [NRCAM] ($P = .01$), Nav1.6 Sodium channel, alpha subunit [SCN8A] ($P = .04$) and Contactin 2 [CNTN2 or TAG1] ($P = .08$). These changes were gene-specific since the mRNA levels of other nodal proteins did not show any significant differences among patients with schizophrenia and normal comparison subjects in BA 22 (all ps> .19). Additional specificity was demonstrated by the lack of changes in any of these genes in the primary occipital cortex, BA 17 (all ps >.12). In patients with schizophrenia, the rs9804190 C allele of ANK3 was significantly associated ($P = .0035$) with lower ANK3 expression levels. Conclusion: We found that four nodal genes were downregulated in patients with schizophrenia only in BA 22. The abnormal expression of Ankyrin G appears particularly important since it functions as a membrane protein scaffold and interacts with Neurofascin, NrCAM and Nav1.6 sodium channel on the neuronal membrane. Interestingly, the risk for bipolar disorder rs9804190 C allele predicts lower ANK3 expression levels in patients with schizophrenia. These data provide mechanistic insights into abnormal oligodendrocyte and myelin-associated interactions with neurons in schizophrenia and implicate abnormalities in the nodes of Ranvier as a possible substrate for the disconnectivity syndrome in schizophrenia.
ID: 978036

META-ANALYSIS OF MTHFR GENE VARIANTS IN SCHIZOPHRENIA, BIPOLAR DISORDER AND UNIPOLAR DEPRESSIVE DISORDER: EVIDENCE FOR A COMMON GENETIC VULNERABILITY?

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Background: Examination of associations between genetic variations in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene and psychiatric disorders has provided mixed and largely inconclusive findings. MTHFR is involved in the one-carbon metabolic pathway essential for DNA biosynthesis and methylation. Methods: We conducted a meta-analysis of all published studies investigating associations, based on case-control comparisons, between two common single nucleotide polymorphisms (SNPs) in MTHFR: MTHFR C677T (sample size 29 502) and A1298C (sample size 7934) and the major psychiatric disorders (i) schizophrenia (SZ), (ii) bipolar disorder (BPD), and (iii) unipolar depressive disorder (UDD). In order to examine possible shared genetic vulnerability between the different major psychiatric disorders, associations were calculated between MTHFR and major psychiatric disorder (SZ, BPD and UDD combined). Results: MTHFR C677T was significantly associated with major psychiatric disorders (SZ, BPD and UDD combined; random effects odds ratio (OR) = 1.26 for TT vs CC genotype carriers; confidence interval (CI) 1.09, 1.46); meta-regression did not suggest moderating effects of psychiatric diagnosis, sex, ethnic group or year of publication. Although MTHFR A1298C was not significantly associated with the major psychiatric disorder, nor with SZ, there was evidence for diagnostic moderation indicating a significant association with BPD (random effects OR = 2.03 for AA vs CC genotype carriers, CI: 1.07, 3.86). Meta-analysis on UDD was not possible due to the small number of studies available. Conclusion: This study provides evidence for shared genetic vulnerability for SZ, BPD and UDD mediated by MTHFR 677TT genotype whereas MTHFR 1298AA genotype may increase risk for BPD.
ID: 978245

JOINT MAPPING OF GENOME-WIDE GENE EXPRESSION AND ASSOCIATION IN A SCHIZOPHRENIA DATASET

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Background: Schizophrenia (SZ) genome-wide association studies (GWAS) have found common-variant low-effect loci, with most signals being intergenic or intronic. Rare large-effect copy number variants (CNVs) have been found to be contribute to SZ in large case-control collections including the Molecular Genetics of SZ (MGS). Each type of variant may regulate mRNA expression as their functional mechanism, but previous work examining this has been hampered by underpowered samples. Methods: We are conducting the largest genome-wide expression study of SZ to date. Excluding MGS lymphoblastoid cell lines (LCLs)showing poor growth and extreme clonality, we selected ~1K European ancestry (EA) SZ case samples and an age and sex matched set of ~1K screened controls. GWAS data (Affymetrix 6.0) was already available. We are studying and controlling for the confounding effects of age, sex, and population stratification, and LCL aspects (cell counts, clonality, energy status, Epstein Barr virus load, batch effects). We grew the selected LCLs under standardized conditions to log-phase with careful quality control (QC), harvested cells for total RNA extraction, and assayed the mRNA with Illumina HT-12v4 microarrays. We will search for expressed sequences that

show case-control differences in expression level and for these genes, we will test association between the expression levels and SNPs in cis in the gene expression sample (~1K cases and ~1K controls). We will then test association between these identified SNPs and SZ in the rest of the MGS EA sample (~1.6K cases and 1.6K controls). In addition, we identically processed MGS samples carrying CNVs for 1q21.1, 2p16.3, 15q13.2, 16p11.2, and 22q11.21 (velocardiofacial syndrome) to compare to the much larger sample without these CNVs. Results: Initial array QC on the first 480 samples shows expected results in terms of variance in expression being lowest in RNA technical (array batch) replicates, intermediate in biological (culture batch) replicates, and highest in separate random samples with the second quarter of the samples now undergoing QC. Conclusion: We will report on the results of the analysis of the full sample, as well as on the CNV carriers at the meeting. The joint analysis of genome-wide expression and association data is expected to lead to discoveries of mechanisms of SZ susceptibility otherwise obscured to either method in isolation. This work was supported NIH RC2MH090030.
ID: 986950

POLYMORPHISMS OF THE INTERLEUKIN-6 RECEPTOR GENE AND PLASMA LEVELS OF INTERLEUKIN-6 AND SOLUBLE INTERLEUKIN-6 RECEPTOR IN SCHIZOPHRENIA

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Background: Elevated serum or plasma levels of interleukin-6 (IL6) are common findings in schizophrenia, suggesting the role of excessive IL6 signaling in the pathogenesis of schizophrenia. IL6 binds to soluble IL6 receptor (sIL6R) to form a complex that enhances the biological activity of IL6. The sIL6R is generated by shedding of the membrane-bound IL6R. This process is influenced by the single nucleotide polymorphism (SNP) D358A of IL6R gene, which substitutes amino acid at the proteolytic cleavage site. The aim of this study was to examine the association of schizophrenia with IL6R polymorphisms and to determine the relation of IL6R D358 to the plasma levels of IL6 and sIL6R in subjects with schizophrenia and healthy controls. Methods: Subjects were 520 schizophrenic patients according to the DSM-IV criteria (mean age 44.1 ± 14.0 years, 289 males) and 1032 healthy controls (45.1 ± 16.2 years, 359 males). All subjects were biologically unrelated Japanese. Six tagging SNPs of the IL6R gene were genotyped by Taqman 5' allelic discrimination assay. Plasma levels of IL6 were determined by a BD(TM) Cytometric Bead Array system using BD FACSCanto II in 113 of the subjects with schizophrenia and 113 of the controls matched for age and sex. Plasma sIL6R levels were determined by enzyme-linked immunosorbent assay in 53 of the subjects with schizophrenia and 50 of the controls. Results: No significant difference in allele distribution in IL6R gene was found between schizophrenia and controls. Plasma IL6 levels ($P = .006$) were significantly higher in schizophrenia compared with controls. No significant difference in mean plasma sIL6R levels was observed between schizophrenia and controls ($P = .89$). The Ala allele of D358A was associated with significantly higher plasma levels of IL6 ($P = .016$) and sIL6R ($P < .00000001$) in the controls. In subjects with schizophrenia, the Ala allele was significantly associated with higher plasma levels of sIL6R ($P < .0000001$) but not with plasma levels of IL6 ($P = .37$). Conclusion: The Ala allele of D358A was found to be associated with higher sIL6R levels in schizophrenia and with higher levels of both IL6 and sIL6R in controls. The overall IL6 levels were elevated in schizophrenia with no significant increase in sIL6R levels compared with the controls. Increased IL6 levels without compensatory decrease in sIL6R levels, as observed in our study, may result in excessive IL6 signaling in schizophrenia.
ID: 979059

COPY NUMBER VARIANTS (CNVS) CORRELATE WITH THE EXPRESSION OF SPECIFIC GENES IN HIPPOCAMPAL GABA CELLS IN SCHIZOPHRENIA (SZ) AND BIPOLAR DISORDER (BD) BRAINS

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Background: The regulation of GAD67 (GAD1) involves complex interactions with genes involved in cell cycle regulation and DNA repair and this raises a question as to whether there is a relationship between genomic integrity and the expression of genes involved in the regulation of GABA cell function. Methods: A cohort consisting of 15 normal controls, 15 SZs and 15 BDs matched for age, postmortem interval, gender and hemisphere was used to determine the number of CNVs for each gene. Laser microdissection (LMD) was used to remove samples of the stratum oriens (SO) of sector CA3/2 where the most significant changes in GAD67 regulations have been observed. The SO in sector CA1 was used as a control site because decreases in the expression of GAD67 have not been found in this sector. The high-density Genome-Wide Human SNP Array 6.0, together with an Affymetrix platform was used to study CNVs as markers for genomic integrity in 28 different target genes associated with GAD67 regulation. Results: A substantial number of GAD67 regulatory genes showed striking changes in CNVs in the CA3/2 subregion. GAD67, GRIK1-3, DAXX, VEGFA and HDAC11 showed the most prominent changes in SZs, while GRIKs1 and 2, RUNX2, PAX5 and SMAD4 showed the greatest changes in BDs. The magnitude of the changes was highest in GAD67, DAXX and HDAC11. In CA3/2 of the patient groups, all genes showed a striking correlation between the respective CNVs and the fold changes for the respective expression profiles ($r = .692$; $P = .0001$), when compared to similar data for sector CA1 ($r = .178$; NS). Linear regression analyses also showed much higher correlations between CNVs and mRNA levels in the subset of genes most closely involved in GAD67 regulation ($r = .7121$) than those showing only indirect involvement with the GAD67 regulatory network ($r = .4920$). Conclusion: These findings suggest that DNA CNVs for specific genes may influence the regulation of their mRNA expression in hippocampal GABA cells in SZs and BDs. This link between the genome and transcriptional mechanisms occurs in a site specific manner within the hippocampal circuit. Genomic integrity as measured by the CNVs may play an important role in regulating the expression of GAD67 and other genes involved in its regulatory network.
ID: 979891

IMMUNE RESPONSE GENES ARE DIFFERENTIALLY EXPRESSED IN SCHIZOPHRENIC SMOKERS

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Background: There is a non-specific over-activation of the immune system in schizophrenia. There is evidence that genes believed to belong to immune function are used for other processes in the brain. The Class I Major His-

tocompatibility Complex (MHC-I) is necessary for remodeling of dendritic trees during development, and a necessary component for long term potentiation (LTP). These processes are aberrant in schizophrenia. The α7 nicotinic acetylcholine receptor is essential for down regulating immune activation and nicotine suppresses the immune response. The prevalence of smoking is high in schizophrenia. To date, there have been no reports of smoking effects on the immune system in schizophrenia. Methods: We compared immune gene expression in human postmortem hippocampus of schizophrenic and control smokers and non-smokers. First we compared gene expression for 12 625 genes from twelve smokers and twelve nonsmokers by oligonucleotide microarray analysis. QRT-PCR was employed to validate microarray results. In situ hybridization was used to visualize the cellular expression patterns of one gene that was found to be differentially regulated by smoking in schizophrenic subjects. Results: Immune response gene expression is decreased in hippocampus of smokers. Decreases were seen in HLA-G, adrenomedullin, NFκB, lymphocyte antigen 6 complex, NFAT, and integrin b1. A set of immune genes was differentially regulated in schizophrenic smokers. mRNA levels of four transcripts were significantly elevated in schizophrenic nonsmokers but were significantly reduced in schizophrenic smokers. Levels for these genes were unchanged between control nonsmokers and smokers. These included allograft inflammatory factor 1, β2-microglobulin, HLA-A, and the interleukin 10 receptor. In situ hybridization was used to visualize the expression HLA-A. Expression of HLA-A was seen in the follicular cells of the dentate gyrus, cells in the hylum, and cells CA3 layer of the hippocampus. Cells in the CA3 layer had the distinctive appearance of pyramidal cells and were positive for glutamate after application of immunofluorescent counterstain. Conclusion: Immune genes tend to be upregulated in the hippocampus of schizophrenic subjects compared to controls and smoking reverses this phenomenon, suggesting that nicotinic receptors modulate their expression in the brain. Upregulated MHC-I and its associated protein, β2-microglobulin may be part of the etiology of decreased LTP and dendritic spine density found in schizophrenia.
ID: 982138

BIOLOGICAL AND PSYCHOSOCIAL ADVERSITIES ACROSS TIME POINTS RELEVANT TO THE PUTATIVE DEVELOPMENTAL TRAJECTORY OF SCHIZOPHRENIA: GENE × ENVIRONMENT INTERACTIONS IN NRG1 AND COMT MUTANTS

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Background: A new generation of epidemiological studies, implicating both biological and psychosocial adversities acting across the putative developmental trajectory of schizophrenia, are now complementing a plethora of molecular genetic findings. This highlights a need for more incisive models of gene × environment interactions that are rooted in these environmental and genetic findings. To this end, we have studied a series of such environmental adversities in mice mutant for two genes bearing different relationships to schizophrenia: neuregulin-1 (NRG1) and catechol-O-methyltransferase (COMT). Methods: NRG1 mutants were subjected to one of three environmental adversities: intrauterine compromise via maternal immune activation; adolescent psychosocial stress via repeated social defeat; and adult, subchronic exposure to the psychotomimetic phencyclidine (PCP). COMT mutants were subjected to adolescent vs. adult, subchronic exposure to the psychotomimetic Δ9-tetrahydrocannabinol (THC). Phenotypic evaluations included ethological assessment, exploratory activity, prepulse inhibition, cognition, social behavior and magnetic resonance imaging. Results: The effects of genetic mutation on the functional consequences of each of maternal immune activation, adolescent social defeat, adult PCP or adolescent vs. adult THC were characterized. For example, the disruptive effects of acute PCP were attenuated in NRG1 mutants given subchronic vehicle but heightened in NRG1 mutants given subchronic PCP; the disruptive effects of adolescent THC were heightened in COMT mutants while no such effects of adult THC were evident. Conclusion: These findings indicate that for a series of environmental factors operating across the developmental trajectory of schizophrenia, both biological and psychosocial, an interaction with psychosis-related genes may be an important component in ''sculpting'' the overall psychosis phenotype. The authors' studies are supported by Science Foundation Ireland and the Health Research Board.
ID: 978216

INVESTIGATION INTO THE MOLECULAR MECHANISMS BY WHICH DISC1 REGULATES THE EXPRESSION OF TRANSCRIPTION FACTORS IMPORTANT FOR CELL FATE DETERMINATION AND DIFFERENTIATION

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Background: DISC1 is a susceptibility gene for major psychiatric illness. Using the zebra fish model system, we previously determined that Disc1 regulates two stem cell maintenance factors (FoxD3 and Sox10) that have many functions in cranial neural crest (CNC) cells, including the maintenance of precursor pools, timing of migration onset, and the induction of cell differentiation [1]. CNC cells are multipotent progenitors that are able to give rise to multiple cell types including craniofacial cartilage, peripheral neurons and glia, and pigment cells. Important for our studies into the pathogenesis of schizophrenia, neural crest and neural cells of the developing brain share many features including their ectodermal origin, ability to migrate long distances, the ability to give rise to multiple cell-types, and their responsiveness to the same intracellular and extracellular signaling molecules. Furthermore, both Foxd3 and Sox10 also play roles in brain development. Foxd3 is a stem cell marker that is present in neurogenic brain regions and Sox10 plays a critical role in oligodendrocyte differentiation. Using the zebra fish model system, we have continued these studies to examine the mechanism by which Disc1 regulates the expression of these transcription factors. Methods: Multiple genetic techniques have been developed to examine gene function in the zebra fish, including morpholino-driven loss-of-function. Using these techniques, we have examined Disc1 function in neurodevelopment. Results: We will present our data that investigates the mechanism by which Disc1 regulates sox10 expression. We have demonstrated that disc1 is expressed in CNC cells and the developing craniofacial cartilage. In addition, knockdown of Disc1 results in the elevated expression of stem cell maintenance factors (foxd3 and sox10) in premigratory CNC cells, delays in the migration of precursors and craniofacial abnormalities. Conclusion: In summary, CNC cells are similar to neurons in their cellular origin, high mobility, and response to signals. Furthermore, Sox10 is emphasized as an integral transcription factor required for the differentiation of both neural crest cells and oligodendrocytes. Therefore, understanding the molecular mechanism by which Disc1 regulates Sox10 expression provides valuable insights into the function of this protein in the developing brain and schizophrenia pathogenesis.
1.Drerup, C.M., Wiora, H.M., Topczewski, J., and Morris, J.A., Development, 2009.
ID: 979966

HERITABILITY OF NEUROLOGICAL SOFT SIGNS IN CHINESE HEALTHY ADOLESCENT TWINS: IMPLICATIONS FOR SCHIZOPHRENIA RESEARCH

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Background: Neurological soft signs (NSS) including motor coordination, sensory integration and disinhibition, are more frequently associated with schizophrenia, and have been considered to be potential endophenotypes for schizophrenia. Studies have also reported increased prevalence rates of NSS in non-psychotic first-degree relatives of schizophrenia patients. However, very little is known about the heritability of NSS, particularly in non-Caucasians. The current study attempted to estimate the heritability of NSS in Chinese healthy adolescent twins. Methods: 177 monozygotic and dizygotic healthy Chinese young twin pairs (aged from 12 to 16) were recruited and administered with the Cambridge Neurological Inventory to assess NSS. Structural equation modeling was applied to test the latent genetic and environmental effects upon NSS. Results: Genetic influences could be explained by additive genetic, shared environmental and unique environmental effects, with heritability estimates of .73 for NSS total scores. The heritability of motor coordination, sensory integration and disinhibition subscales is .54, .41and .30, respectively. Specifically, items such as Finger Thumb Opposition of left hand (r = .30), Oseretsky (r = .33), Fist-Edge-Palm of right hand (r = .41), Graphesthesia (r = .31), and Wink (r = .49) showed significant correlations among twin pairs. Conclusion: These findings indicate that NSS can be accounted for by genetic effects, especially motor coordination. These findings not only suggest that NSS are heritable in healthy Chinese adolescent, but also have implications for schizophrenia research.
ID: 978197

GENETIC ASSOCIATION STUDY OF NEUREGULIN AND ITS RECEPTOR IN TARDIVE DYSKINESIA

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Background: Tardive dyskinesia (TD) is a side effect of chronic antipsychotic medication characterized by involuntary movements mostly in the orofacial regions although it can also affect limbs and trunk. Its etiology and exact pathophysiology remains unclear. A recent study on genetically modified mice pointed to a possible role of neuregulin in orofacial dyskinesia (Tomiyama et al, 2009). Although the NRG1 gene has been associated with schizophrenia, its role in TD has not been investigated. Methods: We explored the possible association of polymorphisms in the genes for neuregulin (NRG1) and its receptor (ERBB4) with TD. We genotyped three single-nucleotide polymorphisms in the NRG1 and ERBB4 genes in our European sample of schizophrenia patients who had been assessed for the presence of TD using the Schooler and Kane criteria (n = 196). We compared the genotype frequency distributions between schizophrenia patients with and without TD. Results: Our findings revealed that the NRG1 markers rs35753505 and rs6994992 were not associated with TD status, while the ERBB4 marker rs839523 C allele was over-represented in schizophrenia patients with TD. Conclusion: Our results suggest that ERBB4 plays a role in TD. Further analysis with additional polymorphisms and functional study of the associated polymorphisms are required to better interpret these findings.
ID: 985287

IDENTIFICATION OF A ROLE FOR CAMK2G IN THE PATHOLOGY OF SCHIZOPHRENIA

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Background: Recent experiments have suggested that microRNAs may play a major role in the pathology of schizophrenia, and that identification of the protein-coding targets of these miRNAs may lead to novel therapeutic targets. The miRNAs miR-219, miR-132, and miR-181b have all been linked to schizophrenia in human patients, or to NMDA signaling in mouse models of schizophrenia. Calcium/calmodulin-dependent protein kinase II gamma (Camk2g), a brain-expressed CamkII isoform, is a target of both miR-219 and miR-181b. However, the function of Camk2g in the nervous system is currently unknown. Methods: In the present experiments, we used in vitro techniques to study the upstream regulation of Camk2g activity and the downstream effects of Camk2g on schizophrenia-associated signaling pathways. In vivo, we examined the expression pattern of Camk2g throughout the brain, and regulation of Camk2g expression in mouse models of schizophrenia. Results: We identified a role for Camk2g in the regulation of the CREB and GSK3b/beta-catenin signaling pathways, both of which have been associated with schizophrenia. We characterized the expression profile of Camk2g both during the developmental period, and within discrete nuclei in the adult brain, including the prefrontal cortex, nucleus accumbens, hippocampus, and amygdala. Conclusion: Our data indicate that Camk2g is highly expressed in the brain compared to peripheral tissues. The effects of Camk2g on CREB activity, GSK3b phosphorylation, and beta-catenin activity suggest a biological function for Camk2g that is relevant to schizophrenia. Current experiments are on-going to determine whether Camk2g represents an activity-dependent input into known schizophrenia-associated molecular pathways, including the Disc1 pathway.
ID: 979357

8. Genetics, Clinical

SEROTONIN TRANSPORTER GENE POLYMORPHISMS, CHILDHOOD TRAUMA AND COGNITION IN PATIENTS WITH PSYCHOTIC DISORDERS

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Background: The short(s-) allele of the serotonin transporter gene (5-HTTLPR) is related to an increased psychological reaction (ie fear and negativity) and greater increase of stress hormones in response to stressful experiences, compared to the long (l-) allele. Furthermore, increased stress levels are associated with cognitive impairments in a variety of clinical and experimental samples. Lastly, patients with psychosis are characterized by increased stressful events, such as childhood trauma, which together with the short 5-HTTLPR variant may contribute to the cognitive abnormalities found in this group. The overall aim of this study is to investigate the link between childhood trauma, 5-HTTLPR gene, and cognition in patients with psychosis across diagnosis. Methods: 118 patients with psychosis (mean ± age: 32.2 ± 11.3; gender: 54% males; both schizophrenia and affective disorder) were recruited from the University hospital in Oslo, Norway as part of the Thematic Organized Psychosis(TOP)study. History of childhood physical abuse, sexual abuse, emotional abuse and neglect were obtained using the Childhood Trauma Questionnaire (CTQ). A standardized neuropsychological test battery was conducted to measure general cognition, memory, working memory, visuo-spatial abilities, and verbal intelligence. 5-HTT was genotyped using standardized 5-HTT polymorphism PCR. Multivariate Analysis of Variance (MANOVA) was conducted to assess childhood trauma experiences, and 5-HTTLPR gene variations (as between subject's factor) and cognitive domains (as within-subjects variables). Results: A significant interaction was observed for physical or emotional abuse, and the homozygote short (s-) allele of the 5-HTTLPR gene, and cognitive impairments across domains. Patients with the homozygote short (s-) allele with early trauma show reduction in cognitive function across cognitive domains, compared to the rest of the sample. Conclusion: Our results indicate that patients carrying the short (s-) 5-HTTLPR variant with a history of physical and emotional abuse, are particularly vulnerable for developing cognitive impairment compared long (l-) 5-HTTLPR carriers, and patients without childhood trauma. These results underscore the need for replications, and the need to investigate gene environmental interaction models when targeting cognitive impairment in psychosis.
ID: 979339

GENETIC FACTORS INFLUENCING CLINICAL OUTCOME AND ADVERSE REACTIONS DURING ANTIPSYCHOTIC TREATMENT

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Background: Decades of pharmacogenetic research have identified several genes in metabolizing enzymes, dopamine and serotonin receptors which influence treatment response to antipsychotic medications. In particular, CYP functional polymorphisms have been directly related with plasma levels of first generation antipsychotics and with development of adverse reactions, whereas polymorphisms in D2, D3 and 5-HT2 receptors have been related to improvement in positive and negative symptoms, respectively. These findings are a direct reflection of the pharmacokinetic and pharmacodynamic properties of currently available antipsychotic medications, and may be directly related to the aetiology of the disease. The clinical value of these ''pharmacogenetic genes'' for the prediction of clinical outcome and treatment selection is still under investigation. Recent GWAs and transcriptomic investigations show that antipsychotic drugs alter the expression of genes involved in lipid metabolism and immunological response. In our own trancriptomic studies we have identified several genes which expression is affected by antipsychotic treatment but not by antidepressant drugs, including genes involved in immune response, cell communication, signal transduction and regulation of lipid metabolic processes. These associations may explain some of the treatment-associated adverse reactions. The implications of these findings for the improvement of antipsychotic efficacy and safety and for the development of novel drugs will be discussed. Methods: inbred rats were treated with haloperidol, citalopram or control vehicle for two weeks. After the treatment period, RNA expression levels were examined using Illumina Technology. A gene-expression programme package (J-Express v.8.0, Molmine) was used to conduct the statistical analyses (SAM and t-tests) of results. Results: Haloperidol altered the expression of several genes involved in immune response, cell communication, signal transduction and regulation of lipid metabolic processes Conclusion: Antipsychotic drugs may alter the expression of genes associated with disease aetiology and with lipid metabolism. These changes may be related to their antipsychotic activity and associated side-effects.
ID: 978447

GENETIC DETERMINANTS OF DOPAMINE SIGNALING IN PHENOTYPES RELEVANT TO SCHIZOPHRENIA

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Background: Several studies and meta-analyses have involved the gene for dopamine D2 receptors (DRD2) in risk for schizophrenia. Moreover, several lines of evidence suggest involvement of the dopamine system and of D2 signaling in the pathophysiology of schizophrenia. Phenomenologically, schizophrenia is characterized by working memory (WM) deficits, prefrontal cortex dysfunction, and abnormal cortical lateralization. Indeed, several authors have hypothesized that these phenomena can be part of a systems level pathophysiological mechanism also involving dopamine D2 receptors in the striatum. D2 receptors exist in two isoforms, one mainly pre-synaptic (D2S, an autoreceptor inhibiting dopamine release), another mainly post-synaptic (D2L). Methods: Several in vitro molecular and in vivo functional imaging techniques have been used in a large sample of healthy subjects and patients with schizophrenia. Results: An intronic SNP, rs1076560 (G>T), predicts alternative splicing such that the T allele is associated with reduced relative D2S in post mortem human prefrontal cortex. Moreover, the T allele is associated with reduced WM performance and disturbed prefrontal cortex activity in controls and in patients with schizophrenia measured with a block-design task like the N-Back. Using an event-related version of the Sternberg Item Recognition task, we have also determined that effect of the T allele is most evident in prefrontal cortex at encoding and retrieval of WM. Using [I123] FPCIT and [I123] IBZM SPECT, we have also determined that the T allele is associated with reduced striatal binding of both radiotracers, suggesting greater dopamine levels. Moreover, striatal binding of the two radiotracers correlates in opposite fashion with prefrontal activity during WM in carriers of the two different alleles. Finally, abnormal functional lateralization of the whole cortico-subcortical motor system is predicted by presence of the T allele. Conclusion: While association of DRD2 with diagnosis of schizophrenia is still debated, these data indicate that rs1076560 genotype recapitulates several aspects of the pathophysiology of schizophrenia suggesting its involvement in genetic risk for this disorder.
ID: 978251

IMAGING GENETICS OF THE D2 SIGNALING SYSTEM

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Background: Risk for schizophrenia is largely determined by genetic variation. The balance of dopamine (DA) stimulation of D1 and D2 receptors plays a critical role in the pathophysiology of prefrontal cognition and of schizophrenia. DRD1 and DRD2 code for these two receptors, respectively. Rs686 within DRD1 is a functional SNP affecting expression of the receptor (A>G). D2 receptors exist in two isoforms, D2S mainly pre-synaptic (autoreceptor) and D2L mainly post-synaptic. A functional intronic SNP of DRD2 (rs1076560) is associated with alternative splicing affecting D2S/D2L relative expression (G>T). Downstream of D2S, expression and activity of c-AMP independent pathway AKT1/GSK3β contribute to determine post-synaptic signaling, especially in cortical neurons. rs1130233 within the AKT1 gene affects expression (G>A) and is associated with prefrontal activity during cognition. Methods: Real-time PCR and Western Blotting were used to examine expression and phosphorylation of the different proteins from anterior cingulate of 33 post-mortem samples (donated by the Stanley Medical Research Institute) and from PBMCs (N = 29) of healthy subjects. Several cognitive tasks have been used to evaluate prefrontal cognition (N = 151). BOLD fMRI during performance of the N-Back and VAC tasks have been used to measure prefrontal activity (N = 277). Results: Preliminary analyses suggest replication of the effects of rs686 on D1 expression (P = .04, one-tailed; A>G) and of rs1076560 on D2S/D2L relative expression (P = .05, one-tailed; G>T) in anterior cingulate. Moreover, there was an interaction between the two genotypes with the number of categories achieved at the Wisconsin Card Sorting Test - DRD2 T and DRD1 A carriers had reduced performance (F = 3.9, P = .04). Consistently, BOLD fMRI data demonstrated an interaction between the two genotypes in prefrontal cortex at the N-Back and at the VAC (N = 277, P <.05, corrected) - DRD2 T and DRD1 A carriers had most inefficient activity. Molecular data from PBMCs also demonstrate interaction between DRD2 and AKT1 genotypes on expression of the latter and on phosphorylation of GSK3β. Consistent results are also indicated by BOLD fMRI activity of the prefrontal cortex during the VAC task - DRD2 T AKT1 A carriers have altered activity. Conclusion: These results demonstrate that genetically determined molecular and physiological interactions within dopamine signaling contribute to determine prefrontal pathophysiology.
ID: 983852

GENETIC INTERACTIONS AND EPIGENETIC EFFECTS FOR RISK OF CORTICAL DYSFUNCTION IN SCHIZOPHRENIA

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Background: Identification of genes involved in schizophrenia has been difficult, probably also because of epistatic interactions and of epigenetic modifications within genes involved in its pathophysiology. Dopamine dysregulation is sensitive to stress and has been implicated in the pathophysiology of prefrontal cortical dysfunction in schizophrenia. We have characterized potential epistatic interactions downstream of D2 receptors and epigenetic modifications of the COMT effect on cognition. The D2/AKT1/GSK-3β signaling pathway has been involved in the downstream intra-cellular effects of dopamine, in the pathophysiology of cognitive deficits and related brain activity in schizophrenia, as well as in response to treatment with antipsychotics. On the other hand, DNA methylation at CpG dinucleotides is associated with gene silencing, stress, and memory. COMT inactivates prefrontal dopamine. The COMT Val158 allele in rs4680 creates a CpG dinucleotide and is associated with differential enzyme activity, stress responsivity, and prefrontal activity during working memory (WM). Methods: Western-blot was used to measure protein levels and phosphorylation from PBMCs. Pyrosequencing was used to measure percent methylation. With BOLD fMRI in 210 individuals we assessed cortical activation during sustained attention and working memory. Response to an eight week trial with olanzapine was evaluated with PANSS in 66 patients with schizophrenia. Results: Our data indicate that in healthy subjects interaction between the T allele of DRD2 rs1076560 and the A allele of AKT1 rs1130233 is associated with reduced AKT1 protein levels and phosphorylation of GSK3-β, with altered cingulate response and reduced behavioral accuracy during attentional processing. Interaction of these two alleles is also associated with greater improvement of PANSS scores in patients with schizophrenia after treatment with olanzapine. Methylation of the Val158 allele of Val/Val humans: is associated with measures of stress and with WM performance; interacts with stress to modulate prefrontal activity during WM; is inversely related with mRNA expression and protein levels, potentially explaining the in vivo effects. Finally, COMT methylation in prefrontal cortex and in PBMCs are correlated in rats. Conclusion: The present data suggest that genetic interactions and environment-related methylation of alleles within functional SNPs are important mechanisms for regulation of gene expression and behavior-related cortical brain activity in humans.
ID: 975838

GENETIC MODULATION OF THE ACUTE PSYCHOLOGICAL EFFECTS OF CANNABIS IN MAN

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Background: The val158met polymorphism of the gene coding for the COMT enzyme has been shown to modulate the induction of acute psychotic symptoms by cannabis and its main psychoactive ingredient, delta-9-tetrahydrocannabinol (delta-9-THC) in individuals with pre-existing liability to psychosis and also modulate the long-term risk of psychotic disorders in regular cannabis users. However, how the COMT gene modulates the acute psychological effects of cannabis in healthy individuals and the specific neurocognitive mechanisms underlying these effects have never been systematically examined in man. Methods: Thirty-six healthy men were tested on two separate occasions employing a double-blind, crossover design to compare the effects of oral administration of 10 mg of delta-9-THC with placebo while they performed a verbal learning and emotional (fear) processing task inside the MRI scanner. They were genotyped for the val158met polymorphism of COMT. Results: Administration of delta-9-THC induced positive and negative psychotic symptoms and anxiety and the COMT genotype significantly modulated the effects of delta-9-THC on negative and anxiety symptoms as well as on performance in the verbal learning task. COMT genotype status also modulated significantly the effects of delta-9-THC in the parahippocampal cortex while learning during encoding, in the parahippocampal cortex, dorsolateral prefrontal cortex and striatum during the recall condition and in the amygdala during the emotional (fear) processing task. The modulatory effects of delta-9-THC in the striatum and dorsolateral prefrontal cortex during learning and in the amygdala while processing fear were respectively related to the positive and negative psychotic symptoms and anxiety induced by it. Conclusion: These results provide novel mechanistic insights into the genetic modulation of the acute effects of cannabis in healthy individuals.
ID: 979646

HUMAN GENETIC STUDIES OF NICOTINIC RECEPTORS AND THE RELATIONSHIP WITH ADDICTION AND PSYCHIATRIC ILLNESS

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Background: Individuals with serious mental illnesses such as schizophrenia are commonly current smokers and often nicotine dependent. Now that genetic contributions to smoking quantity and nicotine dependence have been identified, we can investigate two research questions: 1. Are genetic associations with nicotine dependence seen in the general population similarly seen in subjects with severe mental illness? 2. Do loci associated with nicotine dependence increase the risk of developing a severe mental illness (in other words are there pleiotropic effects)? Methods: Using data from the NIMH Respository, we examined genetic variants in the CHRNA5-CHRNA3-CHRNB4 nicotinic receptor gene cluster on chromosome 15 and the CHRNA6-CHRNB3 nicotinic receptor gene cluster on chromosome 8. We tested the association of these genetic variants with nicotine dependence among individuals with severe mental illnesses. We also examined the contribution of these variants to schizophrenia and bipolar illness. Results: Our initial results suggest that genetic variants that contribute to the risk of heavy smoking and nicotine dependence in the general population similarly contribute to the risk of developing nicotine dependence in individuals with a severe mental illness. This is seen even though the baseline population prevalence of smoking is much higher in a population afflicted with severe mental illness. Secondly, there is some evidence of a pleiotropic effect so that genetic variants that contribute to nicotine dependence may also be a risk factor for developing a severe mental illness, independent of the effect on smoking. Conclusion: This work may help us begin to untangle some of the complex relationship between smoking and mental illnesses.
ID: 989105

ASSOCIATION BETWEEN LEP -2548 (RS7799039) AND OBESITY DURING ANTIPSYCHOTIC TREATMENT

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Background: Weight gain and the development of obesity and metabolic abnormalities are recognized side effects of antipsychotic agents. The amount of weight gain experienced by patients is variable indicating that genetic factors may influence this outcome. Antipsychotic-treated individuals also exhibit abnormalities in the satiety hormone, leptin, which increases after drug exposure and remains elevated during treatment. We investigated the relationship between a functional genetic variant of the leptin gene (LEP) and antipsychotic-associated obesity. Methods: Seventy-five subjects (64% male, mean age 34+/−11 years) meeting DSM-IV criteria for schizophrenia ($n = 63$), bipolar disorder with psychotic features ($n = 10$), or major depressive disorder with psychotic features ($n = 2$) who were on stable treatment with an antipsychotic agent for at least two months were enrolled. Antipsychotics utilized included risperidone ($n = 33$), >/=2 antipsychotics ($n = 14$), clozapine ($n = 9$), aripiprazole ($n = 5$), quetiapine ($n = 5$), olanzapine ($n = 4$), haloperidol ($n = 4$), or ziprasidone ($n = 1$). Clinical symptoms, body mass index (BMI), leptin levels and metabolic variables were assessed. Subjects were genotyped for an LEP polymorphism −2548G/A (rs7799039) known to influence leptin expression and secretion in adipose tissue. Relationships between rs7799039, leptin levels, and obesity related outcomes were characterized. Results: Leptin levels were significantly correlated with BMI (males $r = .75$, $P < .0001$; females $r = .58$, $P = .002$). Genotypes for rs7799039 did not deviate from Hardy-Weinberg Equilibrium. There was no evidence for association between genotypes and leptin levels. The −2548_AA genotype was significantly associated with BMI >30 kg/m^2 with 67% of AA genotype subjects exceeding this criteria for obesity as compared to 34% of AG/GG subjects OR = 3.8 (95% CI 1.1, 12.6, $P = .02$). Conclusion: These data provide further evidence for a relationship between LEP variants and risk for obesity during antipsychotic treatment and are consistent with previous findings linking the −2548_AA genotype to metabolic abnormalities during risperidone treatment. The −2548_AA variant is associated with increased leptin secretion and expression in human adipose tissue. If an increased baseline expression of leptin is a marker of leptin resistance, exposure to antipsychotic agents in patients with impaired satiety signaling may predispose these individuals to a greater risk for obesity after chronic drug exposure.
ID: 978872

SEEING THROUGH THE FOG OF MULTIPLE ENDOPHENOTYPE-GENE ASSOCIATIONS IN SCHIZOPHRENIA

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Background: While it is clear that schizophrenia is highly heritable the genetic basis of this heritability is complex and challenging. Human genetic (GWAS, candidate genes, copy number variant, epigenetics), model organism, and imaging studies have yielded interesting yet modest gains. Another research tactic is to evaluate the genetic substrates of carefully selected quantitative endophenotypes with demonstrated deficits and heritability in schizophrenia. Methods: We have used a Consortium on the Genetics of Schizophrenia (COGS)/UCSD Illumina Custom 1,536-SNP array to interrogate 94 functionally relevant candidate genes for association with schizophrenia and schizophrenia-related endophenotypes in 219 Caucasian and 76 African American schizophrenia patients and normal subjects. This is a modified replication of COGS association findings. Quantitative phenotypic measures for analysis were derived from the following neurophysiological and neurocognitive endophenotypes: Prepulse Inhibition (PPI), P50 Suppression, the Antisaccade Task, the Letter-Number Span Test, the California Verbal Learning Test-2, and the Wisconsin Card Sort Test-64. Results: Schizophrenia patients showed significant deficits on most of the endophenotypic measures assessed, replicating prior studies and facilitating genetic analyses. A total of 41 genes were found to be associated with at least one endophenotype or schizophrenia itself with a P-value <.01 after surviving permutation and simulation tests for total significance of multiple endophenotypes and genes. Major results paralleled COGS reports of significant endophenotype-gene associations that survived 10 000 whole family simulations in a test for total significance developed by L. Lazzeroni. Many of these genes interact on a molecular level, and eleven genes displayed profound evidence for pleiotropy, revealing significant associations with three or more of the endophenotypes. "First" among these highly pleiotropic genes in this and the COGS sample were ERBB4 and NRG1, providing further support for a substantial role for these genes and related glutamate dysfunction in schizophrenia susceptibility. Conclusion: The observation of extensive pleiotropy for some genes and

singular associations for others in our data suggests both converging and independent pathways mediating the heterogeneous pathogenesis of schizophrenia and endophenotype dysfunction linked to schizophrenia.
Supported by MH065571, MH079777, MH042228
ID: 979939

ASSOCIATION OF GENETIC VARIANTS OF THE H1 AND M3 RECEPTORS WITH BMI AND HBA1C IN CAUCASIAN PATIENTS USING ANTIPSYCHOTICS

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Background: Antipsychotic treatment has been associated with weight gain and type 2 diabetes mellitus. Antipsychotic affinity for the histamine H1 receptor and the muscarinic M3 receptor have particularly been associated with weight gain and development of diabetes, respectively. We investigated two polymorphisms (rs346070 and rs346074) of the H1 receptor gene (HRH1) and one polymorphism (rs3738435) of the muscarinic acetylcholine receptor M3 (CHRM3) for an association with body mass index (BMI) and glycated hemoglobin (HbA1c). Methods: We included 430 Caucasian patients with a psychotic disorder and cross-sectionally measured BMI and HbA1c. Inclusion criteria were: DSM-IV criteria for a non-affective psychotic disorder, 18 years or older, one or more antipsychotics for at least three months. The primary endpoints of the study were BMI, HbA1c (%). Primary determinant were the genotypes of the two SNPs in the HRH1-gene, rs346070 (A/G) and rs346074 (C/T), and one SNP in the CHRM3-gene, rs3738435 (C/T). Results: No substantial differences in BMI (range: 27.4–29.3 kg/m^2) were found between users of the various antipsychotics (*P*-value ANOVA .583) or between different diagnoses. HbA1c values (range: 5.5%–6.8%) were significantly different between the various antipsychotics (*P*-value ANOVA .033). In users with antipsychotics with high H1 affinity there was a (non significant) increase in BMI per T-allele of rs346070 and per A-allele of rs346074. An opposite trend can be seen in users with a low H1 affinity antipsychotic. Conclusion: A significant association of interaction between haplotype rs346070- rs346074 and BMI (*P*-value .025) and obesity (*P*-value .005) in patients using high H1 affinity antipsychotics vs patients using low H1 affinity antipsychotics was found. We found no association of CHRM3 gene variant rs3738435 with BMI and observed no association with HbA1c in any of the variants. This study, for the first time, demonstrates a significant association between HRH1 variants and BMI in patients with a psychotic disorder. In future, genotyping of HRH1 variants may help predicting weight gain in patients using atypical antipsychotics.
ID: 980061

BRAIN DERIVED NEUROTROPHIC FACTOR AS A POTENTIAL BIOMARKER FOR RELAPSE IN SCHIZOPHRENIA: INITIAL OBSERVATIONS FROM THE PROACTIVE (PREVENTING RELAPSE IN SCHIZOPHRENIA: ORAL ANTIPSYCHOTICS COMPARED TO INJECTABLES: EVALUATING EFFICACY) STUDY

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Background: Brain-Derived Neurotrophic Factor (BDNF), the most extensively studied neurotrophin in schizophrenia, plays a formative role in neuronal development and in orchestrating neuronal responses to stress/noxious stimuli. There is convergent evidence from both preclinical and clinical studies including reports from our group (at MCG) indicating that BDNF may be a likely biomarker for relapse in mood disorders. We are presently studying- as a component of the PROACTIVE study-the trajectory of neurotrophin expression in relation to relapse to address the fundamental clinical question as to whether plasma BDNF could be a potential biomarker for relapse in schizophrenia. PROACTIVE is a federally funded 8 site multicenter comparative study of long-acting injectable antipsychotic and oral antipsychotic medications. Methods: Three hundred and five patients are being evaluated for up to 30 months. We have now conducted a preliminary analysis examining the relationship between the initial plasma BDNF levels (determined by ELISA) collected in PROACTIVE and subsequent hospitalizations. In this analysis, 58 of 181 patients (32%) had one or more hospitalizations. Proportional hazard survival regression used BDNF mean concentration as the predictor of first and subsequent hospitalization. Results: This analysis yielded $\chi^2 = 4.96$, $df = 1$, $P = .026$ with a negative regression parameter (.00531), indicating that lower BDNF is associated with higher risk of hospitalization. Conclusion: This is consistent with the hypothesis that higher BDNF levels are neuroprotective and with the potential utility of BDNF as a biomarker for relapse in schizophrenia. Further analyses on the role of BDNF in relapse are now in progress.
ID: 979205

ASSOCIATION STUDY OF LEPTINERGIC GENE POLYMORPHISMS WITH ANTIPSYCHOTIC INDUCED WEIGHT GAIN

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Background: Antipsychotic induced weight gain (AIWG) may lead to the metabolic syndrome in schizophrenia patients. The Leptin-Melanocortin system has been consistently implicated in the control of food intake. Single nucleotide polymorphisms (SNPs) located downstream of the Melanocortin- 4 receptor (MC4R) gene have been associated with higher body mass index in healthy human populations. The MC4R has a downstream effect on brain-derived neurotrophic factor (BDNF), resulting in altered eating behavior and energy expenditure. It has recently been found that the Val66-Met polymorphism in the promoter region of BDNF is associated with antipsychotic induced weight gain. Thus, we hypothesized that candidate SNPs of MC4R and BDNF can influence development of AIWG. Methods: Four tagged MC4R SNPs (rs2229616, rs17782313, rs11872992, rs8087522) and four tagged BDNF SNPs (rs6265, rs11030104, rs7103411 and rs7934165) were analysed in 224 patients who underwent treatment for chronic schizophrenia and were evaluated for antipsychotic induced weight gain for up to 14 weeks. Our refined sample consisted of 67 African Americans and 87 European Americans on clozapine/olanzapine, prospectively. We compared weight change (%) across genotypic groups using analysis of variance and covariance for the three tagSNPs (r2 $\geq$.8) near the MC4R and BDNF genes. Variants were genotyped using ABI TaqMan assays. Results: The MC4R rs2229616 SNP was monomorphic in our population. No significant genotypic or allelic associations were found between rs11872992 and rs17782313 polymorphisms and weight gain (P >.05). A trend towards association was found between rs8087522 and weight gain in patients of European Ancestry taking either olanzapine/clozapine (P = .088). The haplotype comprised of rs8087522-rs11872992-rs17782313 was nominally significant. No significant genotypic or allelic associations were found between the BDNF polymorphisms, val66met, rs11030104, rs7103411 and rs7934165, and weight gain in patients. No significant interaction was found between MC4R and BDNF SNPs. Conclusion: In this study we suggest that the polymorphisms near and within the MC4R gene may be associated with AIWG in chronic schizophrenia patients. We were unable to replicate the previous finding in the literature of the BDNF rs6265 polymorphism and weight gain in schizophrenia patients. However, these observations were made in a relatively small patient population. These results need to be replicated in larger sample sets.
ID: 979960

RISK FOR HOSPITALIZATION FOR SCHIZOPHRENIA AND AFFECTIVE DISORDERS AMONG FULL AND HALF SIBLINGS OF PROBANDS WITH SCHIZOPHRENIA: A POPULATION-BASED STUDY

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Background: Compared to the general population, siblings of patients with schizophrenia have a higher risk of developing schizophrenia (Laurson et al, 2005; Mortensen, 1999). There is also some evidence that this relationship may be non-specific, ie, that siblings of patients with schizophrenia may have a higher risk for psychiatric disorders in general. Methods: This study analyzed a population-based dataset to examine the relative risk of hospitalization for schizophrenia and affective disorders among full vs. half siblings of patients with schizophrenia, as well as among persons with 1 or more siblings with schizophrenia vs. those with 2 or more. The full (n = 12 555) and half (n = 2707) siblings of 6115 consecutively admitted patients with schizophrenia (ICD F20.0–20.9) were identified from the Israeli Psychiatric Hospitalization Registry. Age and gender matched controls (n = 61 048) were identified from the Israeli Population Registry. Psychiatric hospitalizations of siblings and controls were recorded from the registry. Results: Compared to controls, risk for schizophrenia was higher among persons with one or more (OR = 9.36, 95% CI: 7.73–11.33) or 2 or more (OR = 13.76, 95% CI: 8.84–24.15) full siblings with schizophrenia. Similarly, persons with one or more (OR = 7.91, 95% CI: 5.15–12.14) or 2 or more (OR = 8.44, 95% CI: 3.57–19.94) half siblings with schizophrenia had a higher risk of schizophrenia. Similarly, siblings of patients with schizophrenia also have increased risk for affective disorders: risk for hospitalization for affective disorder was higher among persons with one or more (OR = 7.29 95% CI: 5.60–9.49) or 2 or more (OR = 10.25, 95% CI: 5.50–19.10) full siblings with schizophrenia. Conclusion: This large, population-based study strengthens existing knowledge that schizophrenia has a strong familial, perhaps genetic component; and the greater the familial load, the greater the risk. These same familial, perhaps genetic factors also increase risk for affective disorders, emphasizing the overlap between these disorders.
ID: 983772

IS ZNF804A ASSOCIATED WITH REACTIVITY TO STRESS IN DAILY LIFE IN PATIENTS WITH PSYCHOSIS?

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Background: In genome-wide association studies ZNF804A (rs1344706) almost reached significant association with schizophrenia and recent evidence suggested an association with a variant with relatively spared cognition. Reactivity to stress has been repeatedly shown to be greatest in psychotic patients with relatively spared cognition, which could imply a role for ZNF804A in reactivity to stress. Methods: 88 patients with schizophrenia and 113 healthy controls were genotyped for rs1344706 and 8 additional common ZNF804A-SNPs: rs12477430, rs12613195, rs12693385, rs13393273, rs1480481, rs17508595, rs4667001 and rs7603001. All subjects were assessed with the Experience Sampling Method evaluating their psychotic and affective reactivity on event-related and social stress during daily life. Multilevel analyses were performed. Results: After Bonferroni correction for multiple testing the GWAS-identified rs1344706 risk-allele was not associated with affective or psychotic reactivity in daily life, neither were the other genotyped SNPs. This applied for the patient group, as well as for the complete sample. Conclusion: In this study ZNF804A genotype was not associated with stress-related psychotic or affective symptoms in the daily life of patients with schizophrenia. It is therefore unlikely that ZNF804A increases risk for psychosis through increased reactivity to stress.
ID: 979799

EFFECT OF PLACEBO AND REINTRODUCTION OF ANTIPSYCHOTICS IN PATIENTS WITH SCHIZOPHRENIA BASED ON COMT VAL108/158MET POLYMORPHISM

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Background: The goal of the current study was to assess whether genetic variation in the COMT gene will affect the decompensation magnitude of patients with diagnosis of schizophrenia during a coded drug withdrawal

placebo phase and subsequently on recovery when placed back onto active medication. Methods: We examined the effects of drug-withdrawal and substitution of blinded placebo in 59 patients with schizophrenia and their symptomatic recovery rate after the introduction of antipsychotic drugs based on the COMT Val108/158Met polymorphism. Patients either received placebo or standard antipsychotics for 4 weeks under a double-blind, cross-over design: Group 1 ($N = 29$) received 4-weeks of placebo followed by 4-weeks of coded standard antipsychotics, whereas Group 2 ($N = 30$) underwent the inverse sequence, receiving 4-weeks of coded standard antipsychotics followed by 4-weeks of placebo. Ratings during the blinded period were performed twice weekly and for four weeks after the completion of the study. The data was analyzed using a general linear model taking into account both main effect of genotype and difference in trajectory of PANSS over time, and their interactions. Results: We found that Val/Val individuals were significantly worse symptomatically on several variables during the 4-week coded placebo arm of the study, in comparison to Val/Met and Met/Met individuals (positive syndrome (Group 1: $P = .0009$; Group 2: $P < .001$), composite index (Group 1: .0062; Group 2: $P < .001$), general psychopathology (Group 2: $P = .0500$), thought disturbance (Group 1: $P < .0001$; Group 2: $P < .0001$), and activation (Group 2: $P = .0321$). Strikingly, Val/Met and Met/Met individuals overall remained at both a steady and attenuated state symptomatically in comparison to Val/Val individuals. Since Met carriers remained relatively stable in symptom rating severity while on coded placebo, recompensation was not relevant for these patients during this protocol. While Val/Val individuals recompensated symptomatically, they failed to reach the attenuated level of symptom severity manifested by Val/Met and Met/Met individuals (positive syndrome (Group 2: $P < .001$), composite index (Group 1: $P = .0112$; Group 2: $P < .0001$), general psychopathology (Group 2: $P < .0001$) thought disturbance (Group 2: $P < .0001$), and activation (Group 2: $P < .0001$)). Conclusion: These findings suggest that the Met allele provides both an alleviating and stabilizing effect on several symptoms related to medication withdrawal in this study.
ID: 984237

TRAVERSING THE BOUNDARIES OF THE DSM-IV: THE GENETICS OF SYMPTOM-BASED PHENOTYPES

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Background: Molecular genetic studies increasingly suggest that genes do not respect the boundaries of the current diagnostic system. For example, several well known candidate genes have been linked to multiple diagnostic groups including schizophrenia, schizoaffective disorder, bipolar disorder and major depressive disorder. Although efforts to identify quantitative trait loci (QTLs) associated with the symptom dimensions of major psychiatric disorders have met with early success this analytic approach has been limited to specific diagnostic groups. Thus, data seeking to elucidate the basis of common genetic risk across diagnostic groups are extremely limited. Methods: We genotyped a multi-diagnostic group of 764 patients with psychosis and 193 healthy individuals using a custom Golden Gate Illumina 1536 SNP chip. The chip was designed to comprehensively assess several genes, including NRG1, ERBB3, CACNA1C, ZNF804A and ANK3, which showed prior association to multiple diagnostic groups. Using lifetime ratings of psychosis we then assessed the relationship between genetic variation at these loci and phenotypic variation without regard to diagnostic group membership. Results: We identified several associations to symptom domains in each of these genes. After correction for multiple testing, however, only SNPs in ANK3, ZNF804A and NRG1 remained significant. In each case, the significant association was to a lifetime history of hallucinations. Follow up analyses indicated that none of these SNPs were significantly associated with case-control status in either the full group or in any individual diagnostic group. Conclusion: The present results suggest that delineation of the role of specific genes on symptom dimensions, rather than diagnostic entities is possible. Moreover, such methods may lead to more refined approaches to understanding the etiology of psychiatric disorders characterized by psychosis and may suggest novel treatment targets for specific domains of illness.
ID: 980096

INFLUENCE OF FAMILY HISTORY OF PSYCHOSIS ON AGE-AT-ONSET, SEX, AND SYMPTOM PRESENTATION IN AN URBAN SAMPLE OF FIRST-EPISODE PSYCHOSIS PATIENTS

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Background: A positive family history of psychosis has been shown to be associated with increased susceptibility to the development of schizophrenia, but less is understood about its impact on the clinical characteristics of the disorder. A recent meta-analysis (Esterberg et al, 2010) revealed that family history plays a role in reducing age-at-onset and increasing severity of negative symptoms; however, much of this research has been conducted with chronic samples, with less reliable age-at-onset measurement and decreased variability in symptomology. Thus, more research is needed on the potentially important influence of family history in first-episode psychosis patients. Methods: The current study examined a large sample ($n = 164$) of urban, primarily African American patients hospitalized for a first episode of a psychotic disorder in Atlanta, Georgia. Patients were assessed shortly after the first hospitalization and after being stabilized with antipsychotic medications. Presence of a first-degree family history of psychosis, age-at-onset of prodrome and psychotic symptoms, and severity of positive and negative symptoms were assessed. Results: Results showed that patients with a family history of psychosis had a significantly younger age-at-onset relative to patients with no such family history, but the two groups did not differ with respect to either positive or negative psychotic symptoms. However, there was a significant interaction between family history and sex for age-at-onset of both the prodrome and psychotic symptoms, as well as negative symptoms. In patients with a family history, there was a significant sex difference in age-at-onset, such that males had a younger age-at-onset of the prodrome and of psychotic symptoms. Furthermore, in male patients only, those with a family history of psychosis showed more severe negative symptoms relative to those males with no family history. Conclusion: These results will be discussed in light of recent findings on the relationship between family history and clinical presentation in schizophrenia, as well as the diathesis-stress model. Particular emphasis will be placed on discrepancies between the current findings and past research results. Finally, directions for future research will be presented.
ID: 979071

ABERRANT TYROSINE TRANSPORT ACROSS THE FIBROBLAST MEMBRANE IN PATIENTS WITH SCHIZOPHRENIA - INDICATIONS OF MATERNAL INHERITANCE

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Background: In previous studies of the present patients with schizophrenia, aberrant tyrosine transport across the fibroblast membrane was found. A low Km, a kinetic factor indicating high affinity between tyrosine and the binding site at the cell membrane, was found to be associated with poor

cognitive functions in patients. The present study aimed at investigating possible relationships between patients with schizophrenia and their first degree relatives in aberrant tyrosine transport indicating that it may be a biological marker for the genetic susceptibility. Methods: Thirty-three parents, 13 fathers and 20 mothers, from 23 families with a schizophrenic patient agreed to enter the study. They underwent skin biopsies for fibroblast cultivation, neuropsychological and psychiatric investigations and were classified as family history positive or negative. Tyrosine transport kinetics (Km and Vmax) were calculated from in vitro trials of gradients of extracellular tyrosine concentrations in fibroblast cultures. Results: An association between patients with schizophrenia and their mothers were found for a low Km indicating maternal inheritance. Mothers displaying a low Km performed worse on the neuropsychological tests compared to mothers with normal Km. Corresponding relationships between a low Km and neurocognitive dysfunction had previously been found for the patients. Conclusion: An aberrant tyrosine transport across plasma membrane may constitute a biological marker for an endophenotype within the schizophrenia spectrum with low cognitive functioning. A plausible mode for genetic transmission is maternal inheritance.
ID: 978776

KIBRA AND COGNITION: EXPLORING THE ASSOCIATION OF WWC1 SNPS WITH COGNITION IN SCHIZOPHRENIA AND HEALTHY SAMPLES

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Background: KIBRA is a protein found in kidney and brain and involved in synaptic plasticity. An early genome wide association (GWA) study of memory identified a SNP in WWC1, the gene that codes KIBRA, that was associated with delayed, but not immediate, verbal memory (rs17070145; Pappasotiropoulos, 2006). There have been several independent reports of the same association, and at least two negative studies, all focusing on this one SNP. Cognitive impairment, including verbal learning and memory, is an intermediate phenotype for schizophrenia genetics analyses. Methods: We examined the association of the WWC1 gene with cognition in data from a GWA analysis of 364 schizophrenic probands and 398 controls from the NIMH/CBDB/GCAP Sibling Study (Straub & Weinberger, unpublished data), using composite scores for specific cognitive domains and a general cognition composite, ''g.'' Results: WWC1 SNPs were associated with cognition in the healthy volunteers, but not in the schizophrenic probands. Two SNPs in complete linkage disequilibrium with rs17071045 showed stronger association to a processing speed composite score (eg, P = 1.98e-3 for rs9313411) than to other composites, including verbal memory. However, analyses revealed stronger associations between cognition in healthy volunteers and several other WWC1 SNPs. SNP rs4976606 was closely associated with cognition, and it correlated more highly with g (P = 2.71e-05, the 9th strongest association to general cognition among 495 089 SNPs analyzed) than with any specific cognitive domain composite, including a verbal memory composite (P = 8.76e-1). The association also differed in 187 male participants (P = 5.16e-05) as compared to 211 females (P = .228). Conclusion: These findings did not reach genome wide significance and should be interpreted with appropriate caution. We cannot rule out epistatic or environmental interaction effects, but current data do not support a simple role for WWC1 variation in schizophrenia cognitive impairment. However, confirmation of a difference in impact between healthy men and women could enhance understanding of sex-based differences in cognitive performance. Future work will include analysis of other WWC1 SNPs, haplotype and epistasis analysis, and efforts to confirm key findings in independent datasets. These analyses could strengthen the case that KIBRA is associated with cognition in the healthy population, although our current data suggest that the effect is not specific to delayed verbal memory but is more general.
ID: 979573

IDENTIFYING GENES INFLUENCING GRAY MATTER REDUCTIONS IN SCHIZOPHRENIA: AN ENDOPHENOTYPIC STRATEGY

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Background: Reduced gray-matter density may provide important information about the pathophysiological mechanisms underlying schizophrenia. Advances in image-based quantitative meta-analytic methodology has spurred a number of recent reviews which consistently report that patients have reduced gray-matter density relative to controls in a distributed network of regions, including bilateral insular cortex, anterior cingulate, left parahippocampal gyrus, left middle frontal gyrus, postcentral gyrus, and thalamus. As most of these deficits have been observed in unaffected relatives of schizophrenia probands, it is possible that reduced gray-matter in this network of regions is a marker of genetic liability for the illness (eg an endophenotype). Methods: Given that gray-matter density in this network varies within the normal population, and that the genes influencing normal variation likely predispose the illness, we developed a strategy to identify schizophrenia risk genes by: (1) delineating the network of regions with reduced gray matter in schizophrenia with a new ALE meta analysis (1784 total subjects); (2) determine the heritability of this network and establish the pleiotropy between regions within the network in a sample of 724 randomly-selected individuals from large extended pedigrees; (3) perform a genome-wide association on 1M SNPs in these families to localize quantitative trait loci influencing gray-matter density variation within this network; (4) localize the functional variant(s) most strongly associated with this trait in these families; and (5) test for pleiotropic effects of endophenotypically-nominated SNPs on risk of schizophrenia in independent data obtained from the NIMH repository. Results: To date, we updated our large-scale imaging meta analysis and estimated the heritability of gray-matter density in this network to be .624, $P = 8.89 \times 10^{-16}$. Genetic correlation analyses between regions in this network indicate that all regions are influenced by a set of common genetic factors. Genome-wide association analyses are underway. Conclusion: The proposed analytic approach harnesses powerful image-based meta analytic methods, extant neuroanatomic and genome wide association data in randomly selected pedigrees, and the NIMH genomics repository to provide novel candidate genes for schizophrenia.
ID: 979745

FOLATE SUPPLEMENTATION IN SCHIZOPHRENIA AND EFFECTS OF THE MTHFR C677T POLYMORPHISM

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Background: Folate deficiency and the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism have been linked to negative

symptoms in schizophrenia both independently and synergistically. This study examined the effect of folate supplementation on negative symptoms overall and in relation to MTHFR 677T allele load. Methods: Forty-six stable adult schizophrenia outpatients were enrolled and 32 were randomized, double-blind, in a parallel-group, twelve week add-on trial of folate 2 mg/day or matching placebo. The primary outcome measure was change from baseline to week 12 on the modified SANS total score using a mixed-model analysis. In addition, we measured the effect of MTHFR genotype on treatment effects and on changes in serum folate by grouping participants with T/T genotype together with C/T genotype and comparing their interactions to patients with C/C genotype. Results: Twenty-eight participants completed the trial. Folate supplementation did not significantly affect negative symptoms compared to placebo. However, there was a significant genotype x treatment effect on negative symptoms (F = 7.13, df = 1,39, P = .01). In addition, MTHFR status significantly moderated the relationship between change in serum folate and change in negative symptoms with negative symptoms in participants with at least one copy of the T allele significantly more likely to improve with increased serum folate (P = .03). Conclusion: We did not detect a therapeutic benefit of folate supplementation in a sample of patients with residual negative symptoms. A possible association between genotypes associated with reduced MTHFR activity and benefit from folate supplementation should be investigated further.
ID: 979784

MODULATION OF A CINGULATE CORTEX CONNECTIVITY: INFLUENCE OF NICOTINE, GENETICS AND SCHIZOPHRENIA

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Background: Nicotine addiction and schizophrenia are both highly heritable brain diseases. The disproportionately high rate of smoking in schizophrenia suggests a shared genetic or brain circuit pathway(s) between the comorbid conditions. Methods: We used gene-circuit analysis, resting fMRI, DTI, and circuit-addiction behavior analyses to examine the dorsal anterior cingulate and the ventral striatum/extended amygdala (dACC-VS/EA) circuit in smoking and schizophrenia. Results: In a series of recent studies, we found that a dACC-VS/EA circuit is associated with several aspects of nicotine addiction. Using resting state functional connectivity (rsFC) analysis, we initially found that dACC-VS connectivity strength was inversely correlated with nicotine addiction severity. Subsequently, we found that the nAChR α5 subunit gene functional variant rs16969968 was associated with dACC-VS/EA rsFC, such that (1) the risk allele leads to reduced rsFC in the circuit; (2) this gene-derived rsFC strength was reduced with smokers compared to nonsmokers; and (3) reduction of rsFC in the circuit predicts more severe nicotine addiction in smokers. Importantly, preliminary analyses of schizophrenia by gene interaction on this circuit revealed that reduced rsFC strength in the same circuit was present in schizophrenia patients and was independently and additively present along with effect of the nAChR α5 genetic variant, suggesting that a smoking-related genotype and schizophrenia exert similar effect on the same circuit that is related to nicotine addiction severity. Finally, using diffusion tensor imaging (DTI), we found multiple brain regions with reduced white matter integrity as measured by fractional anisotropy (FA) in schizophrenia and in smoking independently. The only overlapping FA reduction between the two conditions was localized to the left anterior thalamic radiation/anterior limb of the internal capsule, a fiber track that connects frontal cortex (including dACC) to the striatum. Conclusion: While many brain circuits and mechanisms can explain different aspects of smoking, our work provides preliminary converging evidence that implicates a dACC-ventral striatum/extended amygdala circuit in smoking and in high risk of smoking in schizophrenia. If validated using confirmatory study designs, a brain circuit capable of incorporating key aspects of smoking and smoking-related comorbid pathophysiology may provide a particularly salient biomarker for guiding and testing new treatment development.
ID: 977216

VARIATION IN SUCCINIC SEMIALDEHYDE DEHYDROGENASE (ALDH5A1) GENE IS ASSOCIATED WITH EYE TRACKING AND EARLY VISUAL PROCESSING DEFICITS IN SCHIZOPHRENIA

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Background: Earlier studies have shown a significant linkage of smooth pursuit eye movement (SPEM) abnormality in schizophrenia families to chromosome 6p24–21. We examined several candidate genes mapped on this locus selected based on earlier findings of associations with schizophrenia (DTNBP1), dyslexia (another complex disorder with oculomotor abnormalities; TTRAP, KIAA0319, and DCDC2), or their role in the GABA pathway (ALDH5A1) Methods: We tested 13 SNPs covering the five candidate genes in 344 unrelated subjects (173 with schizophrenia) for associations with SPEM. For replication, we genotyped the most significant SNPs in 440 subjects (150 with Schizophrenia) in an independent sample, on whom we collected eye tracking(SPEM)measures. Statistical analyses used false discovery rate (FDR) adjustments for multiple comparisons. The replication study is being analyzed and will present the results. Results: There was a significant ALDH5A1 rs2328824 genotype by diagnosis interaction effect on predictive pursuit (a highly heritable subcomponent of SPEM) (corrected P <.05) such that the two groups were similar for the ALDH5A1 heterozygous, and were significantly different for both minor and major homozygous genotypes. Our initial findings are being analyzed in the larger separate replication sample. ALDH5A1 gene codes for succinic semialdehyde dehydrogenase (SSADH), an enzyme that degrades gamma-amino butyric acid (GABA). Based on literature suggesting that variations in SSADH affect early visual processing as measured by P1 amplitude in visual evoked potential (VEP), secondary analyses examined the effects ALDH5A1 genotype on VEP and initiation acceleration. Findings demonstrated significant effects on P1 amplitude with the minor homozygous allele genotype and a robust effect of a functional ALDH5A1 C545T polymorphism on initiation acceleration (corrected P <.0001).Our initial findings are being analyzed in the larger separate replication sample. Conclusion: Using SPEM as a phenotype, we identified a novel schizophrenia risk gene, ALDH5A1, which is associated with a subgroup of schizophrenia patients with poor smooth pursuit eye movements, and abnormal early visual and motion processing.
ID: 986867

CATECHOL-O-METHYLTRANSFERASE (COMT) GENE AND RESPONSE TO COGNITIVE REMEDIATION IN SCHIZOPHRENIA: PRELIMINARY FINDINGS.

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Background: Neurocognitive deficits are core features of schizophrenia and have a significant impact on functional outcome. A functional polymorphism of the catechol-O-methyltransferase (COMT) gene (Val108/158 Met) partially influences cognitive performance both in schizophrenia patients and in healthy controls by modulating prefrontal dopaminergic activity. Our aim was to evaluate the effect of the association of the COMT Val108/158 Met genotype with the response to a computerized neurocognitive rehabilitation treatment (CRT) in patients with chronic schizophrenia. Methods: 102 patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder were assigned to 3 hours/week of CRT for 12 weeks and were evaluated on a standardized battery of neuropsychological assessments, functional skills, and PANSS at baseline and at endpoint (Week 12). Met/Met patients (N = 9) were combined with Met carriers (Met/Val = 48) in one group and compared to Val homozygotes (Val/Val n = 45). Response to CRT was defined as $\geq$20% performance improvement on the Trail Making and CPT-IP to categorize patients into Responders and Non-responders. Results: No significant demographic differences were noted at baseline. Mean overall PANSS was 78.12 ± 12.84. A mixed model linear regression for each cognitive domain (Executive Functioning, Processing Speed, Working Memory - WM, Attention/Vigilance, Global Cognitive Index- GCI) was based on all Met/Val + Met/Met patients (n = 48 + 9) vs. Val/Val patients (n = 45). A significantly greater improvement was found for the GCI (P = .050; partial eta square = .231), Trail Making Test scores measuring processing speed (P = .049; partial eta squared = .291) and WM tasks (P = .048; partial eta squared = .231) for the (Met/Val + Met/Met) group compared to the Val/Val group. The primary outcome variable for the CPT-IP (Attention/vigilance) was the signal discrimination index d'. Mean d' was 1.17 ± 1.1 for the Val/Met+Met/Met, and .91 ± 1.0 for Val/Val. Conclusion: These findings support the hypothesis that COMT polymorphism influences cognitive functioning through CRT, though they could be due to Type I Error. Primarily, the presence of Met allele was associated with significantly greater improvements in overall neurocognitive functioning after 12-weeks of CRT. As we accrue a larger sample size we may be able to determine if the two effects (ie, improvement from CRT and COMT polymorphism) act at different levels.
ID: 979809

ASSOCIATIONS BETWEEN *DRDS* AND SCHIZOPHRENIA IN A KOREAN POPULATION: MULTI-STAGE ASSOCIATION ANALYSES

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Background: The dysregulation of the dopaminergic system has been implicated in the pathophysiology of major psychosis, including schizophrenia, with dopamine receptor genes (*DRDs*) presently targeted as the most promising candidate genes. We investigated *DRD1-5* for association with schizophrenia using a multi-stage approach in a Korean sample. Methods: One hundred forty-two SNPs in *DRD1-5* were selected from the dbSNP, and the associations of each SNP were then screened and typed by MALDI-TOF mass spectrometry using pooled DNA samples from 150 patients with major psychosis and 150 controls. Each of the suggested SNPs was then genotyped and tested for an association within the individual samples comprising each pool. Finally, the positively associated SNPs were genotyped in an extended sample of 270 patients with schizophrenia and 350 controls. Results: Among the 142 SNPs, 88 (62%) SNPs in our Korean population were polymorphic. At the pooling stage, 10 SNPs (*DRD1*: 2, *DRD2*: 3, and *DRD4*: 5) were identified (P <.05). SNPs rs1799914 of *DRD1* (P = .046) and rs752306 of *DRD4* (P = .017) had significantly different allele frequencies in the individually genotyped samples comprising the pool. In the final stage, with the extended sample, the suggestive association of *DRD4* with rs752306 was lost, but the association of *DRD1* with rs1799914 gained greater significance (P = .017). Conclusion: In these large-scale multi-stage analyses, we were able to find a possible association between *DRD1* and schizophrenia. These findings suggested the potential contribution of a multi-step strategy for finding genes related to schizophrenia.
ID: 977539

GENOME-WIDE ASSOCIATION STUDY IN A LARGE ASHKENAZI COHORT, FOLLOWED BY LARGE-SCALE REPLICATION, REVEALS NOVEL GENETIC LOCUS FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Recent genome-wide association studies (GWAS) in schizophrenia have, for the first time, provided strong support for a few susceptibility loci. However, the overwhelming majority of genetic risk for schizophrenia, a highly heritable disorder, remains unknown. Consequently, we performed a GWAS in a large (total n >3000), ethnically homogeneous case-control cohort of Ashekenazi Jewish individuals from Israel. Methods: After data cleaning, including elimination of individuals with genetic evidence (identified using the ADMIXTURE program) of 1 or more non-Ashkenazi grandparents, we examined DNA from 938 patients with schizophrenia, 1672 controls, and a small ancillary cohort of 195 patients with bipolar disorder. All samples were genotyped on the Illumina 1M-Quad platform with mean call rates >99%, resulting in ~750K high-quality, common (MAF >2%) SNPs for analysis. Publicly available GWAS datasets, including GAIN and non-GAIN MGS samples (Shi et al 2009), GAIN bipolar (Smith et al 2009), and a German cohort of bipolar patients (Baum et al 2008) were examined for replication. Results: In the comparison of Ashkenazi schizophrenia cases and controls, one SNP met strict criteria for genome-wide significance (allelic P = 9.74e-09; OR = 1.397; 95% CI = 1.246–1.567); an additional 17 SNPs at the same locus had P-values less than e-06. Residual population stratification was minor, and genome-wide significance was retained after corrections using PCA, MDS, and EMMAX techniques. Bipolar cases demonstrated allele frequencies comparable to the schizophrenia cases, so replication was attempted using 5 cohorts comprising ~6000 patients across both diagnostic categories and ~5000 controls. Meta-analysis confirmed significant results for this SNP, even when the original discovery cohort was removed (P = .0012; OR = 1.104; 95% CI = 1.040–1.172 in the replication samples alone). Conclusion: These results suggest that examination of an ethnically homogeneous founder population

may increase power for detection of at least a subset of susceptibility loci. Location of the SNP and biological implications will be discussed at the meeting.
ID: 979566

ASSOCIATION OF DLG4 VARIANTS WITH SCHIZOPHRENIA

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Background: PSD95 directly interacts with proteins implicated in neurodevelopment and neurodevelopmental brain disorders, including NMDA receptors, ErBB4, neuroligins, neurexins, FMR1. PSD95 is encoded by the DLG4 gene, a member of the membrane-associated guanylate kinase (MAGUK) family. It is recruited into NMDA receptor and potassium channel clusters and is important for signal transduction at the post synaptic site and for dendritic spine maturation. Several studies reported alterations in PSD95 protein or mRNA levels in schizophrenia but the results are inconsistent. Multiple splice isoforms have been found for this gene: a family of beta variants (accounting for ~10% of DLG4 transcripts in human brain), an abundantly expressed in brain alpha transcript and the truncated form. Methods: In this study we measured expression of a variety of DLG4 transcripts in the DLPFC and hippocampus of patients with schizophrenia, bipolar disorder, major depression and normal controls across the lifespan, including 2nd trimester of fetal life, using quantitative RT-PCR (n ~700 subjects). We also examined associations of expression with 14 SNPs, determined by Taqman genotyping, because of their association with schizophrenia or cognitive phenotypes in the CBDB clinical studies. Results: We found that the long DLG4 transcripts (alpha and beta) are present at low levels in fetal samples, and their expression increases with aging, whereas the truncated form is abundantly expressed during fetal life as compared with early postnatal period and adulthood. We also found that DNA methylation of the DLG4 gene changes across development, perhaps influencing expression of the long transcripts. In schizophrenia, the expression of long isoforms is reduced while the truncated, fetal-specific isoform is significantly increased as compared with normal controls. We also found significant SNP-expression associations that may shed light on the nature of genetic association of DLG4 polymorphisms with schizophrenia. Conclusion: The data demonstrate that the pattern of alternative splicing of DLG4 gene in schizophrenia is reminiscent of that in the immature brain. These results identify molecular correlates of the genetic associations with DLG4 polymorphisms.
ID: 981166

GENE EXPRESSION REGULATION IN HUMAN BRAIN GUIDES GENOME-WIDE ASSOCIATION STUDY OF BIPOLAR DISORDER AND SCHIZOPHRENIA

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Background: Genome-wide association studies (GWAS) with illness in psychiatric diseases have yielded limited findings, including a few genome-wide significant associated genes, one polygenic model, and a few rare copy number variations. Functional annotation of SNPs may be able to assist the re-evaluation of the genome-wide association results by reducing the number of tests and providing novel gene-gene interaction networks. One major function of SNPs is to affect gene expression, particularly in human brain. Methods: We used the genome-wide association study to map quantitative trait loci of gene expression and DNA methylation in human brain. Furthermore, we use the identified functional effect information of the SNPs to perform a function-based genome-wide association analysis in bipolar and schizophrenia datasets. Results: We have identified hundreds of SNPs that are associated with gene expression levels, including different splicing isoforms. We also identified hundreds of SNPs that are associated with DNA methylation levels in human brain. We are applying these data into the re-evaluation of existing genome-wide association studies of bipolar disorder and schizophrenia, and have identified novel genes that are associated with disease but have been missed in previous gene hunting. Several genes showed genome-wide significant associations in one sample set and were replicated at nominal significance level in a second dataset. Conclusion: Our study concluded that the gene-centered GWAS analysis limiting to functional variants may increase power of detecting novel disease susceptibility genes.
ID: 977228

GENETIC APPROACHES TO CLINICAL HETEROGENEITY IN SCHIZOPHRENIA

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Background: Clinical heterogeneity is a hallmark of schizophrenia, with marked interindividual variation in phenotypes that include symptom presentation, neurocognitive function and treatment response. To date, there are few biological markers that reliably differentiate between clinical presentations of the disorder. Molecular genetic approaches offer the prospect of development of such biomarkers as they can be readily assessed in large patient populations of varying clinical descriptions. Methods: We have assessed the genetic contribution to a number of illness phenotypes in extensively characterized clinical cohorts. Results: Early work suggested that the schizophrenia susceptibility gene, DTNBP1 or dysbindin, is associated with cognitive function and severity of negative symptoms, with more recent data indicating that these effects may be mediated by an influence on total brain volume. Recently, we have assessed the role of another schizophrenia susceptibility gene, ZNF804A, and found that the reported risk allele is associated with regional brain volume differences, specific neurocognitive functions, and clinical diagnosis. Moreover, these effects grow stronger as the phenotype progresses from clinical assessments to brain structural measurements. Finally, we will report on the first genome-wide association study (GWAS) of antipsychotic-induced weight gain in a treatment-naïve pediatric patient population. Results implicate a genome-wide significant locus that acts recessively to predict a subgroup of patients who experience the most severe weight change associated with treatment. Conclusion: Taken together, these studies suggest that molecular genetic differentiation of illness phenotypes within schizophrenia may be feasible. Further understanding of the relationships between genetic variation and clinical phenotypes will require additional comprehensive analytic strategies as well as data on the underlying neurobiological substrates of clinical heterogeneity.
ID: 978736

CYP2D6 AND CYP2C19 GENE TESTING IN PATIENTS TREATED WITH ANTIPSYCHOTIC AND ANTIDEPRESSANT MEDICATION

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Background: Antipsychotic and antidepressant medication are widely used for psychiatric conditions such as schizophrenia, depression, anxiety or OCD symptoms. Two polymorphic enzymes, CYP2D6 and CYP2C19, metabolize a large number of these medications. Functional polymorphisms in these enzymes can confer altered enzymatic activity, potentially leading to toxic or subtherapeutic drug levels. Methods: We here report of two different analyses: 1) As part of our AmpliChip © Study, 39 individuals with OCD were genotyped for CYP2D6 and CYP2C19. Individuals' liver enzyme activity was classified as poor, intermediate, extensive (normal) and ultra-rapid metabolizers. Subjects were tested for association with response and non-response and occurrence of side effects. 2) As part of a new study at our Pharmacogenetics Research Clinic, the first set of patients with a diagnosis of schizophrenia and mood disorders with complicated medication histories have been enrolled prospectively and genotyped for CYP2D6 and CYP2C19. After 6 weeks, the physicians were provided with an interpretation of the genotypic results and informed about the potential clinical implications which they then discussed with their patients. The physicians were asked to complete a questionnaire evaluating the usefulness of the genotypic information. After 12 weeks, patients were assessed again to monitor potential adjustments of medications and their overall treatment outcome. Results: (1) Abnormal CYP2D6 activity (ie non-extensive metabolizer) was significantly associated with non-response to antidepressants. Two individuals who were ultrarapid metabolibzers (UM) failed to respond with 9 antidepressants and showed only repsonse with two trials, and one individual who was poor-responder did not respond to any SSRIs trial ($P = .006$). This data, including a thorough chart review, showed that CYP2D6 non-extensive metabolizers are significantly more likely to have complicated medication histories. (2) Overall, physicians have returned excellent feedback that the genotyping results have been very helpful in allowing them to either select medications their patients are likely to better tolerate, or to adjust doses based on geneotype results and serum levels. Conclusion: In summary, our findings suggest that CYP2D6 and CYP2C19 genotyping provides useful information that help physicians to improve pharmacotherapy for individual patients.
ID: 980040

THE CNR1 GENE IN DEPRESSION AND SCHIZOPHRENIA - IS THERE AN ASSOCIATION WITH EARLY RESPONSE AND RESPONSE?

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Background: The endocannabinoid system's CB1 receptor gene (CNR1) is associated with the susceptibility and course of psychiatric disorders. An association between the CNR1 gene and treatment response in depression and schizophrenia was proposed. Data on early response concurrently analysing depressed and schizophrenia patients is still standing. Methods: 567 patients and 427 controls were genotyped for the CNR1 gene G1359A polymorphism and examined using the HAMD, PANSS and the CGI. Early response and response were defined according to accepted definitions of the literature using the HAMD, PANSS and CGI scales. Statistical analyses were performed using the statistical program R2.6.1. Results: No significant difference in genotype frequencies between depressed ($N = 293$) and schizophrenia ($N = 274$) patients ($P = .6060$), depressed patients and healthy controls ($P = .4195$) or schizophrenia patients and controls ($P = .8019$) was found. Compared to the homocygote G allele carriers the depressed homocygote A genotype patients featured a significantly lower HAMD total score at admission ($P = .04$) and a lower mean maximum HAMD score ($P = .0454$). Schizophrenia A allele carriers suffered from less depressive symptoms (PANSS item G6) at discharge ($P = .0668$) concurrently reaching response more often compared to G allele carriers ($P = .0596$). A significant association was neither found between genotypes and early response and response when examining the depressed patient subgroup nor for the combined group of depressed and schizophrenia patients. Conclusion: The CNR1 was not significantly associated with early response in depressed and schizophrenia patients. However, the A allele might be a marker for illness severity of depressive symptoms.
ID: 976467

GENETIC ASSOCIATION AND PATHWAY ANALYSIS OF 94 CANDIDATE GENES IN SCHIZOTYPAL PERSONALITY DISORDER

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Background: Schizotypal personality disorder (SPD) has been demonstrated to be genetically related to schizophrenia with common underlying pathophysiologic mechanisms, but there has been little prospective study identifying specific candidate genes associated with SPD, their overlap with genes associated with schizophrenia, and intermediate phenotypes related to the schizophrenia spectrum to examine precisely the mechanisms implicated by these genes. Methods: We utilized the custom Consortium on the Genetics of Schizophrenia (COGS) 1,536-SNP chip to genotype 45 SPD patients and 41 healthy controls. We conducted both categorical association (SPD/HC) and dimensional quantitative phenotypes of SPD (cognitive impairment, interpersonal deficits and paranoia) genetic association analysis of allelic and haplotypic data using the UNPHASED package. p values corrected for multiple testing by running 1000 permutations. Genetic networks was determined by SNP Ratio Test and Ingenuity Pathway Analysis. Results: The ERBB4 ($P = .003$), NRG1 ($P = .0004$) and genes involved in glutamate, dopamine, GABA and serotonin receptors signaling, as well as cell signal transduction, were highly associated with our outcome variables. Among these genes, there were 2 SNPs [GRIK3_rs1027599 ($P = .0003$) and GRM5_rs1532548 ($P = .0004$)] that were significant in both qualitative and all three quantitative traits. TAAR6_rs8192624, a nonsynonymous polymorphism (Val265Ile) was significantly associated with interpersonal deficits ($P = .0035$) with associations for 3 SNPs previously linked to schizophrenia. Ingenuity Pathway Analysis showed that Glutamate Receptor Signaling was the most significant biological pathway in both qualitative and quantitative data ($P < .00001$). Similarly, the SNP Ratio Test revealed significance for the Neuroactive ligand-receptor interaction KEGG pathway ($P = .001$). Conclusion: These preliminary results support a role for genes involve in glutamate signaling in mediating susceptibility to SPD, consistent with the glutamate hypothesis of schizophrenia. NRG1 and ERBB4, two important genes in the pathogenesis of schizophrenia are also associated with SPD. The observation of pleiotropy for some genes and singular associations for others in our data suggests alternative, independent pathways mediating pathogenesis in SPD. Further investigation can help define the genetic architecture and neural mechanisms of schizophrenia spectrum disorders remains.
ID: 979981

CANDIDATE GENE AND CNV GENOTYPE/PHENOTYPE ASSOCIATIONS IN THE SCHIZOPHRENIA SPECTRUM

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Background: While candidate gene associations have been reported for chronic schizophrenia, their specificity for schizophrenia and association with intermediate phenotypes including psychosis, interpersonal, and cognitive related phenotypes are unclear. Some variants may be more related to psychosis, some to cognitive deficits, and others, to all three. To delineate the specific genotypes and neural pathways related to these dimensions of spectrum pathology, cohorts of schizotypal subjects and volunteers were genotyped in relation to intermediate clinical (cognitive impairment, interpersonal deficits, and paranoia) and cognitive phenotypes. Methods: Study 1: 45 subjects with SPD and 41 healthy controls were genotyped for 94 candidate genes related to schizophrenia on the 1536 SNP COGS chip. Study 2: A cohort of 95 SPD subjects was genotyped for CNVs implicated in schizophrenia and compared to base rate in controls. Study 3: A cohort of 530 young male army conscripts from the Greek LOGOS project was genotyped and phenotyped for PPI, neurocognitive tasks and personality dimensions. Results: Study 1: A large number of variants including haplotypes for neuroactive receptor ligand genes [especially glutamate but also serotonin (HTR2A), dopamine (DRD2), GABA], NRG1/ERBB4 pathway, gap junction and long-term depression pathway genes associated with schizophrenia were highly significantly associated after correction for multiple tests with SPD diagnosis and multiple intermediate clinical domains. Interpersonal deficits were associated with several SNPS including a functional SNP (val265ile) in TAAR6 (P = .0035) and SLC6A1_rs2675163 (P <.002) while paranoia was associated with others including DAOA (P = .015) and several CTNNA2 SNPs (P <.0001). Glu receptor genes were consistently associated with cognitive impairment as well as other intermediate phenotypes. Study 2: In our pilot analyses SPD patients demonstrated a greater number of CNVs than control values. Study 3: Risk alleles and haplotypes of DAO (P = .002) and NRG1 (P = .003) genes were associated with PPI reductions. Conclusion: These data are consistent with a major role for glutamate receptors and NRG1/ERBB4 in SPD as in schizophrenia and suggest differential associations with specific intermediate phenotypes (eg, DAO with PPI, psychosis, TAAR6 with interpersonal) pointing the way to genetic identification of neural pathways for these phenotypes.
ID: 979404

ASSOCIATION STUDY OF AKT1 POLYMORPHISMS WITH CLOZAPINE RESPONSE

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Background: Clozapine is an effective antipsychotic especially in patients which have been refractory to treatment with other antipsychotic drugs. There is a significant variability in clinical response during treatment with clozapine. The Akt/glycogen synthase kinase (GSK) 3 signaling cascade has been strongly associated with the action of dopamine, serotonin and antipsychotics in different rodent models. We investigated whether AKT1 polymorphisms would predict clozapine response in schizophrenia patients. Methods: We evaluated eight polymorphisms (rs2498784, rs1130214, rs2494746, rs10149779, rs2494738, rs3730358, rs3803304 and rs2494731) in 208 schizophrenia patients who were refractory to typical antipsychotics. These subjects underwent six month treatment period with clozapine and they assessed prospectively using the Brief Psychiatric Rating Scale (BPRS). Response was defined as 20% BPRS reduction after six months from the baseline. In a second step of our analysis, we evaluated whether AKT1 genetic variants were correlated with the psychopathology alterations during clozapine treatment. We carried out these tests using the percentage change in the BPRS (total psychopathology), BPOS (positive symptomatology) and BNEG (negative symptomatology). Results: Our results indicate no association of AKT1 polymorphisms with clozapine treatment response in schizophrenia subjects with European Caucasian ethnic background. The rs10149779 polymorphisms presented a trend towards an association with clozapine response in subjects with African-American background (permuted P = .123). Our findings suggest that haplotypes comprised of AKT1 polymorphisms do not predict treatment response in subjects with both European Caucasian and African-American ethnic backgrounds. Moreover, rur results suggest that there is no association of AKT1 polymorphisms and BPRS, BPOS or BNEG change after six months of clozapine treatment. Conclusion: We have found no significant association of AKT1 polymorphisms with clozapine response in our sample. This result corroborates with previously published findings that showed that rs1130214 and rs3730358 polymorphisms were not predictors of response to risperidone treatment in first-episode schizophrenia subjects from a Japanese cohort or treatment response to chlorpromazine or clozapine in a Chinese sample. Taken together, our results further suggest that polymorphisms in the AKT1 gene are not associated with antipsychotic treatment response in schizophrenia patients
ID: 926934

PSYCHOSIS SUSCEPTIBILITY GENES - DISCRETE AVENUES OF VULNERABILITY DETECTED AT THE POPULATION LEVEL

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Background: Candidate genes for psychosis may exert detectable effects on population based - psychosis related phenotypes such as prefrontally mediated cognitive ability, trait schizotypy and/or stress induced psychotic-like experiences. Within the Athens Study of Psychosis proneness and Incidence of Schizophrenia (ASPIS), we assessed the potential impact of several frontrunner candidate psychosis genes on these phenotypes, in a national cohort of 2000 healthy young male conscripts undergoing military induction. Methods: We examined whether variants coding for the functional receptor to the Neuregulins: ERBB4 (Silberberg et al AJMG 2006, Nicodemous et al Mol. Psych 2006), and variants within the ZNF804A gene (O'Donovan et al Nat Genet 2008, Riley et al Mol. Psych. 2010), exhibit discrete patterns of association with these population based phenotypes. Results: ERBB4: Stress induced psychotic-like experiences as reported from the Symptom Checklist 90 Revised questionnaire, were associated with rs7598440 (P = .006) and rs839523 (P = .048) but not rs707284. Working memory performance, as assessed with the N-Back task was associated with rs7598440 (P = .031), rs839523 (P = .005) and rs707284 (P = .006), thus indicating a simultaneous impact of ERBB4 variation on stress-induced and cognitive, psychosis related phenotypes. ZNF804A: Single-marker analysis revealed significant associations between three individual ZNF804A variants: rs7597593, rs1344706, rs4667001, with the Paranoid Schizotypy dimension derived from the Schizotypal Personality Questionnaire (best P-value = 9×10^{-5} for rs7597593), with no demonstrable effect on cognitive function. Conclusion: Population based phenotypes may provide a useful platform for refining specific routes of vulnerability associated with candidate genes for psychosis. This body of work supports the notion of an overlapping genetic continuity between sub-

clinical and clinical expression of psychosis. Pleiotropic effect of ERBB4 variants on stress-induced sub-clinical psychosis and working memory. Nicholas C. Stefanis, Nikos Smyrnis, Dimitrios Avramopoulos, Alex Hatzimanolis, Ioannis Evdokimidis, Jim van Os, Costas N. Stefanis, Richard E. Straub, Daniel R. Weinberger (submitted) Variation in psychosis gene ZNF804A is associated with paranoia in a large population-based sample of normal males. Nicholas C. Stefanis, Alex Hatzimanolis, Dimitrios Avramopoulos; Nikos Smyrnis, Ioannis Evdokimidis, Costas N. Stefanis, Daniel R. Weinberger; Richard E. Straub (submitted)
ID: 979734

EXAMINING SYNAPTIC STRENGTH AT GLUTAMATE SYNAPSES OF TRANSPOSED NEURONS TO DEVELOP CASE-SPECIFIC CELLULAR PHENOTYPES OF PSYCHOSIS IN SZ AND BD

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Background: Learning and memory processes and plasticity markers in MTL tissue are known to be complexly altered in psychotic illness. Moreover, plasticity changes can be predicted from known risk genes for SZ and BD, like NRG1, DISC1 and dysbindin, which regulate synaptic plasticity especially at glutamate synapses. In an attempt to identify a simple cell system which will reflect plasticity differences in psychosis, we have been deriving cultured neurons directly from case-specific fibroblasts cultured from dermal biopsies obtained from well phenotyped SZ and BDP and will examine the neuronal cultures, enriched for risk genotypes, for anatomic, cellular and molecular intermediate-phenotypes for psychosis. Methods: Dermal biopsies are obtained under sterile conditions from volunteers with SZ, BDP and their relatives as well as from healthy controls. Fibroblasts are cultured under usual conditions and 6 passes are cryo-protected. Fibroblasts are transformed directly to neurons using specific vector combinations. We have confirmed neuronal identity using molecular markers and functional activity. Characteristics of the neurons, enriched for glutamate-containing cells, and their synaptic architecture will be examined using cellular imaging, anatomic criteria and molecular measures. Results: We have developed over 60 fibroblast cultures to date, with atleast 18 from SZP, 12 from BDP, and the remainder from relatives and normals, all extensively phenotyped. Biopsy tissue grows to confluent fibroblast cultures in 5–10 days. Fibroblasts are transformed into cellular populations using specific transcription factors; cells fire to depolarizing stimuli and demonstrate molecular characteristics of neurons. Under usual culture conditions and with depolarizing stimulation, we will characterize dendrite anatomy, molecular characteristics and synaptic strength, contrasting case-specific proband, relative and healthy cultured neurons. We will correlate specific cellular phenotypes with case endophenotypes and genotypes. Conclusion: Considerable enthusiasm accompanies a focus on case-specific neuronal cultures from volunteers who have brain diseases. The extent that these neuronal cultures can be taken to represent in vivo neuronal activity, especially around their plasticity characteristics, remains to be demonstrated, however.
ID: 987503

STRUCTURAL BRAIN CORRELATES OF SCHIZOPHRENIA GWAS TOP SNPS

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Background: A recent ''mega-analysis'' of the Psychiatric GWAS Consortium with 12 200 schizophrenia cases and 9300 controls yielded five SNPs associated with schizophrenia with genome-wide significant *P*-values. The functional effects of these SNPs are yet unclear. Imaging genetics offers a powerful approach to determine the role of these SNPs in brain structure and function. Methods: We acquired a 1.5T MRI scan of the brain for 169 schizophrenia cases and 159 healthy controls. Volume measures of total brain, cerebral graygray matter and cerebral white matter were estimated and corrected for age, sex and intracranial volume. Subjects were genotyped using the Illumina HumanHap550 beadchip. Only SNPs available on this beadchip were used (others will be imputed). When less than 20 subjects had homozygous minor alleles this group was collapsed to the heterozygous subjects. In linear regression analyses the brain volumes were used as dependent variables and the four available SNPs (one-by-one) and disease status as independent variables. Results: None of the SNPs showed a significant association after Bonferroni correction for 24 tests (4 SNPs × 3 volumes × with/without disease status). The strongest signal was found for rs7004633 (*F* 4.6; *P* 0.03), a SNP on chromosome 8q21.3 near MMP16 (matrix metallopeptidase 16) gene, for an effect on cerebral white matter volume. Conclusion: This is one of the largest samples with genotyped subjects with MRI scans to date. Collaborative effort is however needed to create larger samples with sufficient power for imaging genetic studies.
ID: 977235

MARKED REDUCTION OF AKT1 EXPRESSION AND DEREGULATION OF AKT1-ASSOCIATED PATHWAYS IN PERIPHERAL BLOOD MONONUCLEAR CELLS OF SCHIZOPHRENIA PATIENTS

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Background: Recent studies have suggested that deregulated AKT1 signaling is associated with schizophrenia. We hypothesized that if this is indeed the case, we should observe both decreased AKT1 expression as well as deregulation of AKT1 regulated pathways in Peripheral Blood Mononuclear Cells (PBMCs) of schizophrenia patients. Therefore we examined PBMC expression levels of AKT1 in schizophrenia patients vs controls, and examined whether functional biological processes in which AKT1 plays an important role are deregulated in schizophrenia patients. Methods: A case-control study, investigating whole-genome PBMC gene expression in male, recent onset (<5 years) schizophrenia patients ($N = 41$) as compared to controls ($N = 29$). Genes, differentially expressed between patients and controls were identified using ANOVA with Benjamini-Hochberg correction (false discovery rate (FDR) = .05). Functional aspects of the deregulated set of genes were investigated with the Ingenuity Pathway Analysis (IPA) Software Tool. Results: We found significantly decreased PBMC expression of AKT1 ($P < .001$, $t = -4.25$) in the patients. AKT1 expression was decreased in antipsychotic-free or -naive patients ($N = 11$), in florid psychotic ($N = 20$) and in remitted ($N = 21$) patients. A total of 1224 genes were differentially expressed between patients and controls (FDR = .05). Functional analysis of the entire deregulated gene set indicated deregulated canonical pathways involved in a large number of cellular processes: immune system, cell adhesion and neuronal guidance, neurotrophins and (neural) growth factors, oxidative stress and glucose metabolism, and apoptosis and cell-cycle regulation. Many of these processes are associated with AKT1. Conclusion: We show significantly decreased PBMC gene expression of AKT1 in male, recent-onset schizophrenia patients. Our observations suggest that decreased PBMC AKT1 expression is a stable trait in recent onset, male schizophrenia patients. We identified several

AKT related cellular processes which are potentially affected in these patients, a majority of which play a prominent role in current schizophrenia hypotheses.
ID: 929741

FAMILY-BASED ANALYSIS OF GENETIC VARIATION UNDERLYING PSYCHOSIS-INDUCING EFFECTS OF CANNABIS: SIBLING ANALYSIS AND PROBAND FOLLOW-UP

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Background: Context. Individual differences exist in sensitivity to the psychotomimetic effect of cannabis; the molecular genetic basis underlying differential sensitivity remains elusive. Objectives. To investigate whether selected schizophrenia candidate single nucleotide polymorphisms (SNPs) moderate effects of cannabis use. Methods: Design. Interactions between recent cannabis use, determined by urinalysis, and 152 SNPs in 42 candidate genes were examined in 740 unaffected siblings of 801 patients with psychosis, in order to examine genetic moderation of the association between SIS-R positive schizotypy and recent cannabis use (at-risk paradigm). SNPs showing Bonferroni-adjusted association in the at-risk paradigm were used in a case-only analysis in the 801 patients, as well as in a case-sib and case-control analysis (using 419 controls) focusing on genetic moderation of developmental effects of cannabis on later psychotic disorder. Setting. The Netherlands and Flanders (Belgium). Main outcome measure. Significant interaction between any of the selected SNPs and cannabis in the at-risk paradigm, followed by selective case-only, case-sib and case-control analyses. Results: In the unaffected siblings, 16 SNPs in 12 genes showed significant interaction at $P < .05$, 3 of which survived correction for multiple testing ($P < .0003$), situated in AKT1 (rs2494732, rs1130233) and LRRTM1 (rs673871). Follow-up analysis supported AKT1 rs2494732 X cannabis interaction in the case-only ($B = .20$, $P = .007$), case-sib (interaction $P = .040$) and case-control analyses (interaction $P = .057$), C/C genotypes having an approximately two-fold odds of being diagnosed with a psychotic disorder when having used cannabis. In the unaffected sibs, the AKT1 X cannabis interaction explained 2.2% additional variance in schizotypy in the whole sample and 19.0% additional variance in the exposed siblings with recent cannabis use. Conclusion: Genetic variation in AKT1 may mediate both short-term as well as longer-term effects on psychosis expression associated with use of cannabis, possibly through a mechanism of cannabinoid-regulated AKT1-GSK3 signaling downstream of the dopamine D2 receptor.
ID: 978335

ANTIPSYCHOTIC TREATMENT RESPONSE IN CAUCASIAN PATIENTS: ASSOCIATION ANALYSIS OF POLYMORPHISMS IN 7 CANDIDATE GENES IN THE GROUP STUDY

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Background: The large variation in individual clinical responses to antipsychotic treatment hampers the management of psychotic disorders. Genetic factors are considered a main cause of this variation. Pharmacogenetics studies have demonstrated significant associations between several candidate genes (a.o. D2, D3, 5HTR2A and 5HTR2C, GRM3, COMT and MTHFR) and the response to antipsychotic drugs. The present study investigates the effect of 12 polymorphisms for an association with antipsychotic treatment response in patients with a psychotic disorder. Methods: 335 Caucasian patients with a non-affective psychotic disorder using antipsychotics were included. All patients participated in the longitudinal GROUP-study in The Netherlands. We genotyped 12 SNPs in 7 candidate genes (DRD2: TaqI_A, TaqI_D, −141-C, C957T; DRD3: Ser9Gly; HTR2A: 102-T/C, His452Tyr; HTR2C: Cys23Ser, −759-T/C; COMT: Val108/158Met; MTHFR: 677-C/T, GRM3: rs274622) using standard protocols. Polymorphisms were based on previous studies showing associations with treatment response. The Clinical Global Impression-Schizophrenia scale was cross-sectionally used to assess improvement in positive psychotic symptoms since the start of current antipsychotic treatment. Ordinal regression was used to test for an association between polymorphisms and improvement in positive symptoms. All polymorphisms were tested in an additive model, with minor allele dose as the dependent variable. Results: Ninety percent of the patients used atypical antipsychotics, with olanzapine (31%) and risperidone (29%) being the most prescribed drugs. Ser9Gly of the dopamine D3 receptor gene (P value .029) and 677-C/T of MTHFR (P value .029) were tested significant. Gly carriers and T-carriers, respectively, showed better clinical improvement on the positive scale. All other polymorphisms did not show any association with treatment response (all P values $>.10$). Conclusion: We were able to replicate only two of the previously reported associations between polymorphisms and treatment response. Heterogeneity in patient samples and outcome variables as well as publication bias and false positive findings may all play a role in lack of replication, found in our study, as in others. The direction of the associations presented here in D3 (Ser9Gly) and MTHFR (677-C/T) are in line with previous association studies in Caucasian patients. These polymorphisms may be of value for predicting clinical response.
ID: 979108

INITIAL INVESTIGATION OF THE RELATIONSHIP OF KYNU AND CORTICAL KYNURENINE PATHWAY METABOLISM TO COGNITION IN SCHIZOPHRENIA

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Background: Recent experimental evidence frames the hypotheses that increases in kynurenic acid (KYNA) concentration, caused by abnormalities in the kynurenine pathway of tryptophan degradation, contribute to the cognitive deficits associated with schizophrenia, and that medications targeting this pathway may be cognition-enhancing. KYNA, an antagonist for the *N*-methyl-D-aspartic acid receptor (NMDAR) and the α7 nicotinic acetylcholine receptor (α7nAChR), causes decreases in the extracellular concentrations of glutamate, dopamine and acetylcholine, three neurotransmitters associated with cognition and reported to be abnormal in schizophrenia. Methods: A genome wide association (GWA) analysis of cognitive variables in 364 schizophrenia patients and 398 controls from the NIMH/CBDB/GCAP Sibling Study was performed (Straub & Weinberger, unpublished data). Results: The analysis identified associations between SNPs in the gene for kynureninase (KYNU) and cognitive ability in the patient population, but not in controls. Of several associations, the strongest was between rs7607734 ($P = 6.24e\text{-}05$) and a broad composite score representing general cognitive ability, ''g''. This SNP yielded the 47th strongest association to g in people with schizophrenia out of 495 089 SNPs analyzed, but the result was not genome wide significant and thus must be interpreted very cautiously. The initial GWA results also in-

dicate a stronger association between KYNU and cognition in 281 males (P = 5.63e-05) than in 83 females (P = .14). Thus, we will explore whether this distinction relates to statistical power or sex-related biological differences. Conclusion: Future work will include more detailed analysis of other KYNU SNPs in these data, haplotype and epistasis analyses, examination of the relationship of the KYNU finding to other components of the biochemical cascade of tryptophan degradation, and confirmation in independent datasets. Of possible importance, the noted association with general cognitive ability was stronger than associations with composite variables representing specific cognitive domains. Among other questions, we will investigate whether general cognitive phenotypes may be more informative than domain specific phenotypes in schizophrenia.
ID: 979571

CONFIRMATION OF THE EFFECT OF THE ZNF804A SNP RS1344706 ON CEREBRAL CORTICAL WHITE MATTER VOLUMES

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Background: The SNP rs1344706 within the gene ZNF804A has been repeatedly found to be associated with schizophrenia. In studies of schizophrenia-related traits, the gene has also been found to influence brain structure. Specifically, Lencz et al (2010) found that, in a group of 39 healthy individuals, carriers of the risk (T) allele had increased total white matter volume compared to homozygotes for the non-risk allele. We sought to test this finding in a much larger sample of both individuals with schizophrenia and healthy controls. Methods: Our sample included 330 individuals with schizophrenia spectrum disorders (95% with schizophrenia) diagnosed with the CASH semi-structured interview instrument and 198 healthy comparison subjects ruled out for mental illness in themselves and their first degree relatives. All subjects provided DNA and underwent a multi-modal high-resolution magnetic resonance (MR) brain imaging scan. Scans were analyzed using the BRAINS2 suite of analysis tools to produce automated volume measurements of gray and white matter for the frontal, parietal, and occipital lobes of the cerebral cortex. Subjects were genotyped at rs1344706 using a Taqman assay. The effect of genotype on the brain structure volumes was tested using an analysis of variance (ANCOVA) with genotype and diagnosis as predictors and age, intra-cranial volume, and gender as covariates. Results: Genotype produced a significant overall effect on total white matter volume (F = 3.49, P = .03) and frontal white matter volume (P = 4.07, P = .02). The effect was most pronounced in the patient group (cerebral white matter, P = .01; frontal white matter, P = .002). Importantly, the effect was in the same direction as the Lencz et al report, with the risk (T) allele being associated with larger volumes. None of the other brain regions were affected by rs1347706 genotype, nor was the genotype associated with schizophrenia in our sample. Conclusion: This data confirms that the schizophrenia risk T allele of the SNP rs1344706 produces a significant effect on white matter volume in the human brain. Our study, which examined larger samples of both individuals with schizophrenia and healthy controls, found the effect to be more pronounced in the patient sample. Further studies are being pursued to examine the effects of the polymorphism on symptoms and cognitive abilities.
ID: 986903

GENETIC ARCHITECTURE OF COGNITION IN SCHIZOPHRENIA: WITHER WORKING MEMORY?

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Background: Executive cognition and working memory (WM)deficits are extensively documented characteristics of patients with schizophrenia and of their healthy relatives, including unaffected siblings and identical cotwins. Working memory associated neural function measured with fMRI also show characteristic abnormalities in patients with schizophrenia and in their healthy siblings. These data implicate working memory function as a reflection of basic causal mechanisms implicated in the disorder. We have explored the relationship of cognitive deficits with genetic variation in a GWA study of patients with schizophrenia, their healthy siblings and normal controls. Methods: Cognitive function was assayed with standard neuropsychological measures of processing speed, WM, executive function, episodic memory, and IQ which were reduced to six factors including a general cognivie factor (''g'')(Dickenson et al Schiz Bull 2009) in 364 schizophrenic probands, 140 of their unaffected siblings, and 398 controls who also underwent genome wide SNP genotyping performed with the Illumina 550k GWA chip. Genotype association with factor scores was determined separately for each group using linear regression in PLINK following MDS based culling for population stratification. Results: Significant association at the genome wide level was found for only a few SNPs, and the pattern of association was different in patients and in controls. In general, in the control sample, individual factors showed distinct genetic associations while in the patients, the associations tended to be much stronger for ''g'' than for individual cognitive factors. These results will be presented using more sophisticated analyses, including MLA based data driven searchers of epistatic interactions, cluster analytic techniques and pathway analyses. Conclusion: The genetic architecture of cognitive factors in patients with schizophrenia suggests that at least with the GWA blunt instrument strategy, "g" is a more robust predictor of genetic effects than is WM. However, genetic association with cognition in patients with schizophrenia is confounded by state related variables that also affect cognition and may have genetic associations of their own. These included medication effects, smoking effects, etc.
ID: 978969

SUSCEPTIBILITY GENES DO NOT RESPECT DSM-IV CRITERIA OR NEURAL CIRCUIT SPECIFICITY

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Background: Psychiatric diagnoses are phenomenologically based and lacking in biological specificity. Not surprisingly, recent genetic association studies have identified considerable overlap in genes that are implicated in schizophrenia and in mood disorders. We have explored the potential underlying neural system mechanisms that might account for the nonspecificity at the level of clinical phenomenology. Methods: Genetic variants associated with both schizophrenia and mood disorders in the following genes were investigated with imaging genetics strategies: COMT, GRM3, GRM7, CACNA1c, ZNF804a, DISC1, and AKT1. Normal subjects carrying risk associated genotypes for each of these genes were compared to non risk genotype carriers during fMRI studies of cognitive and emotional processing related to the biology of schizophrenia and mood disorders, respectively. We hypothesized that genes showing clinical association to both diagnoses would predict relative engagement of the canonical neural systems implicated in processing relevant cognitive and emotional information. Results: For each of these genes, risk associated genotypes are significantly associated with relatively abnormal engagement of prefrontal and temporolimbic neural circuitries implicated in schizophrenia and mood disorders, respectively, and in genetic risk for these disorders. These findings emerged even in normal subjects and the effect size on imaging based physiology is much greater than on clinical association. Conclusion: These data illustrate that genes associated with major psychiatric disorders cross traditional clinical phenomenological boundaries because they affect the engagement of classic neural circuitries underlying the biology of these conditions. Specifically, genes related to both schizophrenia and mood disorders affect the function of cognitive and emotional process-

ing in canonical neural circuitries that likely represent the underlying biological mechanisms of susceptibility.
ID: 978941

CIDAR RESEARCH CORES: GENETIC AND NEUROBIOLOGICAL INVESTIGATION OF SCHIZOPHRENIA PROGRESSION BIOMARKERS

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Background: The Genetics and Postmortem Cores are conducting translational studies linking the constituent CIDAR projects by evaluating genetic associations with progression phenotypes across project domains and by investigating cell type-specific transcriptome changes in dysfunctional neural circuits. Methods: The Genetics Core is examining the contribution of candidate gene polymorphisms and copy number variants (CNVs) to progression biomarkers, most of which are known to have a large genetic component. Selection of genes and CNVs is based on prior evidence for involvement in SZ from published genetic studies, such as the major histocompatibility complex (MHC) locus, neurogranin, and TCF4 genes, or for function within neural circuitry underlying gamma oscillations, as investigated in the Postmortem core. Genetic associations are tested by multivariate regression analysis of select biomarkers found by the projects to track with disease stage. Analysis across phenotypic domains (eg, imaging, neurocognition) is expected to highlight genetic relationships between progression biomarkers. Results will be incorporated into meta-analyses with other studies to identify genotype-phenotype associations for subsequent investigation of their relationship to neural circuit dysfunction in SZ. Using laser capture microdissection in combination with Affymetrix microarrays, the Postmortem Core has examined the transcriptome of layer 3 pyramidal cells, which are believed to be key neuronal populations that mediate gamma oscillations, in the superior temporal region from 10 SZ and 10 normal control subjects. Results: We found that genes within the transforming growth factor beta superfamily and extracellular matrix regulation cascades, those that regulate cytoskeletal plasticity, and a number of synaptic plasticity-related genes such as HLA-A, which is located in the MHC locus investigated by the Genetics Core, are differentially expressed in subjects with SZ. Microarray data from the parvalbumin-immunostained inhibitory neurons, which regulate pyramidal neuronal network oscillations, are being analyzed. Conclusion: Together findings from these two Cores will offer genetic, cellular, and molecular insight in how cortical circuit dysfunction may contribute to disease onset and progression in SZ.
ID: 978934

EPISTATIC INTERACTIONS OF DISC1 AND ITS BINDING PARTNERS IN RELATION TO A SCHIZOPHRENIA ENDOPHENOTYPE

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Background: Most genetic studies of schizophrenia focus on main effects of specific genetic markers. Since schizophrenia is known to be associated with a number of different genes, interaction between them is likely to play a role in its etiology. An approach focusing on genetic main effects fails to account for such interaction. A potentially informative approach to gene discovery involves modeling epistasis (gene-gene interaction) between markers of genes of interest. To narrow the range of interactions to be modeled, one can limit the markers to those in genes that are known to interact with one another at the protein level. Such an approach has the potential to allow us to model the non-additive genetic effects that are suspected to influence predisposition to a multitude of complex phenotypes. Such a model, if viable, also promises to give us more information about the likely signaling pathways that might be implicated in the pathophysiology of schizophrenia. A substantial literature exists linking the DISC1 gene and its binding partners to a number of neurocognitive deficits associated with schizophrenia. Methods: We examined 209 SNPs from the DISC1 gene and its binding partners in a dataset of 200 Finnish twin pairs (monozygotic and dizygotic cases and controls) in relation to scores on standardized measures of working memory function previously associated with genetic susceptibility to schizophrenia. Using mixed model ANOVA we tested possible two-way interactions between the categorical SNP data and continuous scores on memory performance tasks. To minimize our chances of making a type I error we used a conservative Bonferroni correction. Results: We found several markers of the DISC1 gene to interact with markers of the ATF5 gene, and a single marker of the PAFAH1B1 (LIS1) gene to interact with a marker on FEZ1, in predicting working memory performance (corrected p-values ranging from .0066 to .033). Conclusion: Our findings of epistatic interactions between DISC1 and the genes encoding proteins that are known to bind with DISC1 constitute "proof of principle" evidence that the genetic determination of cognitive impairment in schizophrenia goes beyond main effects and includes epistasis.
ID: 978621

9. Health Economics & Services Research

DIFFERENCES BETWEEN SCHIZOPHRENIA PATIENTS WHO SWITCH VS. DISCONTINUE ANTIPSYCHOTIC THERAPY

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Background: To compare patients who switch vs. discontinue antipsychotic medication on illness characteristics and early changes in patients' clinical status during the long-term treatment of schizophrenia. Methods: This post-hoc analysis used data from a 1-year randomized open label cost-effectiveness study of antipsychotics in the treatment of schizophrenia. The study permitted switching of antipsychotics when clinically warranted. Baseline patient characteristics and their clinical and functional status were assessed using standard psychiatric measures and reviews of medical records. Patients who switched medication were compared with discontinuers (dropouts without a switch prior to study discontinuation) on baseline sociodemographics, comorbid conditions, body weight, clinical and functional variables, as well as change scores on standard efficacy and tolerability measures after the first 2 weeks of treatment. Chi-square, Fisher's exact, Wilcoxon rank-sum, and independent t tests were used to conduct group comparisons. Results: Compared to patients who switched antipsychotics ($n = 191$), the discontinuers ($n = 153$) were significantly more likely to be males, uninsured, to be less adherent with antipsychotics in the prior year, to have substance use disorders and to have been previously incarcerated. At baseline, the discontinuers had a more severe illness profile, with lower GAF scores and poorer level of functioning (lower social functioning, fewer family contacts, and poorer financial status). Following 2 weeks of therapy, the discontinuers evidenced less symptom improvement (PANSS total score). Moreover, despite comparable scores on the Barnes Akathesia Scale at baseline, the switchers experienced lack of improvement or some worsening of akathesia compared to improvement among the discontinuers, resulting in significant group differences on akathesia change scores at week 2. Conclusion: Patients with schizophrenia who switch antipsychotic medication appear to significantly differ from patients who discontinue therapy on sociodemographic characteristics and illness profile at baseline. Discontinuers were also found to experience less clinical and functional improvement early in treatment (week 2) but greater early change in akathesia. Findings have implications for schizophrenia research and highlight the importance of early clinical improvement in therapy.
ID: 977620

CONCORDANCE BETWEEN PHYSICIANS' AND PATIENTS' RATINGS OF COGNITIVE IMPAIRMENTS AND FUNCTIONING ASSOCIATED WITH SCHIZOPHRENIA

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Background: The objective of this study was to compare physicians' ratings and patients' self-assessments of cognitive impairments, functioning, and medication adherence. Methods: Data analyzed were from a cross-sectional study of schizophrenia patients and their physicians (the Adelphi US Psychoses XI Disease Specific Programme). Physicians evaluated their patients' cognitive impairment, functioning (overall level of function, ability to meet basic needs) and non-adherence. Patients completed self-assessments of their cognitive symptoms (difficulty in thinking clearly, having trouble concentrating, feeling confused), functioning (completing tasks/chores in the home, self-care, performing usual activities) and medication non-adherence. Comparisons of the assessments were made by chi-square tests. The analysis was restricted to outpatients ≥18 years old who had ≥4 visits to their physician's office in the past 12 months. Results: Matched records were available for 385 patients. Overall, physicians' rating of cognitive difficulties was in greater agreement with patient-reported presence of cognitive impairment rather than severity. The best concordance was seen with patients' reports of feeling confused ($P < .001$); the least was for patients' reports of difficulty thinking clearly ($P = .04$). Physicians' rating of their patients' overall functioning was most congruent with patients' self-reported ability to complete tasks/chores in the home ($P < .001$) and physicians' assessment of patients' ability to meet basic needs was most congruent with patients' rating of their ability to perform self-care activities($P < .001$). Neither of the physician assessments of functioning was related to the patients' self-reported ability to perform usual activities. Physicians' evaluation of medication non-adherence was consistent with the patients' rating (ever stopped all drug treatment) ($P < .001$), but not with patients' reports of forgetting to take medications in the past week. Fewer patients (29.8%) reported medication non-adherence compared to the physicians' estimates (42.3%). Conclusion: There was concordance between physicians and patients on the presence of cognitive impairment, however there was some disagreement regarding the severity, with patients acknowledging less impairment compared to physician ratings. There was discrepancy in physician-patient ratings of functioning and adherence. The findings support the need for standardized, quantifiable measurements of patients' real world functioning.
ID: 978487

MONITORING FOR METABOLIC SYNDROME IN A COMMUNITY MENTAL HEALTH CENTER

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Background: Guidelines formulated by the American Diabetes Association (ADA) and the American Psychiatric Association (APA) recommend a specific monitoring protocol for metabolic syndrome (MetS) for everyone started and maintained on atypical antipsychotic medications which includes obtaining measures of Body Mass Index (BMI), waist circumference, blood pressure, fasting glucose and a fasting lipid profile at the initiation of an atypical antipsychotic and at regular intervals thereafter. These guidelines are poorly followed and only a third to a half of individuals with risk factors of MetS are appropriately treated. Methods: In a Community Based Participatory Research project, we tested the Plan Do Study Act (PDSA) model for incrementally improving compliance with guidelines for monitoring MetS in a public mental health outpatient setting. We assisted the clinic system in removing barriers, developing procedures, and initiating documentation and staffing changes to improve compliance with guidelines. We compared compliance with guidelines once prior to intervention and twice post-intervention in a multiple baseline design in which one test clinic in the system received intervention and two other clinics served as controls. 50 random

charts were pulled from each clinic for 3 specific, 1–2 week periods over the course of 18 months. Results: There were significant improvements in the ordering of needed labs, the presence of lab results in the chart, and documentation of BMI and waist circumference in the intervention clinic over time in comparison to the control clinics. However, logistical barriers continue to be addressed, documented evidence of physician action with respect to MetS components remains low, and additional follow-up is planned. Nearly a thousand patients have been assessed for MetS to date. Results of monitoring indicate that 89% of individuals have at least one component of MetS, and 43% meet the full criteria for MetS. Conclusion: Results highlight the need for treatments that can address MetS and improve health outcomes for this population.
ID: 979600

CLINICAL INDICATORS FOR ROUTINE USE IN THE EVALUATION OF EARLY PSYCHOSIS INTERVENTION: DEVELOPMENT, TRAINING SUPPORT, AND INTER-RATER RELIABILITY

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Background: Clinical practice improvement carried out in a quality assurance framework relies on routinely collected data using clinical indicators. We describe the development, minimum training requirements, and inter-rater agreement of indicators that were used in an Australian multi-site evaluation of the effectiveness of early psychosis (EP) teams. Methods: Surveys of clinician opinion and face-to-face consensus-building meetings were used to select and draft conceptual definitions for indicators. Operationalisation of definitions was achieved by iterative refinement until clinicians could be quickly trained to code indicators reliably. Calculation of percentage agreement with expert consensus coding was based on ratings of paper-based clinical vignettes embedded in a two-hour clinician training package. Results: Experienced EP clinicians achieved high levels of consensus about the assessment domains and conceptual definitions for seven clinical indicators judged most relevant to evaluating EP teams. It was possible to operationalise these indicators for ease-of-training. Brief training resulted in clinicians coding indicators with acceptable percentage agreement (60%–86%). Good agreement was only possible with less precise "broad range" expert consensus scores for indicators of suicide risk, psychosocial function, and family functioning. Generally, estimated kappa values indicated fair to good inter-rater reliability (kappa >.65). Inspection of contingency tables (coding category by area health service) and comparison of modal scores across services suggested consistent, unbiased coding across services. Conclusion: Clinicians are able to agree upon and define what information is essential to routinely evaluate clinical practice. Reliable indicators of this information can be designed. However, these tasks can take several years to complete.
ID: 980824

HOSPITALIZATION FROM A MOBILE CRISIS UNIT

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Background: Having a psychotic disorder is a factor risk for hospitalization in an psychiatry unit, however knowledge of why some patients end up requiring hospital admission and some others do not is limited. The development of external Mobile Crisis Units (MCU) seems to be useful as a tool to reduce the number of admissions. The aim of our study is to identify predictors of patient admission with schizophrenia diagnosis in an MCU in Barcelona Methods: A descriptive, observational and cross study made in schizophrenic patients treated from our MCU. Demographic and clinical variables are colleted, including the Global Assessment of Functioning (GAF), the Severity of Psychiatric Illness scale (SPI), the Clinical Global Impression scale (CGI), the positive, negative and general psychopathology symptoms subscales (PANSS) and the rating of Scale to Assess Unawareness of Mental Disorder (SUMD). Results: In our sample, patients with psychotic disorders who needed admission, required presence of law enforcement more often (42.6% vs 57.4%; P <.001), showed worse GAF (average 37.07, DS 23.71 vs average 47.16, DS 14.21; P <.005), higher scores in the CGI scale (average 5.12, DS .66 vs average 4.24, DS .81; P <.001) GEP (average 15.96, DS 3.81 vs average 12.09, DS 4.17; P <.001), PANSS P (average 28.79, DS 6.43 vs average 22.28, DS 7.02; P <.001), and PANSS PG (average 45.28, DS 9.65 vs average 38.8, DS 9.5; P <.001). However, we did not find any correlation with the PANSS N score (average 20.0 DS 8.08 vs average 21.89 DS 8.44; p .187), age (average 45.44, DS 16.16 vs average 45.3, DS 17.01; P .960), toxic substances consumption (77.3% vs 22.7%; P .969), admissions history or their living situation. Conclusion: Schizophrenic patients who require admission from MCU have less insight, worse performance and higher aggressiveness. The presence of positive symptoms has also been observed as a determinant admission factor. Reviewing the literature, there are some differences with the conventional hospital emergency services where, for instance, the consumption of toxic substances, the patients living situation and their admissions history have shown to be determinants of admission.
ID: 979155

A RANDOMIZED TRIAL OF THE EFFECTIVENESS OF THE NAMI FAMILY TO FAMILY EDUCATION PROGRAM

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Background: Families of individuals with serious mental illness often play a substantial role in the recovery of their loved one. We evaluated the effectiveness of the National Alliance on Mental Illness Family to Family Education Program (FTF), a program that is delivered by trained family member teachers and available free of charge throughout the country. We hypothesized that individuals randomized to take FTF immediately would show greater coping, less distress and subjective family burden, and better family functioning after FTF compared to individuals asked to delay taking the class but having access to all other NAMI and community supports. Methods: Each family member expressing interest in FTF within the geographic area of five participating Maryland NAMI affiliates was directed to the state FTF coordinator. She evaluated each person's appropriateness for FTF, and then ascertained their interest in the study. If interested, they were referred to research staff and asked to provide informed consent. A total of 1532 individuals were screened, of whom 1168 were eligible. Of these, 27% (N = 318) consented to be in the study, were randomized, and completed the baseline assessment. Staff blinded to treatment condition performed assessments again three months later. Follow up rates exceeded 80% and did not vary by condition. To assess differences in coping, distress, burden and family functioning (measured with continuous variables) we used a General Linear Mixed Model (SAS Proc MIXED)to compare scores at the three

month assessment controlling for baseline and FTF class. Participants had an average age of 51.9 (SD = 10.9) years; 77% were women, and 61% were parents. Results: Individuals having received FTF had significantly greater overall empowerment and empowerment within their family, the service system and their community. Individuals who received FTF also had greater knowledge of mental illness, higher ratings of constructive emotion focused coping, and lower ratings of anxiety than individuals in the control condition. In addition, individuals who received FTF reported higher ratings of personal skills related to family functioning. Subjective burden did not differ by condition. Conclusion: This rigorous community based randomized trial provides strong evidence of the effectiveness of the NAMI Family to Family Education Program, the most widely disseminated family support service in the country, and suggests that FTF merits consideration as evidence based practice.
ID: 937604

EARLY DETECTION AND INTERVENTION (EDI) IN FIRST EPISODE PSYCHOSIS: CAN IT REDUCE THE RISK FOR POOR OUTCOME? TIPS 10 YEAR FINDINGS

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Background: Duration of untreated psychosis (DUP) and outcome in first episode psychosis (FEP) are clearly correlated, but we do not know if early detection (ED) reduces the percentage of patients with poor outcome. The TIPS study was designed to test this question by changing DUP in two of four Scandinavian health care sectors and measuring outcome in all sectors. Baseline assessments ($N = 281$) showed that ED patients had shorter DUP, and less positive and negative symptoms, and suicidality. Follow-up assessments showed that the negative symptom advantage was kept the five first years. Methods: Assessments are now completed for 10 years ($N = 173$) including symptom recovery (PANSS positive and negative symptom scores ≤ 3), and functional recovery. A main question was whether early intervention could reduce the likelihood of poor outcome (non-recovery and need for sheltered living). Results: We found a clear drop-out selection bias. The ED sites had fewer dropouts(28% vs 48%)and at their last interview the ED drop outs had significantly LESS negative symptoms than ED completers [$P = .03$], while the NoED dropouts at their last interview had significantly MORE negatives symptoms than NoED completers [$P = .03$]. All sites had a considerable number of patients with neither symptomatic nor functional recovery (ED: 48%, NoED 52%). The ED sites had more non-recovered patients with no capacity for independent living (No-IL) (21 % vs 11% of the followed up patients). Across the sites, the No-IL patients had a significantly higher percentage of drug abuse both at baseline (41% vs 18% ($P = .012$)) and at 5 years (40% vs 8% ($P = .000$)), a slightly higher level of negative symptoms at baseline (PANSS negative component score at baseline 22.8 vs 19.7 ($P = .06$)), and significantly higher level at 5 years (26.8 vs 14.5 ($P = .000$)). Conclusion: (1) The percentage of non-remitted NoED patients most likely is an underestimation, as the NoED sites lost many highly symptomatic patients to follow-up. Therefore the ED sites most likely had substantially fewer poor outcome patients than the NoED sites. (2) Nonetheless it is clear that an ED program gives no guarantee against poor outcome. (3) Drug use and a high level of negative symptoms seem to increase the risk for poor outcome. Implications: (1) The ultimate limits to what can be gained by reducing DUP have yet to be ascertained. (2) Once psychosis is present it appears critical to keep treatment active and vigorous with special focus on persistent negative symptoms and drug use.
ID: 978292

SECOND GENERATION ANTIPSYCHOTICS IN COMMUNITY TREATMENT FOR SCHIZOPHRENIA

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Background: The Schizophrenia PORT 2003 Treatment Recommendations and Mt. Sinai Conference Safety Monitoring recommendations have generated guidelines for the pharmacological treatment of schizophrenia and monitoring of side effects. This study sought to determine if community-based treatment of people with schizophrenia was conformant with these recommendations. Methods: The study included 73 outpatients receiving care from local community mental health centers and currently treated with a second generation antipsychotic. Six Schizophrenia PORT treatment recommendations (maintenance antipsychotic treatment, maintenance antipsychotic dose, antiparkinsonian agents, clozapine treatment for residual positive symptoms, adjunctive antidepressants, adjunctive antianxiety agents) and four Mt. Sinai Conference Safety Monitoring recommendations (weight gain and obesity, glucose dysregulation, hyperlipidemias, and extrapyramidal side effects (EPS)) were chosen for conformance evaluation. Individuals were identified as conformant or non-conformant. The impact of conformance on outcome was examined through the collection of symptom (BPRS, CGI, SANS), cognitive (RBANS), functioning (LOF, QOLI), laboratory (glucose, lipid profile), and side effect (SAS, BAS, MIMS, weight, waist circumference) assessments. Results: In general participants were conformant with maintenance outpatient antipsychotic treatment (100%), antipsychotic dose (83%), antiparkinsonian agents (97%), adjunctive antidepressants (100%), and adjunctive antianxiety agents (90%), but not with clozapine treatment for residual positive symptoms (31%), weight gain and obesity (48%), glucose dysregulation (53%), hyperlipidemia (34%), or EPS (11%). Individuals treated with clozapine compared to those who were non-conformant had lower BPRS total ($P < .05$) and positive symptom ($P < .05$) scores. Individuals conformant to Mt. Sinai Safety recommendations had more metabolic dysfunction and higher weight. Conclusion: Most individuals receiving treatment at local community mental health centers were conformant with the Schizophrenia Port Treatment Recommendations, except for clozapine treatment. The barriers to prescribing and monitoring clozapine may contribute to the decreased conformance. Clozapine conformance is meaningful because non-conformant individuals were more likely to be symptomatic. There was little evidence of ongoing safety monitoring in outpatients with schizophrenia.
ID: 979318

PREDICTORS OF RESOURCE UTILIZATION COSTS IN PSYCHOTIC DISORDERS BASED ON THE CANADIAN OSCAR STUDY

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Background: The OSCAR study collected 12 months of prospective resource utilization (RU) and clinical outcomes data in an open-label, naturalistic study of stable patients currently treated with quetiapine, risperidone, or olanzapine monotherapies. The goal was to identify the predictors of resource-utilization costs. Methods: A total of 138 subjects with schizophrenia or a related psychotic disorder were enrolled from 5 Canadian centers. Baseline predictors including: age, gender, ethnicity, education, marital status, family history of schizophrenia, ratings of symptoms and functioning (SOFAS = Social and Occupational Functioning Scale, PANSS = Positive and Negative Syndrome Scale, SDS = Sheehan Disability Scale, CGI = Clinical Global Impressions Scale), and history of street-drug, alcohol, marijuana, and cigarette use, were entered into a multivariate regression model (incorporating univariate predictors with $P < .2$) to identify the most important predictors of costs. Resources consumed were valued in $ CAN 2007 using non-generic drug costs. Results: 117 subjects (85%) provided sufficiently complete data for analyses. Mean age was 42 years (19–65), 74% were male, 91% were Caucasian; 15% were married, and 22% had a family history of schizophrenia. Diagnoses were: 65% schizophrenia, 25% schizoaffective disorder, 10% other psychoses. Baseline antipsychotic medication was: quetiapine = 33, risperidone = 38; olanzapine = 46 subjects. Baseline PANSS and SOFAS scores (mean ± SD) were 62 ± 18.8 and 59 ± 13.8, while 31% were at least moderately ill according to the CGI. Mean SDS scores were Work/School: 4.4 ± 3.75, Social Life: 5.2 ± 3.32, and Family/Home 4.3 ± 3.16. Tobacco, marijuana and street-drug use in the month before baseline was 43%, 14%, and 2%. Alcohol use was reported by 42% of subjects in the month before baseline. Using a multivariate regression model, the mean (95% confidence intervals) for the adjusted monthly costs were: quetiapine $1072 ($721, $1423); risperidone $620 ($297, $942); olanzapine $1067 ($767, $1368) ($P = .077$). Significant predictors included: Total PANSS ($14 per point, $P = .04$), age (−$16 per year; $P = .03$) and education level ($409 for greater than high school education vs. others; $P = .04$). Conclusion: Our analysis indicates that older patients with a higher level of education, and more prominent symptoms were predictors of greater resource use. Total costs also varied by the type of antipsychotic medication used even after controlling baseline confounders.
ID: 977376

EFFECTS OF A COMPREHENSIVE WELLNESS INTERVENTION ON ESTIMATED 10-YEAR CORONARY HEART DISEASE RISK IN PATIENTS WITH SEVERE MENTAL ILLNESS

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Background: Coronary heart disease (CHD) is a major contributor to the increased rates of mortality in patients with schizophrenia. We hypothesized that participation in a Comprehensive Wellness Intervention program (CWI), which has shown to improve metabolic parameters (Lindenmayer et al, 2009), will result in a significant risk reduction for CHD- related cardiac events amongst predominantly African-American chronic schizophrenic inpatient participants. Methods: Ten-year risk for CHD was calculated for 325 inpatients with chronic mental illness who participated in the 52-week comprehensive and manualized psycho educational program for healthy lifestyles (CWI) using the Framingham CHD risk function both at baseline and at endpoint. Metabolic variables (total cholesterol, HDL cholesterol, blood pressure, and cigarette smoking and glucose levels) were compared between baseline and endpoint. Results: At baseline, 25.5% of patients had a ≥5% risk of developing CHD, and 30.5% had between >1% and 4.9% risk of developing CHD. The number of patients in the highest (≥5%) 10-year CHD risk group at baseline decreased significantly to 20.9% after CWI ($\chi^2 = 29.45$, $P = .005$), while the number of patients in the lowest risk group (≤1% or not at risk) increased significantly after CWI, from 44.0% at baseline to 47.1% at endpoint ($\chi^2 = 23.24$, $P = .010$). There was also a significant 7.5% reduction in the prevalence of metabolic syndrome (MetS) from baseline to endpoint ($\chi^2 = 155.641$, $P = .000$), an effect that was independent of changes in BMI. Following treatment with CWI, a significant decrease was seen in HDL ($P = .002$), total cholesterol ($P = .030$), fasting glucose ($P = .010$), and diastolic blood pressure ($P = .000$), as well as an average weight loss of 2.9 lbs ($P = .002$). Conclusion: We found that a structured wellness and psychoeducational program can effectively reduce the estimated 10-year CHD risk and MetS risk in a large naturalistic sample of unselected, predominantly African American chronically mentally ill inpatients. While our results show a higher 10-year CHD risk as compared to the CATIE study, they are consistent with evidence of increased cardiac mortality in schizophrenia patients. Factors contributing to CHD risk will be discussed in the context of specific antipsychotic agents, diet, exercise, and quality of medical care.
ID: 977876

EARLY-REHOSPITALIZATION RATES OF INDIVIDUALS WITH PSYCHOTIC DISORDER AND BIPOLAR DISORDER IN SÃO PAULO, BRAZIL

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Background: Long-lasting psychiatric hospitalization has always been a sign of stigmatization of the mentally ill. To manage this, number of psychiatric hospital beds has decreased drastically around the world. Although this also occurred in Sao Paulo, there is a conviction that many patients become heavy users of acute psychiatric beds. Multiple brief hospitalizations would substitute the old long-lasting hospitalization, masquerading stigma. This survey is a 12-month study of rehospitalization taxes in individuals with bipolar and psychotic disorder in Sao Paulo. Methods: The sample consists of acute inpatients of a psychiatric hospital in Sao Paulo, Brazil. Patients are admitted from emergency units from all regions of the city randomly on an as-needed basis. Excluding those with primary diagnoses other than bipolar, psychotic or related disorders, all patients (ICD-10 F2x.x and F31.x) discharged from may to august 2009 were invited to participate in the study ($n = 222$); 21% refused to take part or could not be contacted, resulting in a final sample of 176 individuals. Subjects were submitted to a telephone interview at month 1, 2, 6 and 12 after hospital discharge using a specific instrument, including stereotypes related to the patient, medication issues and opinions about mental health policies. Results: One year after hospital discharge 70 of the individuals (40%) had already been readmitted at least once. Haloperidol was protective for readmission in 2 months (OR = .4, 95% CI = .2–.9). For 6 months readmission stereotype "dangerous" ($chi^2 = 12.4$) and "abnormal" ($chi^2 = 16.5$) were positively related. For 12 months readmission, number of previous hospitalizations ($chi^2 = 8.0$), stereotype "dangerous" ($chi^2 = 9.6$) and "abnormal" ($chi^2 = 12,2$) were related. For "rehospitalization survival" after 1 year, having a previous hospitalization (OR = 1.5, 95% CI = 1.2–1.9), stereotype "dangerous" ($chi^2 = 13.0$), "less controlled" ($chi^2 = 11.1$) and "abnormal" ($chi^2 = 15.6$) were positively related. Desire for longer stays at the hospital (OR = 1.7–5.4) and agreement to institutionalization (OR = 1.7–3.2) showed high correlations to rehospitalization. Other measures like quantity and type of medication at discharge (except for haloperidol, shown above), physical restraint and length of hospital stay showed no significant correlation. Conclusion: Family stigma against the patient and belief in

a hospital-based mental health system might play a major role in multiple brief hospitalization, instead of factors related to the illness itself.
ID: 951264

DEMOGRAPHIC, CLINCIAL, AND FAMILIAL CHARACTERISTICS ASSOCIATED WITH ENGAGEMENT AND COMPLETION OF FAMILY PSYCHOEDUCATION INTERVENTIONS

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Background: Family psychoeducation is an effective yet underutilized intervention for the treatment of schizophrenia and bipolar disorder. To increase the accessibility of this intervention, group and single-family formats have been developed as well as a variety of brief family interventions. Presently, little is known about the characteristics of patients who elect each type of intervention. The aim of this study was to identify the demographic, clinical, and familial characteristics associated with acceptance and completion of family psychoeducation and brief family interventions for serious mental illness. Methods: Records of all individuals referred during a two year period for family psychoeducation services at an outpatient mental health clinic were reviewed. Demographic, clinical, and familial characteristics of patients were coded. Analyses were conducted to examine the relationship between these variables and patient engagement and completion of treatment as well as choice of intervention. Results: Patient goals, patient residence, type of familial relationship, and quality of familial relationship were predictive of the type of service accepted. Quality of the familial relationship was also predictive of completion of treatment. Conclusion: To our knowledge, this is one of the first studies to examine factors that influence engagement and completion of family psychoeducation and brief family interventions in routine clinical practice. Patients who lived with family members and had a broader set of treatment goals were more likely to engage in long vs. short-term interventions. Type of family psychoeducation service elected, group vs. single-family format, was related to family constellation, with couples being more likely to elect a single-family format. Completion of any type of family intervention was related to the quality of the relationship among family members at intake. Implications of findings for clinical practice will be discussed.
ID: 979463

DISTRIBUTION OF PSYCHOSIS AND OTHER PSYCHIATRIC SYMPTOMS IN AN INNER CITY HOMELESS POPULATION: THE GEORGIA HELPING HANDS GRANT PROJECT

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Background: The impact of psychotic illness, comorbid substance abuse, and medication non-adherence, coupled with disjointed psychiatric and social services all conspire to a disproportionately high rate of psychotic disorders among people who are homeless in America. We obtained the distribution of psychiatric disorders in a sample of inner city homeless in Augusta, Georgia. We recorded mental health care referrals and appointment follow-ups for the homeless screened and compared them to mental health services utilized in the state of Georgia. Methods: We aimed to identify the distribution of mental illness in the homeless and to expand the outreach services already in place through the local Project for Assistance in Transition from Homelessness. We screened the occupants at 2 inner-city shelters in Augusta, GA Monday afternoons from October-09 through March-10. We screened 106 homeless persons for alcohol and substance use, psychosis, depression, bipolar disorder and PTSD utilizing the modified CAGE questionnaire, the Mental Illness Screening Form and the Mood Disorder Questionnaire. People who qualified for further psychiatric evaluation were offered appointments and bus tickets to access care. Results: 82% of people screened were in need of further evaluation. 71% acknowledged alcohol/substance use, 83% reported depression, 57% reported PTSD symptoms, 57% screened positive for bipolar disorder and 48% admitted to psychotic symptoms. Of people who screened positive for mental illness 41% were referred for mental health evaluation and of those, 61% kept their appointment. Conclusion: Our work has limitations: mental illness distribution in this sub-sample cannot be claimed to be representative of the homeless population in Augusta or in the state of Georgia; psychosis and mood symptoms could have occurred simultaneously with substance use disorders in our sample. The distribution of psychosis and other mental illness in the homeless is high in our sample but consistent with that found in larger studies of US homeless. While the data is not known for the city of Augusta, in Georgia only 25% of the homeless use mental health services, despite of the fact that a much higher proportion (82% in our report) could benefit of those services.
This work was supported by a Helping Hands Grant from The American Psychiatric Foundation
ID: 977569

HELP SEEKING PATHWAYS IN FIRST EPISODE PSYCHOSIS

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Background: Delays to effective treatment for psychosis are associated with poorer longitudinal outcomes. Understanding the help-seeking pathways of individuals with first episode psychosis may aid in reduction of delays to specialized care. The goals are to delineate the progression to specialized services for individuals with first episode psychosis in Nova Scotia, Canada and to identify the main barriers and facilitators to early referral. Methods: Patients and families newly referred to the Nova Scotia Early Psychosis Program were recruited. The Topography of Psychotic Episode (TOPE) and Circumstances of Onset and Relapse Schedule (CORS) were used. Information gathered from patients and/or family members included time of onset of psychotic symptoms, reasons for seeking help, first help-seeking instigator, progression across health care services, and delays of referral to existing specialized care. Results: Currently, 20 patients/families have enrolled in the study (study remains open to enrollment). Patients ranged in age from 19 to 33 (median: 21), with median Duration of Untreated Psychosis of 18 months. Delay from first health care contact to specialized care (using 25th–75th percentiles) was .22–13.5 months. The primary reason for help seeking was positive (50%) and negative (50%) symptoms. The patient most often (60%) instigated the help-seeking, followed by family (25%), and police (15%). General Practitioners were the most often first-contacted professional group (45%), followed by Emergency Rooms (25%). Conclusion: The main barriers to specialized care experienced by patients and families will be discussed with the ultimate goal of further facilitating shorter delays to specialized care.
ID: 960128

SURGICAL RATES OF COMMON PROCEDURES IN VETERANS WITH SCHIZOPHRENIA AND OTHER MENTAL ILLNESS

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Background: Individuals with schizophrenia or other serious mental illness (SMI) suffer from numerous physical comorbidities, while delays in seeking medical care might contribute to deteriorating symptoms and subsequently greater surgical needs. The role of preoperative psychiatric conditions on surgery rates and postoperative outcomes is virtually unstudied. Using national Veteran Affairs administrative data, we examined rates of commonly performed surgeries in patients with and without psychiatric conditions. Methods: Patients were categorized by a 2005 diagnosis of schizophrenia, bipolar disorder, major depression, post-traumatic stress disorder, or no SMI disorder per established algorithms. Surgical codes were reviewed iteratively to define procedures, with the most common surgeries grouped by perioperative experts. Poisson regression compared surgery rates across the 5 groups. Results: 458 170 SMI patients underwent 3.8 procedures per 100 individuals, a rate nearly double that of 5 million non-SMI patients (2.2/100). The most common surgeries were: vascular (peripheral artery disease, amputations, carotid endarterectomy), cancer, orthopedic for traumatic injuries, appendectomy, hysterectomy, and trans-urethral radical prostatectomy (TURP). Unlike overall rates, SMI patients had significantly fewer of these common surgeries, most noticeably vascular procedures (10.1/100 vs 15.9/100 non-SMI). Among SMI veterans, individuals with schizophrenia experienced substantially higher rates of amputations (7.8/100), trauma-related surgery (7.6/100), and TURP (4.0/100). Conclusion: Lower SMI rates for common surgeries are possibly attributable to cognitive impairments preventing timely symptom reporting, a pre-eminence of psychiatric over medical issues, and multiple comorbidities making surgery ill-advised. Alternatively, a later disease stage may require different treatment modalities independent of other factors. Focusing on the higher rates of amputation and orthopedic surgeries in the schizophrenia group, such intriguing findings might reflect poorer diabetes self-care and its subsequent complications, and a greater proclivity for accidents and aggressive behaviors. Further work is needed to understand these implications, along with the influence of detrimental lifestyle or behavioral factors in patients with schizophrenia. Efforts to better coordinate medical and psychiatric needs will enhance the recognition and treatment of complex comorbidity profiles, leading to improved overall quality of care.
ID: 984585

10. Neuroanatomy, Animal

REDOX DYSREGULATION AND OXIDATIVE STRESS AFFECTS PARVALBUMIN INTERNEURONS AND NEURAL SYNCHRONY IN ANTERIOR CINGULATE CORTEX DURING NEURODEVELOPMENT

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Background: Glutathione (GSH), a major cellular redox regulator and antioxidant, is decreased in CSF and prefrontal cortex of schizophrenia patients. Polymorphisms of the key GSH-synthesizing enzyme genes, glutamate-cysteine ligase catalytic and modifier (GCLM) subunits, are associated with schizophrenia. A developmental dysregulation of glutathione (GSH) synthesis leading to oxidative stress, when combined with environmental risk factors generating reactive oxygen species, can play a critical role in inducing connectivity anomalies as observed in the disease (Do &al 2009). Methods: Based on concept of ''reverse translation'', we have tested this hypothesis in gclm-/- mice (70% decreased brain [GSH]): they exhibited morphological, physiological and behavioral phenotypes of the disease, including impairment of parvalbumin-immunoreactive interneurons (PVI) and neuronal synchronization in ventral hippocampus (Steullet &al 2010). Results: In anterior cingulate cortex (ACC) of gclm-/- compared to gclm+/+ WT mice, there is a delayed PV expression at P10, which normalized at P20. Using a novel protocol to induce β/γ oscillations in ACC via co-stimulation of kainate, ACh and D2 receptors, we find that γ oscillations are reduced while β oscillations are intact in ~5 months old gclm-/- mice, at which age there is a 20% reduction of PVI. Additional oxidative stress induced by increased extracellular DA (GBR12909 treatment) at P10–P20, leads to reduced number of PVI in ACC of P20 gclm-/- mice but not in WT. In the adolescent (P40) mice, a similar PVI deficit is observed in ACC of gclm-/- mice only when exposed to GBR at P30–P40. This PVI deficit is prevented by treatment with *N*-acetyl-cysteine, a GSH precursor. Interestingly, gclm-/- mice exposed to GBR at P80-P90 showed no PVI deficit at P90. These data indicate the convergence of a genetic redox dysregulation and of an additional stress, when applied during the early and adolescent age leads to specific cortical decreased of PVI, but much less if applied in adulthood. Similar observations were also obtained with oxidative stress marker 8-oxo-7,8-dihydro-20-deoxyguanine. Conclusion: These data underscore the selective vulnerability of the ACC to the convergence of a genetic redox dysregulation and of an insult during peripubertal age. This might be analogous to the damaging consequences of various early environmental insults during the development of future schizophrenia patients, while they are milder in adulthood.
ID: 978343

THE EFFECT OF NDEL1 ON NNOS SIGNALING IN CORTICAL DEVELOPMENT AND SCHIZOPHRENIA

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Background: Higher brain function and behavior are influenced by neuronal circuit formation during brain development. Many genetic risk factors for schizophrenia, such as Disrupted-in-Schizophrenia-1 (DISC1) and neuronal nitric oxide synthase (nNOS), have key roles in neurodevelopment. Consequently, disturbances in brain development are suggested to underlie the pathology of such devastating condition. Although roles for these factors have been reported at the molecular level, there are limited studies on whether they act in common molecular pathways that contribute to disease pathology. In this study, we explored the role of NudE-like 1 (NDEL1), a schizophrenia-associated protein interactor of DISC1, in nNOS signaling for the development of the prefrontal cortex and resultant behaviors. Given that nNOS and NDEL1 are highly expressed in the cortical plate of developing cerebral cortex, NDEL1 may function as a downstream effecter of nNOS signaling for cortical development, which may contribute to NO-mediated establishment of neuronal circuits responsible for long-lasting behaviors. Methods: We examine the role of S-nitrosylation of NDEL1 via nNOS signaling for cortical development and their underlying molecular mechanisms by using cortical neuron cultures with RNAi approaches and brains from nNOS KO mice. To manipulate NDEL1 function in the developing cerebral cortex, we use a Cre/loxP-mediated inducible expression system with in utero electroporation. Results: We found that NDEL1 is S-nitrosylated in the brain of wild-type mice, but not of nNOS knockout mice. We also found the interaction of NDEL1 with nNOS. Furthermore, our data from behavioral characterization of nNOS KO mice suggest that prefrontal cortex-mediated cognitive functions may be impaired in nNOS KO mice. Conclusion: In utero gene transfer with inducible gene expression system allows us to dissect the temporal requirement for the studies of NDEL1 in nNOS signaling in cortical development as well as explore the molecular basis of disease animal models for further testing of resultant behaviors. Our results will provide us with important clues for the possible involvement of nNOS/NDEL1 signaling in the etiology of schizophrenia.
ID: 978848

NOVEL APPROACHES FOR CREATING NEURAL CELL MOSAICS IN MODELS OF NEURODEVELOPMENTAL DISORDERS

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Background: Many neurodevelopmental disorders, including Schizophrenia, are associated with disruptions in subsets of neurons and glia that can occur during neural progenitor proliferation, migration, differentiation and circuit formation. The inherent nature of these developmental disruptions requires establishing and using animal models that target subsets of neural progenitors and neurons to create neural cell mosaics of disrupted development and function. Methods: In utero electroporation (IUE) has proven to be an outstanding experimental platform for creating mosaic models of neurodevelopmental disruption. We developed two new applications of IUE: i) conditional expression with channel rhodopsin, and ii) piggyBac induced clonal labeling (PICL). In the first approach upper layer neocortical neurons were transfected with channel rhodopsin and a conditional expression vector to express Disc1 or truncated Disc1. We used this system to express Disc1 and mutant Disc1 after migration and proliferation in order to isolate the effects of Disc1 on synaptic transmission independently of early developmental disruptions. Results: Upon presynaptic activation of only genetically manipulated pyramidal neurons that express truncated Disc1 the resulting synaptic responses of connected cells, unlike control cells, had multiple peaks and significantly slowed kinetics. In a second new application of IUE, we used a binary piggyBac transposon system with three fluorescent proteins to label astroctyte clones. The pattern of labeling reveals a new organization of astrocyte clones in neocortex. Conclusion: The expression of truncated Disc1 in pyramidal neurons results in a desynchronization of transmitter release from glutamatergic synapses. The method of piggybac mediated clonal labeling of astrocytes reveals a columnar organization of astrocyte clones that may have significance to the development of columnar synaptic organization in the neocortex.
ID: 979315

CIRCLING IN ADULT MACAQUE MONKEYS EXPOSED TO IRRADIATION IN EARLY GESTATION: THE PRESENCE OF A MOTOR STEREOTYPY IN A NEURODEVELOPMENTAL MODEL OF SCHIZOPHRENIA

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Background: Motor stereotypies, though not typically observed in antipsychotic-treated schizophrenia patients today, were included in the original descriptions of schizophrenia by Bleuler and Kraepelin. We have previously shown that monkeys exposed to x-irradiation in early gestation express a schizophrenia-like phenotype: reduced thalamic volume and neuron number, most prominently in the mediodorsal nucleus, and an adult-onset impairment in working memory performance that is suggestive of compromised prefrontal cortical circuitry. Here we report the presence of a motor stereotypy (circling) in fetally irradiated monkeys (FIMs). Methods: Five FIMs (exposure 150–200 cGy, E30–E41) and 5 control monkeys (CONs: 4 sham-irradiated and 1 non-irradiated matched for age to FIMs) were videotaped while performing the spatial Delayed Response (DR) task as juveniles (12–30 months) and as adults (~5 years). Previous analysis of 2-minute clips of the videotaped sessions revealed increased motor activity in the adult FIMs compared to CONs (Friedman and Selemon, ICOSR 2007), with prominent circling behavior noted in the FIMs. The number and direction of circling events was quantified in these same 2-minute videotaped segments. Results: As juveniles, 2 CONs and 4 FIMs exhibited circling, defined as more than one circling event (full circle, paired semicircle, ie, half circle in one direction followed by half circle in opposite direction, or single semicircle). As adults, 3 FIMs continued to exhibit circling whereas none of the CONs circled. The number of circling events observed in juvenile monkeys was 3, 16, 27, and 31 for FIMs and 5 and 20 for CONs. As adults, circling events numbered 3, 13, and 24 in FIMs. All monkeys showed a preference for circling in one direction; however, as adults the 3 FIMs who persisted in circling did so exclusively in one direction, ie, their preferred direction as juveniles; 2 circled clockwise and 1 circled counterclockwise with paired semicircles always beginning in the preferred direction. Conclusion: Motor stereotypies are thought to arise from disinhibition of corticostriatal circuitry and have been associated with pathologic changes in the basal ganglia and/or dysregulation of the dopamine system. The presence of stereotyped circling in FIMs therefore may indicate that altered corticostriatal and/or mesostriatal dopamine function is a long term consequence of disrupted neurogenesis in early gestation. Support: MH59329, MH71616.
ID: 979426

STRUCTURE-FUNCTION AND GENETIC ANALYSES OF DISRUPTED IN SCHIZOPHRENIA-1 USING IN UTERO ELECTROPORATION IN THE RODENT CORTEX

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Background: In the past ten years there has been an explosion of genetic studies that have identified genes linked to psychiatric disorders, providing key molecular inroads for addressing the underlying causes of these disorders. However, addressing the functional consequences of these genetic alterations in animal models can be expensive and time consuming when using traditional knock out and transgenic approaches. Methods: In utero electroporation in the rodent brain allows for rapid and effective analyses of knock down or expression of specific genes in the developing cortex. Detailed structure-function studies are rapidly performed via shRNA-mediated knock down followed by rescue with constructs encoding alternate versions of the protein. Splice variants and single amino acid alterations can be assessed for activity in quantitative assays for developmental processes such as proliferation, neurite outgrowth, and migration. Results: Using this approach, we address the mechanism by which multiple genes including Disrupted in Schizophrenia-1 (DISC1) and Amyloid Precursor Protein (APP) mediate cortical migration in the developing cortex. We address which regions of APP are required for its function, and examine which splice variants and allelic variants of DISC1 are functional in migration. In addition, genetic interactions between genes can be examined using this approach, and we provide evidence that DISC1 acts downstream of APP in the process of cortical migration. Conclusion: In utero electroporation is an efficient method for analyzing gene function and pathological dysfunction in the developing cortex.
ID: 979263

11. Neurochemistry, Animal

INTRACEREBRAL TRANSPLANTATION OF HUMAN ADULT STEM CELLS PROTECTS AGAINST SOCIAL DEFICIT EXHIBITED BY SUBCHRONICALLY PHENCYCLIDINE TREATED MICE

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Background: Stem cell based regenerative therapy is a promising cellular therapeutic approach, bringing hope for patients affected with incurable deteriorating diseases. Mesenchymal stem cells (MSCs) represent an attractive cell source for regenerative medicine strategies for the treatment of neurodegenerative diseases. Previous studies have shown that intracerebral transplantation of these stem cells may be efficient in treating neurodegenerative diseases such as Parkinson's and Huntington's, exerting neuroprotection and inducing neurogenesis. Schizophrenia (Sz) is a devastating brain disease with poor prognosis, especially due to the debilitating negative symptoms. Beside a neurodevelopmental element, the pathophysiology underlying Sz involves neurodegeneration, impaired neurogenesis and alterations in neurotrophic factor availability. In the current study, we sought to explore the prospect of intracerebral MSCs transplantation for treating the phencyclidine (PCP) Sz mouse model. Methods: PCP was administered subcutaneously to C57bl mice (10 mg/kg daily for 2 weeks). Cell transplantation into the prefrontal cortex was conducted on the day of first PCP administration. Clozapine (6 mg/kg daily) was injected intraperitoneally from the day of first PCP administration. Social preference test was conducted 10 days following the last PCP administration. Results: Human MSCs transplantation resulted in a significant reduction in the impairment of social phenotype induced by the PCP insult, as observed by the social preference test. Importantly, no reduction of the social impairment was observed upon daily clozapine treatment. Immunohistochemical analysis revealed that the human cells survived in the mice brain throughout the course of the experiment (25 days). Western blot analysis of the cortex of the animals showed that MSCs transplantation prevented the significant reduction in Akt phosphorylation following the PCP administration. Conclusion: Delivery of MSCs to distinct brain regions, known to be involved in the pathophysiology of schizophrenia, is beneficial in attenuating the behavioral deficits exerted by the PCP insult in mice. We hereby suggest a novel therapeutic approach for the treatment of Sz negative symptoms.
ID: 978213

LONG-TERM CONSEQUENCES OF BRAIN OXIDATIVE STRESS DURING EARLY POSTNATAL-LIFE

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Background: Evidence derived from patient postmortem tissue and rodent reverse-translational and pharmacological models support the hypothesis of a specific dysfunction of the fast-spiking parvalbumin-positive (PV+) inhibitory neurons in schizophrenia. However, when these deficiencies occur and whether they are cause or consequence of the disease is still unknown. We previously showed that repetitive exposure to ketamine increases the levels of IL-6 in brain and activates the superoxide-producing enzyme NADPH oxidase. This leads to the loss of the GABAergic phenotype of PV+ neurons and to decreased inhibitory activity in prefrontal cortex of mice. In the present work we studied the long term consequences of activation of the IL-6/Nox2 pathway during the critical period of PV+ neuronal maturation. Methods: Using a pharmacological model of schizophrenia ie exposure to ketamine during the perinatal period, we have studied the development of the PV+ neuronal system at the electrophysiological and neurochemical level. We examined the fate of the PV+ neuronal population by determination of parvalbumin and GAD67 content in a mouse line expressing GFP only in PV+ neurons. Using this mouse line, we examined the intrinsic parameters and excitability of PV+ neurons using prefrontal slice-physiology, and auditory evoked potentials in the adult animal. Results: Our results show that sustained activation of the IL-6/Nox2 pathway during the perinatal period produces permanent effects in cortex. We found that activation of the pathway during the second postnatal week led to loss of PV expression in several brain regions in adult animals, and that this was prevented in Nox2-deficient mice. Furthermore, electrophysiological recordings of PV+ neurons showed a decreased response to excitatory transmission. Finally, a pronounced alteration of auditory evoked related potentials was found when animals were tested in adulthood. Conclusion: The PV+ neuronal system is essential for shaping neuronal circuits during postnatal brain development. Dysfunction of this GABAergic system is expected to cause an alteration of the development of the excitatory/inhibitory balance in brain. This alteration resemble what is observed in schizophrenia patients, and suggest that in individuals with genetic predisposition, a persistent activation of the IL-6/Nox2 pathway may be the environmental factor that tips the redox balance in brain leading to schizophrenia symptoms in late adolescence and early adulthood.
ID: 978473

IMMUNE PROTEINS IN BRAIN DEVELOPMENT AND SYNAPTIC PLASTICITY

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Background: Maternal viral infection is an environmental risk factor that increases the chance of schizophrenia in the child. Studies in animal models implicate the maternal immune response, rather than the virus itself, in the disruption of fetal brain development. The adaptive immune response to infection is associated with striking changes in the expression of proteins of the major histocompatibility complex class I (MHCI). Recent studies show that MHCI is unexpectedly expressed in the developing and adult mammalian central nervous system (CNS). Methods: We have used a combination of electrophysiological, biochemical, and immunocytochemical approaches to evaluate the cell biological and functional properties of synapses in MHCI-deficient transgenic animals. Results: Here we report that changes in the levels of MHCI proteins at the cell surface are sufficient to alter the structure and function of synaptic connections in the mammalian CNS, and to affect downstream behavior. Altered MHCI expression causes abnormalities in glutamatergic synaptic transmission and synaptic plasticity in the developing and adult brain, as well as deficits in activity-dependent remodeling. Conclusion: These results suggest that MHCI may mechanistically link maternal immune challenge, a risk factor for schizophrenia, with glutamatergic dysfunction and altered synaptic connectivity, symptomatic correlates of this disorder. Clarifying the role of MHCI at synapses and could lead to novel, immune-based strategies for the diagnosis, treatment, and prevention of schizophrenia.
ID: 979668

BETA-ARRESTIN-DEPENDENT D2 DOPAMINE RECEPTOR SIGNALING MAY DISCRIMINATE BETWEEN VARIOUS PSYCHOSTIMULANT RESPONSES

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Background: G protein-coupled receptors (GPCR-7TM) can signal not only through the activation of G proteins but also through the ability of GPCR/beta-arrestin 2 (Barr2) to scaffold intracellular signaling complexes. A distinguishing feature of these signaling pathways is that whereas G protein-dependent signaling is usually transient, Barr-mediated signaling is more persistent. Many examples of G protein-independent signaling now exist in both cellular and in vivo systems. Interestingly, in the brain, D2 dopamine receptors (D2R) mediate their physiological effects via both of these pathways but their respective role in the actions of psychoactive drugs remains unclear. Methods: We used genetic, in vivo biochemical and in vitro cellular approaches to assess the pharmacological responses to psychostimulants and profile of various antipsychotics. Results: In mice, pharmacological or genetic activation of D2R promotes not only the G protein/cAMP-dependent signaling pathway but also engages an Akt-GSK-3b signaling pathway through the ability of Barr2 to scaffold the kinase Akt and the phosphatase PP2A. Thus, D2R activation leads to a dephosphorylation (inhibition) of Akt (Thr308) and dephosphorylation of GSK-3b (activation) independently of both cAMP and Ca2+ signaling. We have also used genetic elimination of GSk3b in D1R and D2R containing neurons of the striatum to show pathway selectivity for certain pharmacological and behavioral responses but not others. For example in mice lacking GSK3b in D2R neurons (GKS3bflx/D2RCre) the locomotor enhancing effect of amphetamine are reduced as well as the ability of amphetamine to disrupt PPI responses, two schizophrenia-related responses. However, in the same mice CPP to amphetamine is not changed. However, various responses to cocaine are not changed. Deletion of GSK3b in D1R containing neurons does affect the responses to amphetamine. Interestingly, using cellular assays that monitor respectively the two signaling modes at D2R in cells, we find that a large series of antipsychotics more uniformly and potently antagonize the Barr2- rather than the G protein-dependent pathway. Conclusion: Thus, the Barr2-dependent Akt/GSK-3 signaling pathway appears to play an important role in the behavioral actions of dopamine but may display selectivity of action.
ID: 979677

MODELING SCHIZOPHRENIA, DOPAMINE ONTOGENY AND THE SMALL BRAIN

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Background: The epidemiology of schizophrenia indicates the disorder has a developmental basis. For the past 12 years using clues from this literature our group has been developing models in rodents to explore what biological agent/s contribute to abnormal brain development and function. Our findings and those of other respected researchers in this field strongly implicate early abnormalities in dopamine (DA) neuron development. Modeling the ontogeny of DA systems may therefore provide new leads in understanding both the etiology of this disorder and may help to explain the abnormal DA signaling observed in patients. Methods: We have recently decided to examine DA ontogeny in both the zebra fish (*Danio rerio*), and the fruit fly, (*Drosophila melanogaster*), two organisms commonly used in the neuroscience community. Using the morpholino RNA interference approach we have created a zebra fish model where we transiently interfere with dopamine synthesis in a dose-dependent fashion during development. Using Gal4/UAS technology we have also created a model in Drosophila where we can exquisitely control the temporal release of DA during larval development. Results: Results At the larval stage our zebra fish mutants have reduced DA synthesis and truncated dopaminergic innervation in the CNS. As adults these mutants have baseline behavior consistent with an anxiety-related phenotype. In drosophila when DA release is altered only during late developmental stages in larval development the behavioral phenotype is one of impaired attention. We are now characterizing whether there are corresponding abnormalities in DA connectivity in both flies and fish as adults. Conclusion: Conclusions These "Model Animals" combine conserved DA neurobiology with the ability to study large numbers; increased access to genetic tools, short generation times and external development. We plan to use psychomimetics and antipsychotics in future experiments and to characterize more schizophrenia-specific behaviors such as pre-pulse inhibition.
We acknowledge the support of the NHMRC Australia
ID: 978153

THE STUDY OF PLASTICITY-RELATED MOLECULES IN A RAT MODEL OF SCHIZOPHRENIA REVEALS INCREASED GAD67 EXPRESSION IN THE MEDIAL PREFRONTAL CORTEX MPFC AND THE AMYGDALA

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Background: Several lines of evidence indicate that abnormalities in neuronal plasticity play important roles in the pathogenesis of schizophrenia. Since this plasticity underlies basic cognitive/behavioral phenomena, it is important to know how the dysfunctions observed in schizophrenic patients are associated with genes, proteins, cells or signaling pathways related to plastic processes. It is particularly interesting to study neuroplasticity in inhibitory circuits because several studies have demonstrated that interneurons and inhibitory networks show abnormalities in schizophrenic patients and in animal models of this disorder. The aim of this study is to investigate the expression of molecules related to neuronal structural plasticity and inhibitory synapses in post weaning isolation reared rats, an animal model of schizophrenia, which show deficits in learning, memory and brain development, many of which are also observed in schizophrenic patients. Methods: The analyses have been focused in the medial prefrontal cortex (mPFC) and the amygdala, because their close relationship with working memory, cognition and emotional response, which are features affected in schizophrenic patients. Thirty-five male lister hooded rats aged 21days after birth were randomly divided into two groups: isolated rats, without visual contact with other rats (n = 14) and group housed rats (n = 21) three per cage. After 8 weeks, rats were sacrificed. The expression of the polysialylated form of the neural cell adhesion molecule (PSA-NCAM) and the glutamic acid decarboxylase enzymes GAD 67 and GAD65 was evaluated by immunohistochemistry. The expression of the RNAs of the enzymes responsible of NCAM polysialylation (St8siaII & IV), NCAM, GAD67 and GAD 65 were evaluated by qRT-PCR. Results: Our results show that GAD67 protein was significantly increased in layer I of prelimbic cortex, and layer III of Cingulate 2 Cortex (P = .046 and P = .039, respectively), and a trend to towards an increase in expression was

observed in almost all layers of mPFC. The same significant upregulation of the expression of this enzyme was observed in all the three amygdaloid nuclei studied: medial, centromedial and basolateral ($P = .042$, $P = .014$ and $P = .039$, respectively). No significant changes were observed in the genes tested by qRT-PCR in the mPFC or the amygdala. Conclusion: .
ID: 985821

ASTROGLIAL ANTIOXIDANT DEFENSE ALTERATIONS IN SCHIZOPHRENIA - NEW THERAPEUTIC TARGETS TO FACILITATE NEUROPROTECTION

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Background: Main psychiatric diseases, such as schizophrenia, are accompanied by signals of oxidative stress, suggesting that imbalance of reactive species of oxygen (and nitrogen) and antioxidant defense play an important role in the development of these disorders. Brain antioxidant defense is particularly dependent upon astroglial metabolism, which involves synthesis and secretion of glutathione, the major antioxidant compound, as well as recycling of ascorbic acid, a key antioxidant in neuron activity. S100B, calcium-binding protein secreted by astrocytes, has been proposed as marker of astroglial activation in brain injury, including psychiatric disorders. Methods: We have investigated extracellular levels of S100B in human serum and astroglial cultures and hippocampal slices of rats, as well as alterations in glutathione content and glutamate uptake. Results: Our data indicate that oxidative stress, glutamate uptake and S100B secretion are potentially connected. Oxidative stress alters S100B secretion and the neurotrophic activity of this protein. Conclusion: Signals of stress oxidative and changes in the extracellular levels of S100B, in psychiatric patients and in vitro preparations putatively present in these patients, will help us to identify and to understand the neurochemical alterations underlying in brain disorders, as well as in the search for new molecular therapeutic targets and neuroprotection.
ID: 980384

NEURODEVELOPMENT AND DOPAMINE: PRENATAL INSULTS AND THE DYSREGULATION OF DOPAMINE NEURON FIRING

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Background: An abnormal increase in dopamine (DA) system responsivity has been proposed to underlie the psychotic state in schizophrenia. Recent studies from human schizophrenia patents suggest that hyperactivity within the hippocampal formation may drive this psychosis. We have used a rodent developmental model to examine ventral hippocampal function and DA neuron activity. Methods: Methylazoxymethanol (MAM) was administered to pregnant rats during gestational day 17 and the offspring examined as adults. Single unit electrophysiological recordings were made in the ventral tegmental area from identified DA neurons and in the ventral subiculum and nucleus accumbens. Locomotion was measured in automated locomotor boxes. Results: MAM-treated rats exhibited hyperactivity within the ventral subiculum of the hippocampus, which led to an increase in DA neuron population activity, or the number of DA neurons firing spontaneously, in the ventral tegmentum. Hippocampal hyperactivity correlated with a loss of parvalbumin interneuron staining in the ventral subiculum and the medial prefrontal cortex, which was accompanied by a diminished gamma response to conditioned stimuli. Antipsychotic drug treatment was found to reduce the number of DA neurons firing via induction of depolarization block, which was induced rapidly in the MAM-treated rats presumably due to an additive excitatory effect. In contrast, administration of an alpha-5 agonist drug to MAM-treated rats was found to normalize DA neuron firing and restore amphetamine-induced locomotor activity to control levels. Conclusion: These data are consistent with a model whereby abnormally high activity within the ventral hippocampus secondary to parvalbumin interneuron disruption leads to loss of gamma rhythmicity and hyperactivation of DA neuron activity. Therefore, the dopaminergic disruption observed in schizophrenia appears to be secondary to increased hippocampal drive. The increase in DA neuron population activity could be reversed by antipsychotic drug administration, which produced DA neuron depolarization block rapidly compared to the 3 weeks required in control rats. In contrast, by increasing GABA transmission using an alpha 5-selective GABA benzodiazepine agonist that presumably acts at the site of pathology, the DA system was normalized both electrophysiologically and behaviorally.
ID: 978046

GLUTAMATERGIC DISRUPTION BY GABA SYSTEMS AND THE ALTERATION OF DOPAMINE SYSTEM ACTIVITY

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Background: Substantial evidence supports a role for the dopamine (DA) system in psychosis. Recent findings have shown that, in schizophrenia, DA hyper-responsivity is likely due to a dysfunction within the glutamatergic/GABAergic system of the hippocampus. Using two different animal models, we have found that disruption of glutamate/GABA balance within the ventral hippocampus will lead to disrupted DA system regulation that we propose underlies psychosis in schizophrenia. Methods: Pregnant female rats were treated with the mitotoxin methyl azoxymethanol acetate, and the offspring examined as adults. In another study, rats were injected with the pro-convulsant drug pilocarpine into the ventral hippocampus to induce a rodent model of temporal lobe epilepsy. Extracellular recordings were performed in anesthetized rats from identified DA neurons and from neurons in the nucleus accumbens (NAc). Results: In the MAM treated rats, neurons in the ventral hippocampus fired at a faster firing rate, and there was a decrease in staining for parvalbumin interneurons. This was accompanied by alterations in synaptic plasticity within the hippocampal-NAc projection. Thus in control rats the prefrontal cortex (PFC) is required for LTP induction, but in MAM rats PFC inactivation now potentiates hippocampal-NAc drive, and hippocampal stimulation-induced plasticity is altered. In both MAM rats and pilocarpine-induced temporal lobe epilepsy rats, there was an increase in VTA DA neuron population activity, which correlated with increased amphetamine-induced behavioral locomotion. In the MAM-treated rat, VTA DA neuron activity and behavior are restored to baseline by increasing hippocampal GABA function via administration of a GABA A alpha 5 agonist. Conclusion: Both in schizophrenia and in temporal lobe epilepsy, a disruption of hippocampal function characterized by diminished parvalbumin interneuron staining is accompanied by hyper-responsivity of the DA system and, in humans, with psychosis. Moreover, there is alteration in the manner by which the PFC interacts with hippocampal-NAc circuits. We propose that, in both cases, a disruption in GABAergic regulation of glutamatergic projection neurons in the ventral hippocampus underlies this DA hyper-responsivity. Restoration of GABA-glutamate balance within this system is likely to be an effective treatment for psychosis.
ID: 979268

THE EXTENT OF STRIATAL DOPAMINE PERTURBATION BY ANTIPSYCHOTICS AFFECTS THE EXPRESSION OF THE GLUTAMATERGIC GENE HOMER1A: A QUANTITATIVE ANALYSIS OF MOLECULAR IMAGING STUDIES

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Background: Homer proteins are involved in several biological functions within the glutamatergic post-synaptic density (PSD), including dopamine-glutamate interplay. Increasing evidence has been provided that Homers may participate in the pathophysiology and therapy of behavioral diseases, as schizophrenia. We have observed that antipsychotics differentially modulate the expression of the inducible isoform Homer1a and that Homer1a expression is significantly induced by selective antagonists at dopamine D2 receptors. We hypothesized that quantitative amount Homer1a expression may be related to the extent of dopamine perturbation by antipsychotics and that the distribution of Homer1a expression by these compounds may follow dopaminergic afferents. Methods: We pooled data on quantitative expression of Homer1a mRNA transcripts by different antipsychotics obtained by molecular imaging of gene expression in target rat brain areas. Brain areas of interest were chosen among cortical and striatal sites of relevance for psychosis. Homer1a expression by each antipsychotic was expressed as a percentage of mean vehicle relative signal intensity. Moreover, Homer1a mRNA expression was analyzed as a function of subregional distribution of relative signal intensity by each antipsychotic in each paradigm. Results: In caudate putamen, the highest quantitative expression of Homer1a was elicited by haloperidol (>200% vehicle induced expression). High Homer1a transcription was also induced by ziprasidone and aripirpazole (150%–200% vehicle). Intermediate (130%–150% vehicle) expression was observed by risperidone, olanzapine, and sulpiride. Low or negligible expression was induced by quetiapine, sertindole, and clozapine. In the nucleus accumbens, still haloperidol triggered the highest Homer1a expression (150%–200% vehicle). Striatal distribution of Homer1a expression by antipsychotics followed a dorsolateral-to-ventromedial gradient. The amount of gene expression was the highest in the dorsolateral striatum and the lowest in the shell of the nucleus accumbens. Conclusion: These findings appear to confirm that the extent of Homer1a expression within at least the caudate putamen may be a strong marker of dopamine perturbation elicited in vivo by a compound and possibly of its affinity to D2 receptors. Topographical distribution of striatal Homer1a expression moves along a gradient consistent with that of dopaminergic fibers projecting to the striatum.
ID: 979547

KETAMINE AFFECTS GENE EXPRESSION OF KEY MOLECULES OF BRAIN GLUCOSE METABOLISM INVOLVED IN HOMEOSTATIC RESPONSE TO NEUROTOXICITY: IS THERE A MOLECULAR LINK BETWEEN PSYCHOSIS AND GLUCOSE METABOLISM?

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Background: Ketamine, a non-competitive antagonist of *N*-methyl-D-Aspartate (NMDA) receptors, causes a psychotomimetic state in humans and a behavioral syndrome resembling schizophrenia in rodents. Ketamine induces a state of NMDA receptors hypofunction (NRH). NRH may lead to neurotoxicity in target cortical neurons, regarded as a putative histopathological and pathophysiological feature of schizophrenia. Neurotoxic alterations in forebrain by ketamine have been mapped by evaluation of glucose uptake. Moreover, ketamine may affect brain glucose metabolism which in turn may take part in neurotoxic damage. Impairment of glucose metabolism may be involved in neurotoxicity by ketamine and in the pathophysiology of psychosis. Hexokinase 1 (Hex 1) and Glucose Transporter 3 (GluT3) are involved in glucose metabolism and in the homeostatic response to neurotoxic damage, as that induced by ketamine. In this study, we explored whether Hex 1 and GluT3 expression may be affected by a neurotoxic vs. a subanesthetic dose of ketamine. Methods: Sprague-Dawley rats ($n = 4$) were treated by 12 mg/kg ketamine, 50 mg/kg ketamine (subanesthetic and neurotoxic dose, respectively), or saline. Rat brains were fresh frozen after killing (3 hours from treatment) and cut on cryostat. Sections were then hybridized with radioactive probes complementary to rat Hex 1 and GluT3 mRNA. Signal labeling was quantitated by a computer-mediated system in regions of interest within the cortex, the striatum, and the hippocampus. Data were then analyzed by one-way ANOVA and Tukey's post-hoc test. Results: Hex 1 gene expression was significantly increased by the neurotoxic dose of ketamine in several cortical regions, including right medial agranual cortex, right somatosensory cortex, and left motor cortex. Ketamine 50 mg/kg increased the expression of the gene also in right and left granular retrosplenial cortex and in the left disgranular retrosplenial cortex. In the hippocampus, both ketamine doses increased gene expression in CA2, CA3, and dentate gyrus subregions. GluT3 expression was not affected by ketamine at any dose and in any region of interest. Conclusion: These results are consistent with the view that an impairment of glucose metabolism may occur in a condition of ketamine-mediated neurotoxicity. Impairment of glucose metabolism may represent a key step in the induction of some histopathological and pathophysiological alterations putatively involved in schizophrenia.
ID: 979484

DOPAMINE ABNORMALITIES IN DISC1 MOUSE MODELS

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Background: DISC1 is a major susceptibility factor for several neuropsychiatric diseases. Endogenous DISC1 expression starts at early embryonic stage, is expressed preferentially in the forebrain, but widely expressed in both neurons and glia. Here we investigate the dopamine system in two distinct DISC1 transgenic mouse models. The first expresses a putative dominant-negative mutant DISC1 under the control of the alphaCaMKII promoter postnatally mainly in the forebrain pyramidal neurons (Hikida et al 2007, PNAS). The second expresses the same mutant under the control of the prion protein (PrP) promoter from E13 in several cell types (including glia and interneurons) all over the brain. Methods: We performed in vivo microdialysis to measure extracellular dopamine level, High-Performance Liquid Chromatography to determine tissue content of dopamine metabolites, Positron Emission Tomography scan with 11C-raclopride, autoradiography for dopamine D2 receptor (D2R) with 3H-spiperone, and expression study of dopamine-associated molecules. We also conducted behavioral tests and compared the phenotypes between the two models. Results: These two types of DISC1 mouse models displayed distinct molecular changes in the dopamine system. Nevertheless, increased binding of the dopamine D2R antagonist raclopride to the striatum in PET scan, increased spontaneous and amphetamine-induced hyperactivity, reduced Pre-Pulse Inhibition, and increased immobility in the forced swim test were commonly observed. Conclusion: We have connected a genetic risk factor for mental disorders with the classic dopamine hypothesis of schizophrenia. Postnatal disturbance of DISC1 in the forebrain is sufficient to elicit abnormalities in some types of dopamine-associated phenotypes.

Nonetheless, expression of mutant DISC1 prenatally also influences dopamine signaling in adult brains.
ID: 978348

CROSS SPECIES IN VITRO CHARACTERIZATION OF KAT II INHIBITORS

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Background: One route of tryptophan metabolism occurs through the kynurenine pathway. Kynurenic acid (KYNA) is one of three neuroactive products in this pathway. It is an antagonist of the glycine site of the NMDA receptor and the alpha7 nicotinic acetylcholine receptor. KYNA is produced by the irreversible transamination of L-kynurenine, which can be carried out by multiple kynurenine aminotransferases (KATs). KAT II, present in astrocytes, is responsible for the majority of KYNA synthesis in the brain. The elevated levels of KYNA that have been reported in the prefrontal cortex and CSF of schizophrenia patients may produce altered glutamatergic and/or cholinergic transmission and negatively affect cognition. Methods: We have developed a cross species screening strategy to identify potent inhibitors of the KAT II enzyme. The initial screening of the compound library was performed with recombinant enzymes for human KAT II and KATI, and rat KAT II. A recombinant cynomolgus monkey KAT II assay was subsequently added to confirm potency in monkey. A whole cell functional assay in human HEPG2 cells was developed to confirm in vitro potencies and to facilitate SAR design. The whole cell assay was optimized to validate potency in our target cell in the brain, in both primary human astrocytes and primary rat mixed glia cultures. Compounds were further evaluated across species in primary hepatocyte assays (human, rat, and monkey), to confirm rank order potencies. In specific cases, the whole cell assay platform was adapted to measure KAT II activity ex vivo in monkey or rat PFC tissue. Results: Our comprehensive screening strategy has identified potent and selective KAT II compounds. Conclusion: Evaluation of compounds across species has been a valuable component in developing SAR for compound series and understanding PK/PD in preclinical models
ID: 978303

ALANINE DOES NOT AFFECT TYROSINE TRANSPORT INTO THE BRAIN

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Background: Dysregulation of tyrosine transport has been demonstrated in schizophrenia and bipolar disorder, while a combined dysregulation of tyrosine and alanine is evident in autism. One possibility is that abnormal levels of alanine affect tyrosine availability. Initially, tyrosine and alanine were thought to be transported across mammalian membranes by transporters with completely non-overlapping substrates. However, it is now known that at least some tyrosine transporters can have a measurable affinity for alanine. The aim of this study was to determine the influence of systemic alanine administration on brain tyrosine levels in the rat. Methods: Male Harlan rats 250–300 g were used. In the first experiment, we conducted in vivo microdialysis of the striatum in awake rats treated with vehicle or alanine 400 mg/kg IP. In the second experiment, we examined brain tissue levels of tyrosine 60 minutes and 150 minutes after administration of alanine 200–400 mg/kg IP alone or in addition to tyrosine 200 mg/kg IP. Results: Compared to vehicle, alanine 400 mg/kg IP did not affect tyrosine levels in microdialysate collected from striatum over the course of 4 hours. In the tissue studies, tyrosine elevated its own levels as expected, but alanine did not affect tyrosine levels in prefrontal cortex or striatum in any of the groups at either time point. Conclusion: We conclude that at least at the level of the blood-brain barrier in the rat, alanine does not appreciably compete with tyrosine for entry into the brain. Thus, if there is a link between aberrant transport of tyrosine and alanine, the mechanism remains to be defined.
ID: 978855

T. GONDII MAY CONTRIBUTE TO SCHIZOPHRENIA GENDER DIFFERENCES THROUGH THE MODULATION OF PROLACTIN

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Background: *Toxoplasma gondii* (*T. gondii*) has been implicated as an environmental factor in the pathogenesis of schizophrenia and may contribute to behavioral differences seen between men and women with the disease. Methods: In order to better understand the parasite's role in the development of mental illness, we evaluated the effects of Prugniaud (PRU), one strain of Type II T. gondii, on behavior and cortical gene expression in male and female Balb/C mice. Cat odor attraction was tested as a T. gondii-specific manipulation, and a microarray was performed to look at differential expression in the cortex. Results: We found gender differences in cat odor attraction at 2.5 months post infection (mpi). Male infected mice exhibited significantly more attraction to non-feline rather than feline predator odor than uninfected animals did. In contrast, female infected mice showed significantly more attraction to feline rather than non-feline predator odor than uninfected females. No differences in parasite antibody titres were seen between PRU- infected males and females at 7 mpi. Microarray analysis revealed a significant up-regulation of prolactin in the cortex of females compared to males. Prolactin was increased 62-fold in control females and 133-fold in infected females compared to males in the same groups. Conclusion: As increased levels of prolactin are known to have direct effects on the brain and schizophrenia, it is possible modulation of prolactin is a mechanism used by the parasite. The host gender effects of T. gondii may shed more light on the potential heterogeneity of psychiatric conditions associated with parasitic infection in humans.
Funding for this work was provided by the grant No. 08R1998 from the Stanley Medical Research Institute, Chevy Chase, MD.
ID: 979583

PRECLINICAL GENETIC STUDIES ON THE ROLE OF NICOTINIC ACETYLCHOLINE RECEPTOR SUBTYPES IN REGULATING THE BEHAVIORAL ACTIONS OF NICOTINE

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Background: Nicotine is the principal reinforcing component in tobacco smoke responsible for addiction. Nicotine acts in the brain through the neuronal nicotinic acetylcholine receptors (nAChRs). The predominant nAChR subtypes in mammalian brain are those containing α4 and β2 subunits (denoted α4β2* nAChRs). Little is known about the potential involvement of other nAChR subunits in the reinforcing effects of nicotine. Allelic variation in the α5/α3/β4 nAChR subunit gene cluster significantly increases risk of tobacco addiction. Allelic variation in the β3/α6 subunit gene cluster also increases vulnerability to tobacco smoking. Nevertheless, the mechanisms through which these nAChR subunits may influence smoking behavior is unknown. Methods: We investigated the role of α5, α3 and β3 nAChR subunits in regulating the reinforcing properties of nicotine through the use of genetically modified mice and/or viral-mediated gene expression studies. Results: First, we found that α5 nAChR subunit knockout mice consumed significantly more nicotine than wildtype controls. This effect was ''rescued'' in knockout mice through viral-mediated re-expression of α5 subunits in medial habenula (MHb), and recapitulated in rats following α5 subunit knockdown in MHb. The primary output of the MHb is the interpeduncular nucleus (MHb-IPN tract). Second, the role of α3 nAChR subunits in the MHb-IPN tract in regulating nicotine intake was investigated. Because null mutation in α3 subunits in mice results in embryonic lethality, we developed a lentivirus vector to knockdown α3 subunits in the MHb of rats. We found that α3 subunit knockdown in the MHb-IPN pathway again resulted in higher nicotine intake in rats, but this effect was less striking than that observed after α5 subunit knockdown in this pathway. Third, we found that the reinforcing effects of nicotine were entirely conserved in β3 nAChR subunit knockout mice compared with wildtype controls, suggesting that nAChRs containing this subunit do not play a major role in regulating nicotine intake. Conclusion: These studies provide strong evidence that nAChRs containing α5 and/or α3 subunits in the MHb-IPN pathway decrease the reinforcing properties of nicotine such that deficits in their function and/or expression may increase vulnerability to tobacco addiction. Considering that approximately 90% of schizophrenia patients are tobacco smokers, new studies are investigating the relevance of our findings to schizophrenia.
ID: 979208

DOWNREGULATION OF MYELIN MARKERS IN THE PREFRONTAL CORTEX OF RATS PRODUCES BEHAVIORAL DEFICITS SIMILAR TO DEFICITS OBSERVED IN SCHIZOPHRENIA

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Background: Although we tend to believe that intellectual aptitude and brain activity are a consequence of neuronal function, this assumption reflects only part of the narrative. Oligodendrocytes, the cells that form myelin and build white matter tracts, facilitate neuronal performance by increasing the speed of neuronal conduction. Increasing evidence is thus pointing to white matter abnormalities in schizophrenia. Methods: Rats received .2% cuprizone in their chow starting on postnatal day 28. At two and four week exposure, myelin-specific mRNA levels were measured with microarrays and PCR, in the PFC, striatum and hippocampus. Behavioral deficits were examined in PFC-specific paradigms. Results: Myelin-specific mRNA levels were downregulated in the PFC but not in the other brain areas. Rats showed deficits in the attentional set-shifting task and the novel-object recognition task, but had no motor deficits. Conclusion: While myelin abnormalities might not be the sole reason for reduced PFC function in schizophrenia, the data demonstrate that they are sufficient to negatively affect PFC performance. Furthermore, individual brain areas have vulnerable periods during which environmental factors can derail proper myelination.
ID: 977606

BASIC SCIENCE OF THE ENDOGENOUS CANNABINOID SYSTEM

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Background: The endogenous cannabinoid system (ECS) is a signaling system found throughout the body. In the brain it has a prominent role in modulating synaptic transmission. More recently, it has become apparent that the ECS is involved in neurodevelopment. Both of these activities of the ECS are relevant for schizophrenia. Methods: The ECS is comprised of endogenous cannabinoids (endocannabinoids, eCB's), cannabinoid receptors, and the enzymes responsible for eCB synthesis and degradation. The two major eCB's are anandamide (AEA) and 2-arachidonoyl glycerol (2-AG). Both exist as precursors in lipid membranes and are ''made on demand'' in response to specific stimuli by unique enzymatic cascades. As neuromodulators, eCB's have the interesting property that they are primarily synthesized in dendrites and diffuse retrogradely across the synapse, engaging presynaptic cannabinoid receptors to inhibit neurotransmission. Depending on the stimulus generating the eCB, inhibition of synaptic transmission may be brief (tens of seconds) or long (hours, or more). eCB's inhibit both excitatory and inhibitory transmission, as well as the release of other neuromodulators such as serotonin, catecholamines, and neuropeptides, thus their network effects are varied. Results: 2-AG is the primary eCB involved in modulating synaptic transmission. Its interactions with THC, the primary psychoactive component of cannabis, are complex. 2-AG is an efficacious agonist, while THC and AEA are not. Thus, under some conditions (low receptor number, or inefficient receptor-G protein coupling), THC can antagonize the actions of 2-AG, while at other times (efficient receptor-G protein signaling) THC will mimic the actions of 2-AG. These pharmacological considerations need to be kept in mind when trying to understand THC's interactions with the ECS. Emerging evidence supports a significant role for the ECS in several aspects of neuronal development. eCB's are involved in neurogenesis, axonal pathfinding, and the establishment of proper synaptic connections. It is likely that engagement of cannabinoid receptors by THC during nervous system development (pre- and postnatally) may perturb any of these processes. This may contribute to the relationship between heavy adolescent cannabis use and an increased risk for later psychosis. Conclusion: Thus, the ECS is a major neuromodulatory system whose perturbation by THC may be relevant for the development of schizophrenia and the expression of psychotic symptoms.
ID: 976026

REPEATED PHENCYCLIDINE ADMINISTRATION ALTERS GLUTAMATE RELEASE AND DECREASES GABA MARKERS IN THE PREFRONTAL CORTEX OF RATS

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Background: Repeated phencyclidine (PCP) administration induces cognitive disruptions resembling those seen in schizophrenia (Amitai, Semenova & Markou, Psychopharmacology, 193:521–537, 2007; for review, Amitai and Markou, Biological Pschiatry 68:5–16, 2010). Alterations in glutamate transmission and gamma-aminobutyric acid (GABA) functioning in the prefrontal cortex (PFC) have been implicated in these PCP-induced deficits, as well as in cognitive symptoms of schizophrenia. PCP-induced cognitive deficits are reversed by chronic treatment with the atypical antipyschotic clozapine in rats (Amitai et al 2007). Methods: We investigated the effects of a single injection vs. repeated administrations of PCP on glutamate levels in the PFC using in vivo microdialysis. Furthermore, we examined how these PCP regimens affected GABA neuronal markers in the PFC. Finally, we investigated the effects of clozapine on disruptions in glutamate levels and GABA neuronal markers induced by repeated PCP administration. Results: Acute PCP administration (2 mg/kg) increased extracellular PFC glutamate; this increase was blunted, but not eliminated, after repeated PCP pretreatment. PCP administration also strongly decreased levels of parvalbumin and glutamic acid decarboxylase-67 (two markers of GABA function) in the PFC, an effect that was maintained after a 10-day drug-free washout and unaltered by the resumption of repeated PCP injections. All of the observed PCP effects were attenuated by chronic treatment with clozapine, an atypical antipsychotic that has partial effectiveness on cognitive impairment in schizophrenia. Conclusion: These findings suggest that abnormal cortical glutamate transmission, possibly driven by pathological changes in GABA function in parvalbumin-positive fast-spiking interneurons (Behrens, Ali, Dao, Lucero, Shekhtman, Quick, Dugan, Science 318:1645–1647, 2007), may underlie some cognitive deficits in schizophrenia. A better understanding of glutamate and GABA dysregulation in schizophrenia may uncover new treatment targets for schizophrenia-related cognitive dysfunction.
ID: 977455

SYNERGISTIC INTERACTIONS OF THE MGLU2/3 RECEPTOR AGONIST LY404039 WITH ANTIPSYCHOTIC AGENTS IN BEHAVIORAL AND NEUROCHEMICAL ANIMAL MODELS PREDICTIVE OF ANTIPSYCHOTIC EFFICACY

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Background: Extensive preclinical data and recent clinical results indicate that metabotropic glutamate (mGlu) 2/3 receptor subtype agonism has potential to be a novel, non-monoaminergic approach to treating schizophrenia. Similar to that of atypical antipsychotic medications, orthosteric mGlu2/3 receptor agonists (eg, LY354740, LY379268, and LY404039) exhibit an antipsychotic-like behavioral and neurochemical profile in animal models. LY404039 is the active compound of the prodrug LY2140023 which demonstrated clinical efficacy in a recent double-blind, placebo-controlled schizophrenia clinical efficacy trial (Patil et al, 2007. Nat. Med 13: 1102–1107). Unlike all existing clinical antipsychotic treatments, LY404039 does not bind directly to any of the monoamine receptor family and thus constitutes a novel treatment mechanism of action. The objective of these studies was to determine whether LY404039 would enhance efficacy of standard antipsychotic agents in an additive or synergistic manner. Methods: LY404039 was tested for efficacy, both alone and in combination with antipsychotic agents, in blocking phencyclidine-induced activity, inhibiting conditioned avoidance responding, and producing monoamine (ie, serotonin, dopamine, and norepinephrine) efflux within the prefrontal cortex of rats. Results: Results showed statistical evidence of synergy between LY404039 and antipsychotic agents in all assays tested, whereas additivity was most commonly observed with combinations of antipsychotic agents. In locomotor and conditioned avoidance assays, the augmented efficacy occurred in the absence of motor impairment that is commonly observed with high doses of antipsychotic treatments. Strikingly, maximal prefrontal cortical dopamine efflux was significantly higher with a LY404039 (5 and 20 mg/kg) + risperidone (.3 mg/kg) combination treatment than achieved by either agent alone; the combination of aripiprazole (.1 and 1.0 mg/kg) + risperidone (.3 mg/kg) failed to show an augmentation effect on prefrontal dopamine levels. Conclusion: In conclusion, LY404039 augmented the efficacy of known antipsychotics in animal behavioral and neurochemical models predictive of clinical efficacy in schizophrenia. These data suggest a potential for a favorable therapeutic benefit of combination treatment with mGlu2/3 receptor agonists and antipsychotic medicines.
ID: 979590

BOTH DOPAMINE D2 RECEPTOR DEPENDENT AND INDEPENDENT MECHANISMS UNDERLY RESTORATION OF ABNORMAL SALIENCE ALLOCATION BY ANTIPSYCHOTIC DRUGS: A STUDY IN DOPAMINE RECEPTOR DEFICIENT MICE

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Background: The purpose of this study was to ascertain whether the dopamine D2 receptor (DRD2) is necessary for antipsychotic drugs to reverse abnormal salience allocation. Antipsychotic drugs have been suggested to improve symptoms by reversal of abnormal allocation of salience or associability to environmental stimuli via blockade of DRD2. These drugs have affinity for multiple receptors thus they may act indirectly via other targets, making attribution of behavioral effects to specific receptor subtypes difficult. A combined null mouse and pharmacological approach was therefore used to investigate whether DRD2 is necessary for the restorative effects of antipsychotic drugs in two models of abnormal allocation of salience: antipsychotic drug enhancement of experimentally induced low levels of Latent inhibition (LI) and antipsychotic reversal of LI disruption by d-amphetamine (AMPH). Methods: In a standard LI procedure, learning was measured as suppression of drinking on presentation of an 85dB tone previously paired with footshock in water restricted mice. One group had either 60 (LI) or 40 (low LI) tone pre-exposures prior to two pairings of tone with a 1sec, .38mA footshock (pre-exposed/PE), a second group was exposed to the same conditions but without tone pre-exposure (non-pre-exposed/NPE). Testing was over 3 days (PE Day1, conditioning Day2, test to tone Day3). Drugs were given on days 1 and 2, mice were tested drug free on day 3. LI was seen as reduced learning in PE Vs NPE. Locomotor activity was measured in photocell cages over 30 min. Results: Haloperidol (.1 mg/kg) and clozapine (2.5 mg/kg) enhanced low LI in DRD2+/+ mice but not DRD2-/- mice. AMPH (2.5 mg/kg) abolished LI in both DR2+/+ and DR2-/- mice, in contrast AMPH hyperactivity was seen in DRD2+/+ but not DRD2-/- mice. Clozapine and haloperidol reversed AMPH disruption of LI in DRD2-/- mice. AMPH disruption of LI was prevented in DRD1-/- mice. Conclusion: it is concluded (1) DRD2 is required for restoration of abnormal salience allocation by antipsychotic drugs but there is also a second non-DRD2 dependent mechanism that is unmasked in the presence of AMPH (2) AMPH effects on salience allocation, unlike other behaviors, do not require DRD2 but may require DRD1 which may play a role in its psychotogenic effects(3) Amphetamine disruption of LI in DRD2-/- mice may be a useful model to evaluate and identify novel non-DRD2 antipsychotic drug targets.
This work was supported by The Wellcome Trust [WT084592].
ID: 978285

OXIDATIVE STRESS DURING DEVELOPMENT IN PREFRONTAL CORTICAL INTERNEURONS IN DEVELOPMENTAL ANIMAL MODELS OF SCHIZOPHRENIA

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Background: Cortical interneuron function is affected in a variety of rodent models of schizophrenia, including prenatal antimitotics, a neonatal ventral hippocampal lesion (NVHL) and several genetic models. Together with data from post-mortem studies showing altered markers related to GABA transmission in the prefrontal cortex (PFC) of schizophrenia patients, these findings suggest inhibitory interneurons in the PFC are a vulnerable population that may become affected by many genetic and environmental factors during development. As there is also increasing evidence of redox dysregulation in this disorder, we decided to test whether rats with a NVHL exhibit signs of oxidative stress in PFC interneurons. Methods: Sprague-Dawley rats received a bilateral injection of ibotenic acid (lesion) or vehicle (sham) in the ventral hippocampus at postnatal day (P) 6–7. Rats were returned to their dams and left undisturbed until P21 (juveniles) or P60 (adults), when they were euthanized and the brains removed to assay markers of oxidative stress in the PFC. A separate group of rats received the antioxidant *N*-acetyl-cysteine starting on P5. Results: Juvenile rats with a NVHL, but not a sham operation, exhibited high levels of 8-oxo-DG. No differences in parvalbumin (PV) staining were detected between groups. Many PV neurons exhibited 8-oxo-DG. At P60, however, the levels of 8-oxo-DG were not as high in NVHL rats (although still higher than sham rats of the same age) but there was a marked reduction in the density of parvalbumin interneurons. Conclusion: The data indicate that a neonatal hippocampal lesion has deleterious effects on PFC development, yielding PV interneurons with signs of oxidative stress during the pre-pubertal stage and a loss of PV labeling in the adult stage. This suggests that PFC interneurons can present oxidative stress in rodent models of schizophrenia, and this could be the mechanism that renders them into a reduced level of activity, eventually causing cognitive and other deficits associated with the disease.
ID: 978533

LONG LASTING ALTERATIONS IN THE ENDOCANNABINOID SYSTEM INDUCED BY CANNABIS IN ADOLESCENCE INCREASE THE VULNERABILITY TO PSYCHOTIC LIKE DISORDER

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Background: The CB1 cannabinoid receptors are the pharmacological target of cannabis derived drugs that contain delta-9-tetrahydrocannabinol (THC) and convergent findings from epidemiological studies indicate that cannabis consumption constitutes a substantial environmental risk factor for schizophrenia, especially when exposure occurs during adolescence. Adolescence is increasingly viewed as an important developmental window, where ongoing neuroplastic modifications occur in the central nervous system. This remodeling process is thought to support the emerging adult cognitive style. Since the endocannabinoid system plays a role during the different stages of brain development, exposure to cannabinoids during this developmental phase might lead to subtle but lasting changes in the brain and behavior. This hypothesis is consistent with the neuroanatomical distribution of cannabinoid CB1 receptors, which present a high density in brain regions implicated in schizophrenia. Methods: Our own studies have shown that chronic administration THC in adolescent female rats induces long-lasting alterations in the emotional and cognitive circuits that result in a complex psychotic mood disorder. Behavioral observations were flanked by specific structural and biochemical findings, indicating the presence of changes in the pattern of synaptic maturation and in the expression and activity level of key neuronal regulatory proteins, in specific brain areas. Results: In the present study we show that THC exposure during adolescence induces in relevant brain areas persistent changes in the endocannabinoid (EC) system either in term of alteration in CB1 receptor functionality as in EC levels (anadamide and 2 AG) that can profoundly affect neuronal refinement occurring in adolescence. The emerging picture of the EC system alteration will be compared with that obtained in 2 different experimental models of schizophrenia based on repeated PCP injection and post weaning social isolation. Pharmacological modulation of the EC system recovers some psychotic like behavioral signs present in the different experimental designs. Conclusion: These data suggest that exposure to THC in adolescence can induce a permanent dysfunction in the EC signaling contributing to the aetiology of complex psychotic disorders and the pharmacological modulation of the EC signaling could represent a new approach for these disorders.
ID: 981758

MODELING AN ENVIRONMENTAL RISK FACTOR FOR SCHIZOPHRENIA IN MICE LEADS TO PERMANENT CHANGES IN THE IMMUNE SYSTEM. PAUL H. PATTERSON, BIOLOGY DIVISION, CALIFORNIA INSTITUTE OF TECHNOLOGY, PASADENA, CA 91125 USA

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Background: Several types of maternal infection (influenza, rubella, genital and reproductive system viruses, and urinary tract bacteria) are associated with increased risk of schizophrenia or autism in the offspring. Modeling this risk factor in mice using influenza infection or activation of the dam's immune system by injection of the double stranded, synthetic RNA, poly(I:C) yields offspring with characteristic endophenotypes of these disorders. Features consistent with symptoms in schizophrenia include behavioral abnormalities and neuropathology. Methods: Pregnant C57BL/6J mice are injected with poly(I:C), saline, IL-6, or anti-IL-6 antibody (or a control antibody) plus poly(I:C) on E12.5, and the fetuses and postnatal offspring are examined at various ages. Results: The cytokine IL-6 is a key mediator of the effects of maternal immune activation (MIA) on the fetus, as shown by blocking or genetically inactivating IL-6 in the MIA dam. Moreover, MIA activates downstream IL-6 signaling pathways in the placenta and in subpopulations of neurons in the fetal brain. In addition, IL-6 mRNA is induced in both of these tissues, which raises the possibility of a feed-forward mechanism that could lead to permanent changes in immune status as is seen in the brain and peripheral immune system of autistic subjects. Consistent with reports of alterations in the immune system in schizophrenia and autism, we find that MIA leads to significant changes in lymphocytes from the spleen and mesenteric lymph node of adult offspring. CD4+ T cells display elevated levels of the pro-inflammatory cytokines IL-6 and IL-17 in response to stimulation in vitro. Conclusion: These observations support the hypothesis that MIA can cause permanent changes in immune status of the offspring. Thus, the MIA model has face and construct validity for schizophrenia and autism, and is proving useful for exploring the mechanism of how the maternal infection risk factor alters fetal brain and immune system development. Work by others has further shown that the MIA model is useful in evaluating potential therapeutic approaches for schizophrenia.
ID: 980415

CYSTEAMINE ATTENUATES THE DECREASES IN TRKB PROTEIN LEVELS AND THE ANXIETY-LIKE BEHAVIORS INDUCED BY CORTICOSTERONE TREATMENT

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Background: Stress and glucocorticoid hormones, which are released into the circulation following stressful experiences, have been shown to contribute significantly to the manifestation of anxiety-like behaviors observed in many neuropsychiatric disorders. Brain-derived neurotrophic factor (BDNF) signaling through its receptor TrkB plays an important role in stress-mediated changes in structural as well as functional neuroplasticity. Studies designed to elucidate the mechanisms whereby TrkB signaling is regulated in chronic stress might provide valuable information for the development of new therapeutic strategies for several stress-related psychiatric disorders. In the present study, we examined whether cysteamine, a transglutaminase 2 (TG2) activity inhibitor can attenuate corticosterone-induced alterations in BDNF signaling and anxiety-like behavior in mice. Methods: Male CD-1 mice were treated for 7 weeks with vehicle (.45% hydroxypropyl-β-cyclodextrin) or corticosterone (35 ug/ml) in the presence or absence of cysteamine (150 mg/kg/day) during the last three weeks of the corticosterone treatment. The animals were tested in the Open Field paradigm, the Light/dark test and the elevated plus maze test and then sacrificed for protein or mRNA analysis. Results: Corticosterone treatment for 7 weeks induced a significant reduction in TrkB protein levels, but not mRNA levels, both in frontal cortex ($P = .0076$) and hippocampus ($P = .0031$). A significant increase in TG2 activity was found in the frontal cortex ($P = .0104$), but not in the hippocampus following corticosterone treatment. No significant change was found in BDNF and GR protein levels following corticosterone treatment. Chronic corticosterone treatment also increased anxiety-like behaviors in Open Field and Light/dark tests. Finally, treatment with the TG2 inhibitor, cysteamine significantly attenuated corticosterone-induced changes in TrkB protein levels, TG2 activity, and anxiety-like behaviors indicating a role of TG2 in corticosterone-induced anxiety-like states. Conclusion: Since cysteamine tolerability has previously been demonstrated in human subjects, the animal studies described here highlight the potential use of this compound as a novel therapeutic strategy for glucocorticoid -related symptoms of psychiatric disorders.
ID: 979722

INTERPLAY BETWEEN DISRUPTED-IN-SCHIZOPHRENIA-1 AND METHAMPHETAMINE ABUSE: A MOUSE MODEL

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Background: Genetic factors involved in neuroplasticity and brain development have been strongly implicated in both schizophrenia and substance abuse, suggesting the common mechanisms of these two conditions. We propose that Disrupted-In-Schizophrenia-1 (DISC1) can be a converging point for the molecular pathways of drug addiction and schizophrenia as DISC1 is a strong risk factor for schizophrenia and has an extended interactome that includes the signaling pathways associated with addiction. Thus, we set out to determine a role of DISC1 in the mechanisms of methamphetamine (METH) addiction. Methods: Mice with inducible dominant-negative expression of mutant human DISC1 in forebrain neurons were treated with an escalating non-toxic dosing (ED) of METH and 4 weeks after treatment were tested for behavioral sensitization or conditioned place preference followed by D1, D2 and dopamine transporter (DAT) receptor autoradiography and measurements of levels of phosphorylated ERK1/2; AKT and GSK-3β in n. accumbens. Results: ED regimen did not result in overt neurotoxicity as evidenced by unaltered tissue concentrations of monoamines and their metabolites. ED treatment significantly delayed sensitization in DISC1 female but not male mice. Conditioned place preference with .5 mg/kg METH was also impaired in mutant DISC1 female mice only. In contrast to control female mice, METH ED did not significantly affect fear conditioning or object recognition in mutant DISC1 female mice. Compared to control animals, mutant DISC1 mice had decreased biding of 11C-raclopride to D2 sites and altered METH-induced activation of the ERK1/2 pathway in n. accumbens. Conclusion: Our results suggest that disturbances in DISC1 functions may affect the mechanisms of neuroplasticity underlying METH-produced reward and cognitive abnormalities. These alterations function may contribute to co-morbidity between drug abuse and schizophrenia.
ID: 977836

IMPAIRED NMDA RECEPTOR TRANSMISSION ALTERS STRIATAL SYNAPSES AND DISC1 PROTEIN IN AN AGE-DEPENDENT MANNER

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Background: We have generated a genetic mouse model of NMDA receptor hypofunction, NR1 knockdown mice, to explore the role of NMDA receptors in schizophrenia. These mice display schizophrenia-like behavioral endophenotypes that can be normalized to varying degrees with antipsychotics. However, the molecular and cellular underpinnings of their altered behaviors have been largely unexplored. Because reductions in synapse number and spine density have been observed in post-mortem schizophrenic brain, we asked whether reductions in spine density result from impaired NMDA receptor. The striatum represents an ideal brain region to address this question, because the vast majority of neurons within this brain structure are medium spiny neurons (MSN) having densely spinous dendrites, upon which glutamate and dopamine afferents converge. Methods: We measured MSN spine density in NR1 knockdown mice and wild type controls, and measured levels of synaptic proteins by sucrose-density purification of synaptosomes followed by western blot. Results: In the striatum of NR1 knockdown mice, we discovered an age-dependent decrease in striatal spine density. While synapse number is normal in juvenile mice, these mutant mice have a selective reduction in mature, mushroom-shaped spines that occurs after sexual maturity in the mouse. In efforts to uncover the biochemical underpinnings of this phenomenon, we discovered synapse-specific reductions in 14-3-3 epsilon and DISC1, two schizophrenia susceptibility genes that have been implicated in neurite outgrowth and spine density. Like the decrease in spine density, the synaptic reduction of these proteins is more evident at later developmental stages, post-adolescence. Finally, the expression of several schizophrenia-related behavioral endophenotypes shows a similar post-adolescent emergence. Conclusion: These studies highlight the role of NMDA receptors in the maintenance of synapse integrity in the developing and mature striatum. Furthermore, the observation that NMDA receptors regulate synaptic pools of DISC1 and 14-3-3 epsilon points to convergent molecular pathways in the pathophysiology of schizophrenia.
ID: 979975

CORTICOSTRIATAL CIRCUITRY IN SCHIZOPHRENIA AND OTHER MENTAL DISORDERS

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Background: The striatum is a subcortical brain region that many investigators have studied in association with the pathophysiology of schizophrenia. This brain region underlies the pathology of other neuropsychiatric conditions, such as addiction and Huntington's disease. In this presentation a quick anatomical review of corticostriatal circuitry will be made in association with the pathophysiology of schizophrenia, describing rationales of how the following three talks on D2R transgenic mice, DISC1 mutant mice, and NR1 knockdown mice are related with each other. Methods: Data presented here come from biochemical, histological, and behavioral analyses of Huntington's disease mouse model R6/2 in comparison with schizophrenia models. Results: New data from our group on cAMP-dependent phosphodiesterase PDE4 in models for schizophrenia and Huntington's disease will be comparatively introduced to discuss possible pathophysiological link between these two conditions. Analysis of schizophrenia animal models will be introduced by focusing on age-dependent changes in the corticostriatal circuitry. Conclusion: The corticostriatal circuitry in schizophrenia will be reviewed in light of new data from schizophrenia and Huntington's disease models.
ID: 978346

DEVELOPMENT OF THE DOPAMINERGIC SYSTEM IN THE FRONTAL CORTEX: IMPLICATIONS FOR MODULATION OF AXON GUIDANCE

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Background: Dopamine (DA) is a modulatory neurotransmitter implicated in the pathophysiology of schizophrenia (SZ). While the role of DA in the immature brain is not well established, recent studies indicate that monoamines modulate developmental processes such as proliferation, migration, and axon guidance. DA receptors (DR) are expressed early in the developing frontal cortex (FC), a brain region with impaired function in SZ patients. Methods: Using in situ hybridization and QPCR, we analyzed mRNA expression patterns of DRs in the developing rat FC from embryonic day (E) 15 to E21. We studied the signaling mechanisms of DA receptors in cultured embryonic neurons from the FC of prenatal rats at E15 and E18, as well as the morphological response of FC explants to the axon guidance factor netrin-1 (ntn-1) in an axon outgrowth assay. Results: Expression of DR1 in the FC increased from E15 to E18 then decreased from E18 to E21. DR2 expression increased from E15 to E21. Treatment of FC cells with DR agonists and antagonists affected signaling cascades that modulate growth, development, and apoptosis, including glycogen synthase beta 3 (GSK3B), phosphoERK1/2, and cyclic amp response element binding protein (CREB). In addition, our outgrowth assays revealed that cortical FC explants were attracted to ntn-1 expressing Hek293 cells. However, FC axons avoided ntn-1 expressing Hek293 cells in the presence of a D2 agonist. Conclusion: We conclude that abnormalities in the DA system during development can affect molecules that organize connectivity and synapse formation, as DR signaling pathways include molecules known to modulate ntn-1 mediated axon guidance, such as PKA and cyclic nucleotides. We conclude that aberrant activity of the DA system during critical developmental periods can impact the normal trajectory of cortical development and interfere with axon guidance events. Subtle changes in connectivity in the developing brain may not cause drastic, immediate impairment but could affect the function of the FC later in life after maturation.
ID: 978477

ANATOMICAL, PHYSIOLOGICAL AND MOLECULAR ALTERATIONS IN THE STRIATUM OF MICE WITH STRIATAL SPECIFIC D2 RECEPTOR OVEREXPRESSION: A MODEL OF THE COGNITIVE AND NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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Background: To model the increased striatal dopamine D2 receptor activity documented in patients with schizophrenia, we previously generated transgenic mice in which dopamine D2 receptors are reversibly overexpressed in the striatum (D2OE mice). D2OE mice display both cognitive impairments that resemble the cognitive deficits of schizophrenia (defects in working memory and cognitive flexibility) as well as impairments that resemble the negative symptoms of schizophrenia (social interaction, reduced incentive motivation, disrupted reward valuation, with hedonic reaction apparently intact). When the transgene is switched off, the cognitive deficits persist, suggesting that they are developmental in origin. In contrast, whereas some observed negative symptoms persist, other negative symptoms can be rescued. In this presentation we focus specifically on anatomical, physiological and molecular studies of the striatum of the D2OE mice that are aimed at revealing the mechanisms that may underlie the cognitive and negative deficits observed in these mice. Methods: We used unbiased stereological methods to quantify anatomical changes in the striatum of D2OE mice. We used In Vitro slice physiology methods to measure excitability in striatal neurons as well as intrinsic firing rates of dopaminergic cells projecting to the striatum. Gene expression was analyzed initially using gene chips, and results were validated by RNA in situ and qRT-PCR. Results: We found that striatal volume is significantly decreased, as is the length and complexity of the dendrites of striatal medium spiny neurons (MSNs). We further found that striatal MSNs exhibit enhanced excitability in the dorso-medial striatum and nucleus accumbens. Moreover, dopaminergic input to the ventral striatum appears to be changed as we also detected an increase in the intrinsic firing rates of mesolimbic dopamine cells projecting to the nucleus accumbens, core and shell. Finally, exploring the molecular alterations that occur in response to striatal D2R overexpression we found an increase in 5HT-2C receptor expression. Conclusion: We are now in the process of attempting to relate the striatal dysfunctions we have observed with each of the specific cognitive and negative symptoms which they underlie, so that we can devise strategies to ameliorate these deficits in patients with schizophrenia. As a first step, using the 5HT-2C receptor as a target, we were able to achieve pharmacological rescue of the deficit in incentive motivation.
ID: 978584

IDENTIFICATION AND CHARACTERIZATION OF A POTENT, SELECTIVE KATII INHIBITOR

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Background: Kynurenic Acid (KYNA) is the only known endogenous antagonist at the glycine site of the NMDA glutamate receptor (NMDAR) and has also been proposed as a negative allosteric modulator at the alpha 7 nicotinic acetylcholine receptor. KYNA is reported to be elevated in CSF

and postmortem brain from schizophrenia patients, and these elevated levels of KYNA could contribute to the NMDAR hypofunction associated with this disease. Therefore, blocking KYNA synthesis should augment NMDAR function and may provide therapeutic benefit in schizophrenia. Methods: To begin to test this hypothesis, we developed a rapid in vitro assay for kynurenine aminotransferase II (KATII), the main enzyme responsible for the formation of KYNA in mammalian brain, and have used this to identify KATII inhibitors. We determined the in vivo mechanistic effect of this compound by microdialysis, and its behavioral effects in rat radial arm maze assay. Results: We identified an inhibitor that has nM potency against human KATII, and is >600 fold selective for KATII vs KATI, KATIII, and KATIV. Systemic administration of the KATII inhibitor decreased KYNA in microdialysis experiments in prefrontal cortex of rat brain in a dose-dependent manner. A maximum dose lowered KYNA to about 20% of basal level within 40 minutes of administration. Doses that decrease prefrontal cortex KYNA also suppressed a ketamine-induced deficit in performance in radial arm maze. Conclusion: These results provide further support that a KATII inhibitor could lower KYNA in brain and provide possible therapeutic benefit in Schizophrenia and other CNS diseases.
ID: 950130

BEHAVIORAL CHANGES AND MITOCHONDRIAL DYSFUNCTION IN RATS SUBMITTED TO ANIMAL MODEL OF SCHIZOPHRENIA INDUCED BY KETAMINE

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Background: Lines of evidences indicate mitochondrial dysfunction in schizophrenia, as well as in other neurodegenerative disorders. To produce an animal model that simulates psychotic symptoms analogous to those seen in schizophrenic patients, subanesthetic doses of *N*-methyl-D-aspartate (NMDA) receptor antagonists, such as ketamine, have been used. The aim of this work was to evaluate the behavioral changes and mitochondrial dysfunction in rats submitted to ketamine administration for 7 consecutive days. Methods: Behavioral evaluation was realized using an Activity Monitor 1, 3 and 6 hours after the last injection. Mitochondrial respiratory chain evaluation was done through the activity of the complexes I, II, I–III and IV in brain structures as prefrontal cortex, striatum and hippocampus according to Cassina and Radi (1996), Fischer and colleagues (1985), Birch-Machin and colleagues (1994) and by Rustin and colleagues (1994), respectively. Results: Our results showed that the hyperlocomotion was present in ketamine group evaluated for 1 hour after the last injection, as well as in the beginning of the monitoring of the animals 3 hours after the injection. The stereotypic movements were increased only in animals evaluated one hour after receiving ketamine. In addition, we showed that ketamine treatment affected the respiratory chain, altering the activity of the complexes anchored in mitochondria, in striatum and hippocampus after 1 hour; prefrontal cortex and hippocampus after 3 hours and prefrontal cortex and striatum in evaluation after 6 hours of last administration. Conclusion: In conclusion our results showed that the ketamine-treatment alters the behavior of animals and changes the activity of the respiratory chain complexes in different times and structures. Chronic administration of ketamine gives triggers a number of alterations in rats that may be compared to some seen in schizophrenic patients. An animal model can be used to study the alterations and the pathophysiological mechanisms of this disease. However, it is interesting to conduct further studies aiming to investigate other parameters of energy metabolism that may be involved in the pathogenesis of schizophrenia.
ID: 979662

12. Neurochemistry, Clinical

OXIDATIVE STRESS IN FIRST-EPISODE EARLY-ONSET PSYCHOSES

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Background: Recent evidence suggests that patients with a first psychotic episode have impaired detoxification capacity and may suffer from chronic oxidative stress. To our knowledge, there has been no study focusing on oxidative metabolism specifically in children and adolescents with early onset psychosis. Methods: Total antioxidant status (TAOS), non-enzymatic (glutathione and homocysteine) and enzymatic (catalase, superoxide dismutase, and glutathione peroxidase) antioxidants, and lipid peroxidation were measured in plasma or erythrocyte lysates in a group of children and adolescent with a first episode of psychosis ($n = 34$), a group of patients with Aspergers syndrome ($n = 35$) and a group of healthy controls ($n = 34$) at baseline and at 8–12 weeks. TAOS was also analyzed at 1 year. Results: Preliminary results show that psychosis patients had increased homocysteine (Hcy) levels in plasma ($F = 21.44$, $P < .001$) and decreased copper and ceruloplasmin at baseline. However, TAOS was reduced only in Asperger individuals compared with healthy controls and psychosis patients ($F = 4.19$, $P = .018$ at baseline; $F = 5.49$, $P = .006$ at 8–12 weeks, and $F = 8.49$, $P = .001$ at 1 year), after covarying by age and antipsychotic treatment. This reduced antioxidant capacity did not depend on any of the individual antioxidant parameters measured. Conclusion: Hyperhomocysteinemia has been shown to induce oxidative stress and is considered a marker of oxidative stress. It could be speculated that an initial antioxidant reaction as already taken place in the Asperger patients, of the organism takes place against the incipient psychotic process.
ID: 978032

REDOX DYSREGULATION IN EARLY PSYCHOSIS AND RELEVANT ANIMAL MODELS

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Background: Glutathione (GSH), a major cellular redox regulator and antioxidant, is decreased in CSF and prefrontal cortex of schizophrenia patients. Polymorphisms of the key GSH-synthesizing enzyme genes, glutamate-cysteine ligase catalytic (GCLC) and modifier (GCLM) subunits, are associated with schizophrenia. Methods: We investigated if GSH/redox dysregulation observed in chronic schizophrenia is present in early psychosis patients (EP). Results: When compared with sex and age matched control subjects ($n = 34$), EP patients ($n = 38$) showed: -In fibroblasts, decrease of gene expression levels of GCLM (−63%), GCLC (−42%), second synthesizing enzyme (GSS; −33%), redox enzyme glutathione peroxidase (GPX; −63%), and exchanger glutamate/cystine (oxidized form of cysteine, rate-limiting precursor of GSH) (Xct; −62%). -In blood, decrease of GPX activity (−17%), increase activity of the GSH degrading enzyme γ glutamyl transpeptidase (+50%), increase of levels of amino acids taurine (+ 40%), glutamate (+48%) and proline (+35%). Thus, decrease expression in GSH genes observed in chronic patients is already present in EP. They are more pronounced in EP suggesting that chronicity and/or medication may induce compensatory effects. New anomalies, such as decreased Xct mRNA and GPX activity, not present in chronic patients, appear in EP. Impaired GSH synthesis of genetic origin, when combined with environmental risk factors generating oxidative stress, may play a critical role in inducing connectivity anomalies observed in the disease (Do &al 2009). Based on concept of ''reverse translation'', we have successfully tested this hypothesis in gclm-/- mice (70% decreased brain [GSH]): they exhibit morphological, physiological and behavioral phenotypes, including elevated oxidative stress, impairment of parvalbumin interneurons (PVI) and β/γ-oscillations in ventral hippocampus (Steullet &al 2010). In anterior cingulate of developing gclm-/-, the appearance and maturation of PVI are delayed. The latter are more vulnerable to additional insults applied during development but not in adulthood, in analogy to damaging consequences of early environmental insults of future schizophrenia patients. Conclusion: In conclusion, results on GSH/redox dysregulation in EP patients suggest that it is not due to disease chronicity or treatment. In animal models, a redox dysregulation induced by a compromised GSH synthesis leads to region and time selective oxidative stress and impairment of the structural and functional integrity of PVI.
ID: 978290

S100B A BIOMARKER OF PSYCHOSIS SEVERITY IN ADOLESCENTS?

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Background: Studies have shown that patients suffering from depression or schizophrenia often have immunological alterations that can be detected in the blood. Others reported a possible link between inflammation, a microgliosis and the blood-brain barrier (BBB) in suicidal patients. Serum S100B is a marker of BBB function commonly used to study cerebrovascular wall function. Methods: We measured levels of S100B in serum of 40 adolescents with acute psychosis, 24 adolescents with mood disorders and 33 healthy controls. Patients were diagnosed according to DSM-IV TR criteria. We evaluated suicidal ideation using the suicidality subscale of the Brief Psychiatric Rating Scale for Children (BPRS-C). Results: Serum S100B levels were significantly higher ($P < .05$) and correlated to severity of suicidal ideation in patients with psychosis. Patients with a BPRS-C suicidality subscores of 1–4 (low suicidality) had mean serum S100B values +/- SEM of .152 +/− .020 ng/mL ($n = 34$) compared to those with BPRS-C suicidality subscores of 5–7 (high suicidality) with a mean of .354 +/− .044 ng/mL ($n = 30$). This difference was statistically significant ($P < .05$). Conclusion: Our data support the use of S100B as a biomarker to assess suicidal risk in patients with mood disorders or schizophrenia.
ID: 979549

INTERLEUKIN 1 RECEPTOR ANTAGONIST AND TUMOR NECROSIS FACTOR RECEPTOR 1 ARE ASSOCIATED WITH GENERAL SEVERITY AND PSYCHOTIC SYMPTOMS IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Several lines of evidence suggest elevated activity of the Interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor (TNF)-alpha pathways in schizophrenia and bipolar disorder, and recently elevated levels of von Willebrand factor (vWf) and osteoprotegerin (OPG) was found. However, it is still unclear how immune activation is involved in the psychopathology of severe mental disorders. We wanted to investigate if elevated levels of these inflammatory markers were associated with disease severity (trait) or with current symptom level (state), comparing psychotic with general characteristics. Methods: Plasma levels of soluble TNF receptor 1 (sTNF-R1), IL-1 receptor antagonist (IL-1Ra), IL-6, vWf and OPG were measured with ELISA techniques in 322 patients with schizophrenia spectrum and bipolar disorder. Current symptom level was measured with Global Assessment of Functioning (GAF) and Positive and Negative Syndrome Scale (PANSS). Disease severity (trait) was measured with premorbid adjustment scale (PAS), age at onset, number of psychotic episodes and number and length of hospitalizations. Results: After controlling for confounders, IL-1Ra and TNF-R1 were independently associated with GAF. IL-1Ra and sTNF-R1 were also significantly correlated with PANSS negative and positive symptoms, respectively. Further, Il-1Ra was associated with PAS, and sTNF-R1 with hospitalizations and psychotic episodes. VWf was significantly correlated psychotic episodes, OPG with hospitalizations and IL-6 with history of psychosis. Linear regression analysis showed that GAF remained associated with sTNF-R1 and IL-1ra with PANSS negative, after controlling for the other clinical measures. Conclusion: IL-1Ra and sTNF-R1 were associated with state and trait severity measures, both of general and psychotich character. This support the role of immune activation in the pathological mechanisms of severe mental disorders.
ID: 979449

ELEVATED CORTISOL LEVELS AND CORTISOL/DEHYDROEPIANDROSTERONE RATIO IN SCHIZOPHRENIA AS REVEALED BY THE DEXAMETHASONE SUPPRESSION TEST

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Background: We have recently shown that schizotypal personality is related to altered hypothalamic-pituitary-adrenal (HPA) axis function (Hori et al, submitted). Accumulated evidence suggests that schizophrenia is also associated with HPA axis alteration. A large number of earlier studies have used the dexamethasone (DEX) suppression test (DST) to investigate negative feedback inhibition of cortisol in schizophrenia, although the findings are mixed such that the rate of non-suppression to the DST varies from 0% to 73% (reviewed in Tandon et al, 1991). Recently there has been increased interest in the role of dehydroepiandrosterone (DHEA) (and its sulfate: DHEAS) in HPA axis function, partly because this steroid hormone possesses anti-glucocorticoid properties. Several studies have thus investigated baseline DHEA(S) levels and cortisol/DHEA(S) ratios in schizophrenia patients, yielding somewhat controversial results. However, cortisol/DHEA(S) ratio in response to the DST might be a sensitive measure for negative feedback of HPA axis, which is considered to be impaired in schizophrenia. Methods: Thirty patients with schizophrenia (DSM-IV) and 23 age- and sex-matched healthy controls participated in this study. First, participants took .5 mg of DEX orally at 2300 hours. On the next day, plasma and serum samples were collected at 1000 hours. Schizophrenic symptoms were assessed with the Positive and Negative Symptoms Scale (PANSS). Plasma cortisol levels, serum DHEAS levels, and cortisol/DHEAS ratio were compared between the two groups using the Mann-Whitney U test. Correlation between hormonal measures and PANSS scores were calculated using the Spearman's rank correlation test. Results: Schizophrenia patients showed significantly higher cortisol levels ($P = .002$) and cortisol/DHEAS ratios ($P = .014$) than controls, while DHEAS levels were not significantly different between these two groups ($P = .46$). No significant correlations were found between the three hormonal measures and the PANSS positive, negative, or general psychopathology scale scores (all $P > .3$). Conclusion: These results suggest that schizophrenia is related to altered HPA axis function, as indicated by the impaired negative feedback inhibition. In addition to cortisol levels, the cortisol/DHEAS ratio as measured by the DST may serve as a useful biological marker for schizophrenia.
ID: 979078

WHAT DOES PROTEOMICS TELL US ABOUT SCHIZOPHRENIA?

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Background: In the last decade, schizophrenia (SCZ) biomarkers have been searched by genotyping techniques, genome wide association studies and large-scale transcriptome analyses. Proteome analysis has emerged in this context as a promising strategy. Initially, the search for protein biomarkers of SCZ in human brain tissue via proteomics aimed primarily to provide information on the risk for the disease, to contribute to the early diagnosis and to the prediction of the therapeutic response. After several proteomic studies conducted in several brain regions, it became clear that the secondary objective of such type of research which were to provide detailed information about the pathophysiology of the disease and to further confirm the importance of certain pathways have become the main and more useful findings, although potential biomarkers candidates have also been pointed out as primarily expected. Methods: We have studied the post-mortem proteomes of the dorsolateral prefrontal cortex, anterior temporal lobe, Wernicke's area, anterior cingulate cortex, and thalamus from SCZ patients comparing to mentally healthy controls using different proteomic methodologies such as two-dimensional gel electrophoresis and shotgun mass spectrometry. Results: We have found the most often alterations in energy metabolism, oligodendrocyte-function and myelinization, calcium homeostasis and cytoskeleton. Moreover, we have revealed the differential expression of a number of hypothetical or putative proteins, which might be interesting targets to further studies considering their underlie information. Several protein biomarker candidates such as myelin basic protein and myelin oligodendrocyte protein were evaluated and validated by western blot in some of the described brain regions as well as in cerebrospinal fluid from a separate set of samples. A number of glycolysis enzymes have been found differentially expressed in the analyzed brain regions, what have led us to quantify the levels of pyruvate and NADPH in thalamus, which indeed were found altered. Conclusion: The recurrent identification and validation of inter-related protein clusters, determined in different samples by different proteomic approaches not only strongly reinforces the

putative involvement of certain pathways in SCZ, but also reveal new potential biomarkers and paves the way to the development of new therapeutic strategies in order to contribute for reducing the social and cognitive consequences of the disease.
ID: 947128

INCREASED PSYCHOSOCIAL STRESS AND INFLAMMATION REDUCE BDNF EXPRESSION IN FIRST-EPISODE PSYCHOSIS: A CRUCIAL PATHWAY TO A SMALLER HIPPOCAMPAL VOLUME

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Background: Reduced brain-derived neurotrophic factor (BDNF) levels have been reported in patients with first-episode psychosis. The aim of this study was to investigate possible causes and consequences of reduced BDNF expression in first-episode psychosis, exploring its association with measures of stress, inflammation and hippocampal volume. Methods: BDNF, interleukin (IL)-6, and tumour-necrosis-factor (TNF) alpha mRNA levels were measured in leukocytes of 49 first-episode psychosis patients and 30 healthy controls. In the same subjects, we measured salivary cortisol levels, and collected information about childhood trauma, recent stressors, and perceived stress. Finally, brain MRI was conducted, and hippocampal volume was measured, in a subsample of 19 patients. Results: First-episode psychosis patients had reduced BDNF (effect size $d = 1.3$, $P < .001$) and increased IL-6 (effect size $d = 1.1$, $P < .001$) and TNF-alpha (effect size $d = 1.7$, $P < .001$) gene expression when compared with controls, as well as higher levels of psychosocial stress. A linear regression analysis showed that the lower BDNF mRNA levels were related to high levels of childhood and recent stressors through an inflammation-mediated pathway ($r = .54$, $P = .009$). Reduced BDNF gene expression, increased IL-6 gene expression and increased cortisol levels were significantly associated, in a synergic way, with smaller left hippocampal volume in the patients with first-episode psychosis ($r = .87$, $P < .001$). Conclusion: Stressful events represent a significant potential factor influencing neurogenesis in first-episode psychosis. Biological systems involved in the stress response should be considered as a promising target for future therapeutic strategies in patients with psychosis.
ID: 977785

STRESS AND PSYCHOSIS

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Background: Several international studies have focused on patient groups at ultra high risk (UHR) of developing psychosis and on the possibilities for intervention before onset of psychosis. More knowledge about the biological mechanisms involved in the pathogenesis and the pathophysiology of psychosis can form a foundation for future interventions. It is well recognized that the level of stress response is affected in patients with first episode of psychosis (FEP), and UHR subjects also have abnormal level of stress response. Different kinds of treatments/interventions offered can delay, if not prevent the onset of psychosis. Still, we treat many patients who might never develop psychosis. Accordingly, identification of biological predictors for transition to psychosis is of great clinical importance. Methods: In this study we will compare the level of oxidative stress, the cortisol level and the volume of the pituitary gland in three groups of subjects: Healthy controls, UHR and FEP subjects. The cortisol is measured 6 times during one day, and the pituitary gland is manually traced on a structural MRI scanning. Oxidative stress is measured in a urine sample; 8-oxodG and 8-oxoGuo are markers of oxidation of DNA and RNA. Two stress scales (recent life events and perceived stress scale) are used to monitor stress. The tests are performed at baseline and after 12 months. Results: Results from 10 healthy controls, 10 UHR and 10 FEP patients are presented at the conference. We are presenting the psychopathology, the volume of the pituitary gland, the level of oxidative stress and cortisol levels. Conclusion: We will identify how these biological parameters correlate with each other and the psychopathology of the patients.
ID: 978361

GENETICS OF GLUTAMATERGIC NEUROTRANSMISSION IN BIPOLAR DISORDER AND SCHIZOPHRENIA

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Background: Abnormalities in glutamatergic neurotransmission are implicated in schizophrenia, but studies of the glutamate system have been hampered by a lack of in vivo probes. Recent improvements have enabled quantification of glutamine and glutamate separately in proton magnetic resonance spectroscopy (MRS) studies in vivo. Accumulating evidence indicates that the glutamine/glutamate (Gln/Glu) ratio is an index of glutamatergic neurotransmission. Here, we explored whether variation in GLS1 (gene encoding the brain isoform of glutaminase which catalyzes Gln-to-Glu conversion) is associated with Gln/Glu measured in vivo. Methods: We analyzed a hypothesis-generating sample ($N = 41$) and an independent hypothesis-testing sample ($N = 40$) (see Table). MRS data were collected on a 4 Tesla Varian scanner from two brain regions (anterior cingulate cortex (ACC) and parieto-occipital cortex (POC)) as previously described (Ongur et al 2008; Ongur et al 2010). DNA samples from participants were genotyped for SNPs within GLS1. Single base-pair as well as 4 SNP sliding-window haplotypes were entered into multivariate regression analysis with Gln/Glu as outcome variable using PLINK software. Results: A specific haplotype of 4 single nucleotide polymorphisms within GLS1 (starting with rs13000464 and ending with rs12185688; genotype C-G-G-T) was significantly associated with Gln/Glu in the POC in two independent MRS-genetics datasets. Allele frequency = .33 with $P = 7 \times 10^{-4}$ and frequency = .35 with $P = .035$ for association with Gln/Glu in the first and second sample, respectively. Conclusion: These findings suggest that genetic variation in a key component of glutamatergic machinery is associated with an in vivo index of glutamatergic neurotransmission. Thus, GLS1 genotype may provide insight into normal brain function and into the pathophysiology of schizophrenia where glutamatergic neurotransmission has been implicated; it may also become a biomarker for predicting

response to existing and novel therapeutic interventions that target glutamatergic neurotransmission.
Demographic information on study participants

	Group	Sex	Age
Study 1	NC	7M/2F	40.1
	BD	7M/7F	35.6
	SZ	13M/5F	39.8
Study 2	NC	7M/4F	34.7
	BD	5M/9F	34.2
	SZ	7M/8F	44.2

NC = normal control; BD = bipolar disorder; SZ = schizophrenia
ID: 979031

METABOLOME IN SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS

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Background: Persons with schizophrenia and other psychotic disorders have high prevalence of obesity, impaired glucose tolerance, and lipid abnormalities. More detailed molecular information on the metabolic abnormalities may reveal clues about the pathophysiology of these changes, as well as about the disease specificity. Concentration changes of specific groups of metabolites may be sensitive to pathogenically relevant factors, and their study may therefore be a powerful tool for characterization of complex phenotypes. Methods: We applied metabolomics to study serum samples from two cohorts: (1) General population based study in Finland which includes all persons with DSM-IV primary psychotic disorder (schizophrenia $n = 45$, other nonaffective psychosis $n = 57$, affective psychosis $n = 37$) and controls matched by age, sex, and region of residence. Many lifestyle and metabolic variables were also available in this study; and (2) Finnish twin cohort which included serum samples from 19 twin pairs discordant for schizophrenia (mean age 51 +/− 10 years; 7 monozygotic pairs; 13 female pairs) and 35 age and gender matched healthy twins as controls. Neuropsychiatric assessment data and gray matter volume measurements taken from high-resolution magnetic resonance images were also available in this study. Two analytical platforms with broad analytical coverage were applied: (1) lipidomics using UPLC-MS and (2) small-molecule profiling using GCxGC-TOFMS (in general population cohort only). Results: Compared with their matched controls, persons with schizophrenia in the general population cohort had significantly higher concentration of saturated triglycerides and branched chain amino acids. Also, serum glutamate was elevated in all psychoses ($P = .0020$) while proline upregulation ($P = .000023$) was specific to schizophrenia. The observed triglyceride changes were replicated in the twin cohort. Using Bayesian dependency network modeling we associated these changes with specific gray matter volume changes and neuropsychiatric assessment data. Conclusion: Our findings suggest that specific metabolic abnormalities related to glucoregulatory processes and proline metabolism are specifically associated with schizophrenia and reflect two different disease-related pathways. Metabolomics may become a powerful tool in psychiatric research to investigate disease susceptibility, clinical course, and treatment response, sensitive to both genetic and environmental variation.
ID: 979178

NORQUETIAPINE AND DEPRESSIVE SYMPTOMS IN INITIALLY ANTIPSYCHOTIC NAÏVE FIRST-EPISODE SCHIZOPHRENIA

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Background: Recently quetiapine has been approved for treatment of bipolar depression and it has been suggested that the antidepressive effect of quetiapine could be related to its active metabolite norquetiapine. Norquetiapine is similar to its parent compound quetiapine in its dopamine D2 and serotonin 2A receptor binding profile but norquetiapine also inhibits the norepinephrine transporter (NET). As NET inhibition is a known mechanism of action for conventional antidepressants, norquetiapine may explain the antidepressant effect of quetiapine observed in clinical trials. Here we explore pharmacokinetic properties of norquetiapine and its clinical effect on depressive symptoms in first-episode schizophrenia. Methods: Fifteen initially antipsychotic-naïve first-episode patients participated (10 males, mean age: 28.9 years, SD = 5.4). The patients were examined before and after 6 months of treatment with quetiapine in flexible doses according to their clinical condition (mean dose: 383 ± 145 mg/day). For quetiapine and norquetiapine plasma concentration measurements, blood samples were drawn around 3 hours after administration of quetiapine. Symptom severity was assessed by trained raters (ICC .92) using the PANSS scale. The PANSS-D depression cluster (items: somatic concern (G1), anxiety (G2), guilt feelings (G3) and depression (G6) was used to examine the level of depressive symptoms. Results: There was a significant treatment effect on PANSS positive symptoms ($P < .01$) and PANSS-D ($P < .05$) after quetiapine treatment. The reductions in PANSS negative, general and total scores were non-significant. The correlation between plasma levels of quetiapine and norquetiapine were best described by the Michaelis-Menten equation ($r^2 = .59$). Assuming a linear relationship between plasma concentrations of quetiapine and norquetiapine did not improve the goodness of fit ($r^2 = .53$). Plasma concentrations of quetiapine or norquetiapine did not correlate significantly with treatment effect on the PANSS-D. Conclusion: We found a significant treatment effect on PANSS-D, however, this effect was not correlated with quetiapine or norquetiapine plasma concentration. This finding is inconsistent with the hypothesis that it is nor-quetiapine alone by means of NET inhibition that improves depressive symptoms in first episode schizophrenia.
ID: 978227

MOLECULAR PREDICTORS OF MORTALITY IN SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS

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Background: We investigated mortality and its predictors in persons with a psychotic disorder identified from the general population. Methods: The study is based on a nationally representative Health 2000 survey of 8028 persons aged 30 years or over from Finland. Persons with possible psychotic

or bipolar I disorder were screened using information on self-reported symptoms and diagnoses, medical examination, and national health care registers and interviewed with the research version of SCID-I. We obtained case records from all in- and outpatient treatments from all screen-positive people. DSM-IV diagnoses were assigned based on the interview and/or case records. The Health 2000 survey included a comprehensive health examination providing information on general medical problems and lifestyle-related factors. In addition, metabolomics, lipidomics and inflammatory markers were analysed from a sample of 139 persons with psychotic disorders and 139 matched controls. The Register of Causes of Death provided data on causes of death up till 2009. We used Cox proportional hazards model to examine mortality risk. Within the psychosis group, we analyzed metabolic, lifestyle- and medication-related factors predicting mortality. Psychotic disorders were categorized into schizophrenia, other nonaffective psychoses and affective psychoses. Persons with psychotic disorder or delirium induced by substance use or a general medical condition were excluded from the analysis. Results: Adjusting for the effects of age, sex, antipsychotic medication use and its interaction with having a psychotic disorder, persons with schizophrenia and ONAP but not affective psychosis had significantly elevated mortality risk. Persons who were using antipsychotics but did not have any psychotic disorder had elevated mortality risk, whereas antipsychotic medication did not affect mortality risk in those who had a psychotic disorder. In the subsample of participants with available metabolomic and lipidomic data, one lipidomic and one metabolomic cluster and two inflammatory markers predicted elevated mortality risk. Conclusion: Schizophrenia and other nonaffective psychoses are associated with elevated mortality risk. Antipsychotic medication use increases mortality when used for other indications than primary psychotic disorders. Lipidomics, metabolomics and inflammatory markers may provide new methods for predicting mortality risk in psychotic disorders.
ID: 978182

DIFFERENTIAL AGE-RELATED EFFECTS ON THE EXPRESSION OF GENES RELATED TO THE PROSTAGLANDIN SIGNALING PATHWAY IN SCHIZOPHRENIA

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Background: (a) Background - In our previous microarray studies, we detected changes in the expression of genes encoding diverse inflammatory mediators/markers in the dorsolateral prefrontal cortex (Brodmann's area (BA) 46 from subjects with schizophrenia. Methods: (b) Methods - Here we have extended these studies by focusing on expression alterations of genes associated with the prostaglandin-related inflammation pathway using real-time PCR and correlation analyses. Results: (c) Results - we found increased levels of prostaglandin-endoperoxide synthase 1 (PTGS1; aka COX-1) and prostaglandin-endoperoxide receptor 3 (PTGER3) and deceased levels of prostaglandin-endoperoxide synthase 2 (PTGS2; aka COX-2) mRNA in the prefrontal cortex of subjects with chronic illness compared to matched controls. Furthermore, strong age-related and cell-type specific effects were found in the expression of these and other genes related to the eicosanoid signaling pathway, which differed in control subjects compared to those with schizophrenia. Conclusion: (d) Conclusions - These findings contribute to the accumulating evidence suggesting that inflammatory processes in the CNS contribute to pathophysiology of schizophrenia. Given the expression differences detected at different stages of illness or at different patient ages, these findings raise the possibility of specifically tailoring medications to the age, or stage of illness, of the patient. This may be especially relevant to treatment with COX-2 inhibitors, in which our data suggests that they may less effective in patients with chronic illness.
ID: 978525

LACK OF ASSOCIATION BETWEEN BDNF LEVEL AND CHRONIC SCHIZOPHRENIA. A CASE-CONTROL STUDY. PRELIMINARY RESULTS

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Background: Nowadays, the research in schizophrenia is focalized on biomarkers that allow us to understand the neurobiology, prognosis and outcome of this disorder. In that way, brain derived neurotrophic factor (BDNF) could play an important role in schizophrenia's ethiology and development and could be considered a specific marker of disease (both state and trait marker). Most authors have found decreased BDNF level in patients with chronic schizophrenia and antipsychotic treatment, but also has been found decreased BDNF level in drug naïve patients with a first psychotic episode. Instead, fewer authors have found BDNF level unchanged in chronic schizophrenia, even in other cases, increased. These changes in BDNF level could be in relation with antipsychotic drugs, state or evolution of the disease. Other biological parameters have been linked with BDNF level like oestrogens, prolactine, cortisol and DHA. Methods: This is a case-control study with a sample of 20 outpatients with chronic schizophrenia or schizoaffective disorder (with usual antipsychotic treatment, stabilized and without acute symptoms of schizophrenia at the moment of the inclusion to the study) and 20 healthy controls. BDNF level has studied in serum, as well as other analytic parameters as oestrogens, prolactine, cortisol and DHA (dihidroepiandiostendione). For the analysis of clinical issues in patients, the PANSS scale has been used. The computer program Pacs Stadistics 17.0 has been used for the stadistical analysis of the results. Results: To date, 15 patients and 12 controls have been included, but data is only available with a part of the sample due to delay in the analysis of the samples. On preliminary results, BDNF level was higher in schizophrenia outpatients than in controls, but without stadistical significance. Higher oestrogens level were detected in controls. By another hand, higher cortisol and DHA levels were found in patients. Any significant correlation didn't find between BDNF level and positive or negative PANSS subscale. A positive correlation was shown between BDNF level and cortisol. Conclusion: A stadistical significance relationship hasn't been found between BDNF level and chronic schizophrenia. It should wait to draw a final conclusion because these results were obtained with an uncompleted sample. It's important to analyze the completed sample for developing a general hypothesis of this research.
ID: 976162

THE EFFECT OF REBOXETINE AND HALOPERIDOL ON PSYCHOPHYSIOLOGICAL PARAMETERS IN HEALTHY VOLUNTEERS

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Background: Disruptions in filtering of sensory information have frequently been observed in patients with schizophrenia. Successful sensory gating prevents sensory overload of higher brain functions by filtering out irrelevant stimuli before they can reach the higher brain areas. Deficits in sensory gating may therefore result in an overload of irrelevant information reaching the higher brain areas, which in turn might contribute to the

formation of psychotic symptoms. Two well established paradigms to assess sensory filtering are prepulse inhibition (PPI) of the startle reflex and P50 suppression. In both paradigms patients with schizophrenia score significantly lower than healthy controls. In schizophrenia both a reduction in prefrontal dopaminergic activity and an increased noradrenergic activity have been suggested to be involved in the disease. A previous study from our lab indicated that an increased noradrenergic as well as a decreased dopaminergic neurotransmitter activity reduces PPI in healthy volunteers. The current study was designed to replicate and further extend those initial findings. Methods: The design of the experiment is a double-blind, placebo-controlled, cross-over study, where a dose of either haloperidol (2 mg), reboxetine (8 mg), their combination or placebo will be administered to 20 healthy human subjects at four separate times with a minimum of one week apart. The subjects will thereby be tested in The Copenhagen Psychopsysiological Test Battery (CPTB) which, amongst others, measures the above mentioned parameters of sensory and sensorimotor gating. Results: We expect to find reduced PPI and P50 suppression following administration of both reboxetine and haloperidol and their combination to the healthy volunteers. We are currently recruiting subjects for the study, and will present the full PPI data set at the ICOSR. Conclusion: If our hypotheses prove to be correct, then the current study will provide further knowledge on the neurotransmitter systems that are involved in sensory and sensorimotor gating, which in turn may help to clarify the underlying neurotransmitter activity in schizophrenia.
ID: 978284

ASSOCIATION OF HSCRP WITH HIGH-RISK OF CARDIOVASCULAR DISEASE IN PATIENTS WITH SCHIZOPHRENIA

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Background: There is excess and premature mortality in schizophrenia (SZ), from both natural and unnatural causes, when compared to the general population. In a 15-year follow-up study of SZ patients, 22% had died, of which greater than 50% died from cardiovascular and respiratory diseases. Inflammation has been linked to all stages of atherosclerosis. Recent studies suggested a role of C-reactive protein (CRP) as a risk marker for cardiovascular disease (CVD). The purpose of this pilot study was to test whether high CRP was associated with high risk of CVD in patients with chronic schizophrenia (CSZ) with mean duration of illness >20 years. Methods: In clinically stable CSZ patients who were at high-risk of CVD according to the National Cholesterol Education Program Adult Treatment Panel III (ATP-III) guidelines, high-sensitivity C-reactive protein (hsCRP) was compared between those patients currently with ($n = 22$), and those without ($n = 19$) treatment with lipid lowering drugs (LLD). The hsCRP measures were categorized as low risk, <1 mg/L; average risk, 1–3 mg/L; and high risk, >3 mg/L. Results: Among CSZ patients without LLD, 79% had high risk and 21% had average risk of hsCRP values. On the other hand, among CSZ patients with LLD therapy, 14%, 27% and 59% had low, average and high risk hsCRP values, respectively. LLD significantly lowered the total cholesterol, as well as cholesterol in the non-HDL subclasses including LDL, Real LDL, IDL, VLDL, and VLDL3. In addition, high-risk and average-risk hsCRP values were also observed in the clinically stable patients with early course SZ (duration of illness <9 years) who were not identified at high-risk of CVD (30% and 35%, respectively). Conclusion: Therefore, our preliminary data support the notion that the addition of hsCRP to the ATP-III global risk score provides a more accurate assessment of CVD risk in SZ patients. The hsCRP may also be an early marker of CVD risk in schizophrenia. (Supported in part by the American Heart Association and MH58141 grants)
ID: 986482

13. Neuroimaging, Neurochemical

IN VIVO MEASUREMENT OF FLUCTUATIONS IN GLUTAMATE LEVELS: A POSITRON EMISSION TOMOGRAPHY STUDY USING [11C]ABP688 AND *N*-ACETYLCYSTEINE

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Background: In vivo imaging with positron emission tomography (PET) has been used to infer fluctuations in the levels of endogenous neurotransmitters. [11C]ABP688 is a PET radiotracer for the mGluR5 receptor. *N*-acetylcysteine (NAC) has been shown to increase extracellular glutamate through stimulation of the cystine-glutamate antiporter. In this study, we used PET in anesthetized baboons to test if extracellular glutamate increase following NAC could be detected as a change in [11C]ABP688 binding. We compared the change in [11C]ABP688 binding between baseline and NAC challenge conditions to the change between test and retest without pharmacological challenge, in order to determine if an effect of NAC is robust enough to be detected above noise in the measurement. Methods: Four adult male baboons (papio anubis, baboons A, B, C and D, 24 ± 4 kg) were scanned on an HR+ camera under isoflurane anesthesia. All study procedures were approved by the IACUC of Columbia University. Baboons A, B and C were scanned under test-retest conditions. Baboons A, B and D were scanned before and after 50 mg/kg NAC. Scans were performed following a single bolus of [11C]ABP688. Region of interest data were analyzed by compartment modeling with arterial plasma input. The main outcome measure was BPND, the binding potential with respect to nondisplaceable radioligand. The percent change between scans, ΔBPND, was compared across conditions (test-retest vs NAC) by linear mixed modeling. Results: The mean ΔBPND +/− SD across all subjects and regions was 5 +/− 17% for test-retest and -14 +/− 11% for NAC. There was a highly significant effect of condition (test-retest vs NAC, $F(1, 40) = 21.2$, $P < .001$). Conclusion: [11C]ABP688 BPND was significantly decreased following NAC but not different between test and retest. As BPND is proportional to the affinity of the radiotracer for the binding site, these results are consistent with an allosteric interaction in which the affinity of [11C]ABP688 for mGluR5 is reduced compared to baseline due to increased glutamate levels following NAC. Future studies will be required to determine if the observed effect is in fact an affinity shift and if there is an association with glutamate level increases. If the mechanism is confirmed, [11C]ABP688 PET imaging will be a potential tool for probing glutamate transmission in vivo.
ID: 979645

DOPAMINE TRANSMISSION IN COMORBID SCHIZOPHRENIA AND SUBSTANCE DEPENDENCE

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Background: Schizophrenia is often complicated by comorbid substance abuse or dependence. Dopamine (DA) plays a role in both disorders, but no studies have been performed in the comorbid condition. Here, we assessed D2 receptors and DA release in subjects comorbid for schizophrenia and addiction in striatal subregions with [11C]raclopride PET and the amphetamine challenge paradigm. Methods: 12 medically healthy patients with comorbid schizophrenia and cannabis ($n = 12$)-, alcohol ($n = 11$)-, and/or cocaine ($n = 1$) dependence (DD, age 28.9 ± 8.5 years) and 12 healthy volunteers (HC, age 28.1 ± 6.3 years) matched for age, sex and ethnicity were included in the study. Patients were free from both medications and substances for at least 3 weeks prior to the study. Subjects were scanned with a [11C]raclopride bolus plus constant infusion paradigm, using an HR+ camera before and after injection of d-amphetamine (.3 mg/kg) iv. Regions of interest (ROI), drawn on coregistered MRIs, included the AST, (pre- and post commissural caudate and post commissural putamen (preDCA, postCA and preDPU), the postPU, or sensorimotor striatum, SMST, the ventral striatum (VST), and the striatum as a whole (STR). Cerebellum was used as a reference region. Equilibrium analysis was used to derive the specific to non-displaceable equilibrium partition coefficient BPND. The percent change after amphetamine in BPND was analyzed by paired t tests, a linear mixed model and RMANOVA. Results: D2 BPND was lower in DD compared to HC at trend level in STR: RMANOVA $F(1, 22) = 2.86$, $P = .11$. amphetamine induced change in BPND was significantly lower for DD than HC in all ROIs except for the VST. Linear mixed modeling with ROI as repeated variable (5 regions) and diagnosis as between subject variable showed a significant effect of diagnosis: $F(1, 22) = 5.97$, $P = .02$. Despite low levels of DA release, amphetamine induced worsening in psychosis was associated with greater DA release and early onset of drug use was associated with more severe alterations in dopamine transmission Conclusion: Comorbidity involves a distinct set of alterations in the DA system with overall blunted levels of release, but patients may be sensitized to the small fluctuations in dopaminergic transmission and the resulting D2 stimulation. Further research is needed to characterize the time course of the decline in dopamine function in comorbid SCZ and drug dependence and its effects on treatment response, as well as the cellular mechanisms that mediate them.
ID: 979552

THE RELATIONSHIP BETWEEN GLUTAMATERGIC METABOLISM AND RESTING STATE FMRI IN SCHIZOPHRENIA

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Background: Glutamatergic abnormalities and reduced functional network connectivity have been found in schizophrenia (Sz).Glutamatergic dysfunction may adversely affect temporally coherent networks such as the default mode network, but these relationships have not been examined in Sz. Methods: Sz and healthy controls (HC) were studied with chemical shift imaging (CSI) and single-voxel H-MRS (SV-MRS) and resting state fMRI (to examine functional network connectivity; FNC), at 3Tesla. Both MRS acquisitions used PRESS (TE = 40 ms, TR = 1.5 seconds). For CSI (an axial supraventricular tissue slab) 6 anatomical regions were identified (2 gray and 4 white matter). NAAc, Glu, Glx (Glu+Gln), Cre, Cho and Ins were fitted with LC model (CRLBs <20 for all voxels). The SV was acquired from the anterior cingulate (AC;2x2x3cc). Partial volume and relaxation corrections were also implemented. FNC: Subjects completed a five-minute resting state run staring at a fixation cross. Imaging parameters were as follows: FOV 22 cm, matrix size 64 × 64, TR/TE = 2000/30 m/sec, and slice thickness 4mm. FMRI data was preprocessed with SPM5 and INRIalign. Group ICA fMRI Toolbox analyzed the preprocessed data with the minimum description length criteria. The FNC Toolbox assessed correlations between pairs of time courses from the ICA spatial maps. Results: Eighteen Sz and 11 HC completed both SV-MRS and fMRI. In 10 pairs of FNC correlations the SZ had lower correlations than HC (P's <.05; FDR corrected). For the AC SV-MRS there were no significant metabolite differences between the 2 groups. The integrative analysis used group (Sz and HC), the H-MRS metabolites (NAAc, Ins, and Glx), and interaction between group and metabolite as predictor variables for the FNC pairs that

included the AC.There was a groupxmetabolite interaction (F = 5.01, $P = .034$): HNV had a direct correlation between more robust connectivity and higher Glx, while for the Sz this correlation was inverse. Twenty Sz and 16 HC subjects were studied with CSI. There was a diagnosis-by-tissue interaction for NAAc, ($F = 7.96$, $P = .007$), with reduced NAAc in global WM in Sz. Conclusion: The relationships between FNC and glutamatergic metabolism appear to be opposite in Sz and HC. These data suggests that in Sz higher AC glutamate disrupts functional network connectivity between this region and the temporal lobe. Identification of the clinical and cognitive correlates of these functional/metabolic abnormalities may support the use of glutamatergic-modulating agents in subgroups of Sz.
ID: 978561

IMAGING BETA2 NICOTINIC ACETYLCHOLINE RECEPTORS IN TOBACCO SMOKERS DURING ABSTINENCE: PRELIMINARY FINDINGS IN SCHIZOPHRENIA

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Background: Preclinical and clinical studies consistently demonstrate nicotine-induced upregulation of nicotinic acetylcholine receptors (nAChRs). A caveat of imaging living human smokers is potential interference from residual nicotine that may block measurement of beta2-nAChR availability during early abstinence. Our preclinical data suggested ~7 days of abstinence were necessary for nicotine to clear from brain. We imaged smokers with [123I]5-IA-85380 (5-IA) SPECT at 7 days of abstinence and demonstrated significantly higher beta2-nAChR availability throughout the brain in smokers vs. nonsmokers. Next, we found that the higher beta2-nAChR availability persists up to 1 month of abstinence and normalizes to nonsmoker levels by 6–12 weeks of abstinence. Collectively, this suggests that residual nicotine from tobacco smoke takes ~1 week to clear from the brain, and that beta2-nAChR availability decreases progressively over 12 weeks of abstinence. Based on postmortem findings that smokers with schizophrenia do not exhibit nicotine-induced upregulation of nAChRs, we imaged eleven men smokers with schizophrenia (41 ± 13yo) and eleven age- and sex-matched healthy control smokers (40 ± 12yo) after 5–9 days of smoking abstinence. Methods: 5-IA was administered IV as a bolus and constant infusion and subjects were scanned during equilibrium between 6 hours and 8 hours. Patients reported slightly greater nicotine dependence (FTND; 6 ± 2 vs 4 ± 3) and smoked a greater number of cigarettes/day vs controls (22 ± 2 vs17 ± 2) at intake.On the SPECT scan day, craving for cigarettes was significantly greater in patients vs. controls. Results: Preliminary data indicate significantly lower β2*-nAChR availability in smokers with schizophrenia vs. healthy smokers in the parietal (21%, $P = .05$) and frontal (26%, $P = .01$) cortices and thalamus (21%, $P = .04$). We also observed changes in cognition during abstinence in smokers with schizophrenia. There was a significant decline in verbal memory (immediate recall $P = .01$; delayed recall $P = .01$) but not processing speed after tobacco smoking withdrawal. After smoking relapse, processing speed ($F = 7.4$, $P = .01$) and delayed recall ($F = 9.2$, $P = .004$) significantly improved. Conclusion: These preliminary findings suggest schizophrenic smokers do not exhibit the robust nicotine-induced upregulation of beta2-nAChRs observed in healthy smokers and we provide further evidence for the cognitive benefits achieved from tobacco smoking in individuals with schizophrenia.
ID: 977628

FUNCTIONAL BRAIN IMAGING OF VULNERABILITY TO SCHIZOPHRENIA

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Background: Human and animal research suggests that the magnitude of the dopamine response to drugs and stressors may be a marker of vulnerability to schizophrenia. Patients with schizophrenia have an enhanced dopaminergic response to stimulant drugs and stress. We will review evidence that individuals at risk for schizophrenia demonstrate enhanced dopamine release in response to stimulant drugs and psycho-social stress. While this enhanced dopamine response may be partly genetic, environmental factors also play a role. Specifically, we will discuss the role of sensitization and early parental care on the dopamine system. Methods: Dopamine release is measured in humans using positron emission tomography and [11C]raclopride, a D2 receptor ligand. A reduction in tracer binding is indicative of dopamine release. We have used this paradigm to study dopamine release in response to abused drugs (alcohol, amphetamine, nicotine) and natural rewards such as food and money, and to psycho-social stress. The neural response to stressors can also be measured using functional magnetic resonance. FMRI is more sensitive and has greater temporal resolution than PET, but lacks its specificity with respect to dopamine. Results: Sensitization refers to the increase in psychomotor and neurochemical effects of abused drugs or stressors with repeated administration. Sensitization to amphetamine occurred after three doses in humans, and the effect persisted for at least one year. Placebo amphetamine, when paired with conditioned contextual cues, can also release dopamine in the human brain. These effects appear to be increased in vulnerable individuals. Psycho-social stress caused dopamine release in humans, and the effect was greater in individuals who reported poor parental bonding in early life. We will present preliminary data suggesting that amphetamine can also sensitize the dopamine system to stress. Finally we have shown with PET and fMRI that healthy individuals who have elevated scores on schizotypy scales, a risk factor for psychosis, demonstrate enhanced dopamine release in response to social stress. Conclusion: These results suggest that poor early life experiences, repeated drug use, and repeated exposure to stress, may all act on the dopamine system to promote vulnerability to schizophrenia in susceptible individuals.
ID: 978805

INCREASED GLUTAMATE IN THE ASSOCIATIVE-STRIATUM OF SUBJECTS WITH PRODROMAL SYMPTOMS OF SCHIZOPHRENIA AND PATIENTS WITH FIRST-EPISODE PSYCHOSIS

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Background: The involvement of the glutamatergic and dopaminergic systems in the pathophysiology of schizophrenia has been suggested. Interaction between glutamate and dopamine neurotransmission systems has been widely documented and could be important to understand the neurobiological basis of the disease. The aim of this study was to compare the

Glutamate levels in the precommissural dorsal-caudate, as a dopamine rich region, and the cerebellar cortex, as a negligible dopamine region, in: (1) 18 antipsychotic-naïve subjects with ultra high-risk for schizophrenia - or prodromal symptoms (UHR), (2) 18 antipsychotic-naïve first episode-psychosis patients (FEP) and (3) 40 age-and-sex equated healthy controls Methods: All subjects underwent a proton magnetic resonance spectroscopy (1H-MRS) study. 1H-MRS was performed on a 3T scanner, Glutamate levels were quantified including corrections for the proportion of cerebrospinal fluid in the voxel and for the percentage of graygray matter. Results: In the precommissural dorsal-caudate, the UHR and FEP groups showed higher levels of Glutamate than controls without differences between UHR and FEP. In the cerebellum, no differences were shown between the three groups. Conclusion: The increase of glutamate in the precommissural dorsal-caudate and not in the cerebellum suggests an interaction of glutamate and dopamine with the presence of psychotic and pre-psychotic symptoms.
ID: 979909

DOPAMINERGIC FUNCTION IN TREATMENT RESISTANT SCHIZOPHRENIA

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Background: Molecular imaging studies have consistently reported presynaptic striatal dopaminergic elevation in schizophrenia, but no such studies have investigated the dopaminergic function in treatment resistant patients, and it remains unknown whether the neurobiology of treatment resistance is linked to dopamine dysregulation. We thus examined the dopaminergic function in a cohort of treatment resistant patients with schizophrenia by means of [18 F] -DOPA uptake and a high sensitivity 3 dimensional positron emission tomography. Methods: Eight patients with treatment resistant schizophrenia (mean age 45 years) and 8 healthy volunteers matched for gender, age, weight and cigarette smoking underwent [18 F] DOPA PET scanning (ECAT EXACT 3D). Striatal dopamine uptake influx rate constants (Ki values) were measured for the whole striatal region of interest (ROI) and for the functional subdivisions relative to uptake in the reference region. Independent t test statistics was used to compare ROI based Ki values between patients and healthy volunteers. Results: No between-group differences were observed for age, gender, weight or cigarette smoking. We observed no significant differences between groups for [18 F] -DOPA uptake Ki values for the whole striatum ($P = .99$) or for its sensorimotor ($P = .58$), limbic ($P = .99$) or associative ($P = .93$) sub divisions Conclusion: Our preliminary findings suggest that the dopaminergic dysregulation may not be the primary neurochemical abnormality in treatment resistance. This may indicate that treatment resistant schizophrenia constitutes a distinct subtype of psychotic illness.
ID: 979181

OXIDATIVE STRESS AND SCHIZOPHRENIA: 1H-MRS AT 14.1 T IN DEVELOPING MICE WITH GLUTATHIONE DEFICIT

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Background: Glutathione (GSH), a major cellular redox regulator and antioxidant, is decreased in CSF and prefrontal cortex of schizophrenia patients. Polymorphisms of the key GSH-synthesizing enzyme genes, glutamate-cysteine ligase catalytic and modifier (GCLM) subunits, are associated with schizophrenia. This impaired GSH synthesis of genetic origin, when combined with environmental risk factors generating oxidative stress, may play a critical role in inducing connectivity anomalies as observed in the disease (Do &al 2009). Based on concept of ''reverse translation'' (Insel 2009), we have successfully tested this hypothesis in gclm-/- mice (70% decreased brain [GSH]): they exhibited many morphological, physiological and behavioral phenotypes of the disease, including impairment of parvalbumine interneurons and neuronal synchronization in ventral hippocampus (Steullet &al 2010). Methods: We investigated the impact of redox dysregulation on the neurochemical profile (18 metabolites) of anterior and posterior cortex in gclm-/- and wildtype (WT) mice with 1H-MRS at 14.1T on postnatal days 10, 20, 30, 60 and 90. Results: Gclm-/- display nearly undetectable [GSH] compared to WT and this GSH depletion triggers alterations of its metabolic precursors, namely an increase of glycine and glutamate between P20 and P30. Glutamine and aspartate, both produced from glutamate, are increased in gclm-/-. Interestingly, the ratio glutamine/glutamate is increased in late adolescence/early adulthood, as in anterior cingulate of early schizophrenia patients (Bustillo &al2009). Gclm-/- show in addition higher [*N*-acetylaspartate]. As these metabolites are implicated in neurotransmission and mitochondrial metabolism, their alteration may indicate impaired mitochondrial function. Chronic supplementation by *N*-acetyl cysteine (NAC), a GSH precursor and antioxidant, has no measurable effect on total [GSH] in gclm-/-, consistent with a drastic enzyme deletion. However, preliminary data suggest that glutamate, glutamine, glycine and *N*-acetylaspartate levels of NAC treated gclm-/- normalize to WT levels at P20–P30 as well as [aspartate] at P60–P90. Conclusion: The observed metabolic alteration in mice cortex with redox dysregulation suggest impaired mitochondrial metabolism and altered neurotransmission and highlight P20–P30 as a particularly sensitive period for these alterations. Chronic NAC supplementation seems to have protective qualities during this critical period suggesting that it can partially restore the redox status.
ID: 979232

GLUTAMATE, *N*-ACETYLASPARTATE AND GABA LEVELS IN HIPPOCAMPUS IN SCHIZOPHRENIA AS MEASURED BY 3T 1H-MRS

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Background: Schizophrenia pathophysiology is not understood, but may be most prominent in discrete brain regions like hippocampus (Hipp) and prefrontal cortex (PFC). Pharmacologic, animal model and postmortem studies suggest that glutamate transmission may be decreased in these target regions. Neuroimaging techniques such as proton magnetic resonance spectroscopy (1H-MRS) provide additional evidence that the Hipp, and PFC are involved in the neuropathology of schizophrenia. *N*-acetylaspartatate (NAA), presumed to be a marker of neuronal integrity, has been repeatedly measured in schizophrenia and is reliably found to be reduced in Hipp and PFC (Fannon et al, 2003 and Steen et al, 2005). Methods: Here, we have used NAA as an ''internal standard'', to allow us to reliably contrast MRS measures of GABA and glutamate levels in Hipp between schizophrenia and healthy controls. We used 1H-MRS to measure glutamate (Glu), NAA and GABA levels in hippocampus in 18 normal volunteers (NV) and 22 schizophrenia patients (SV) (8, untreated (SV-off) and 14, treated (SV-on)). Data were collected from a 50 × 15 × 15 mm voxel that was placed over the left hippocampus. Experiments were carried out on a whole-body Philips 3T scanner. A standard birdcage head RF coil was used for transmission and signal reception. T1-weighted (MP-RAGE) images were used for voxel positioning. GABA was measured using a dif-

ference editing method (MEGA-PRESS). Editing 180 degree pulses, tuned to 1.9 ppm, were switched on and off in alternate scans, giving edit-on and edit-off subspectra, respectively. An edited GABA signal at 3.0 ppm was obtained via subtraction between the subspectra. Glutamate, NAA, and creatine (Cr) were estimated from the edit-off spectra. MRS data were acquired with 2 s repetition time and 256 signal averaging for each subspectrum. LCModel software was used for spectral fitting of the data. Metabolite estimates were normalized to Cr. Results: The results show the predicted reduction in Hipp NAA ($P = .011$), an outcome that strengthens our confidence in the overall approach; the additional data shows a reduction in Hipp Glu ($P = .006$) without a change in tissue GABA. Conclusion: We interpret these findings to be consistent with existing ideas of hypoglutamatergic function in Hipp in schizophrenia. Because these results derive from the whole Hipp, additional experiments need to be done to derive subfield-specific levels.
ID: 977947

GLUTAMATE CONCENTRATIONS IN THE ANTERIOR CINGULATE OF PEOPLE WITH SCHIZOPHRENIA VARY BASED ON PAST ALCOHOL USE

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Background: Alcohol use disorders (AUDs) are more common in schizophrenia compared to the general population. People with schizophrenia may be at increased risk for developing AUDs because alcohol affects the glutamatergic neurotransmitter system, which has also been implicated in the pathophysiology of schizophrenia. Drinking may be an attempt by people with schizophrenia to affect a pathologic glutamatergic system. Alternatively, glutamatergic pathology in schizophrenia may affect how alcohol is experienced and lead to increased vulnerability to misuse. This study used proton magnetic resonance spectroscopy (1H-MRS) to investigate anterior cingulate (ACC) glutamate (Glu) concentrations in people with schizophrenia with and without a past history of an AUD. The ACC is associated with both schizophrenia pathology and cravings for substances of abuse. Methods: Participants were diagnosed with schizophrenia; none were actively dependent or abusing any substance other than nicotine. Past history of alcohol abuse/dependence was confirmed by interview and chart review. Nine individuals had a past history of an AUD (+AUD), 12 had no history of an alcohol use disorder (No AUD). 1H-MRS was collected on a Philips ACS-NT 3T scanner (Best, Netherlands) with an 8-channel head coil. Spectra were acquired from a 2 × 2 × 2 cc voxel encompassing the bilateral ACC using point-resolved pulse sequence (PRESS; TR = 2000 ms, TE = 35 ms, 1024 points, 2000 Hz spectral width, 256 averages, scan time 8 minutes 34 sec). Water suppression was achieved with variable pulse powers and optimized relaxation delays (VAPOR) presaturation pulses. Spectra were analyzed using the fully automated, standard curve-fitting software, LCModel. Glu concentrations were normalized to unsuppressed water peaks. Group difference in Glu levels were compared using Student's t. Results: The +AUD participants had a mean ACC Glu of 7.63 + .62 institutional units (IU). This was significantly higher than the mean ACC Glu of the No AUD group; 6.21 + 1.92 IU ($t19 = 2.13$; $P = .05$). Conclusion: The higher concentration of glutamate in the ACC in people with schizophrenia with an alcohol history compared to their non-drinking peers supports the hypothesis that the glutamatergic system may be involved in the co-occurrence of schizophrenia and AUDs. Currently, it is unclear whether this glutamatergic difference is a consequence of previous alcohol use or an innate risk factor in some people with schizophrenia conferring vulnerability to AUDs.
ID: 979540

IN VIVO BINDING OF ANTIPSYCHOTICS TO D3 AND D2 RECEPTORS: A PET STUDY IN BABOONS WITH [11C]-(+)-PHNO

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Background: Measuring the in vivo occupancy of antipsychotic drugs at dopamine D2 and D3 receptors separately has been difficult due to lack of selectivity of available tracers. The recently developed [11C]-(+)-PHNO is D3-preferring, allowing estimates of the relative D2 and D3 binding of antipsychotic drugs. We used PET imaging in baboons with [11C]-(+)-PHNO to examine the binding to D2 and D3 receptors by clozapine (CLOZ) and haloperidol (HAL). Methods: Four animals were scanned with dynamically acquired PET and arterial plasma input functions. First, test and retest scans were acquired in single scanning sessions to assess the reproducibility of [11C]-(+)-PHNO scans. The observed percent change in BPND (ΔBPND) following the second scan was <10% in putamen (PUT) and caudate (CAD), whereas there were changes >20% in all D3-rich regions, suggesting a mass carryover effect of [11C]-(+)-PHNO at D3. Subsequent studies included only 1 scan per session. Post-antipsychotic drug only-scans were acquired in 3 subjects (CLOZ .5534 mg/kg, HAL .0109 mg/kg, twice for each drug in each subject) and compared to baselines. HAL and CLOZ were each administered as a slow bolus 15min prior to the scan. ΔBPND following challenge with antipsychotic drugs was measured. A regression model based on literature values of regional D2 and D3 fractions of [11C]-(+)-PHNO BPND in PUT, CAD, substantia nigra (SN), globus pallidus (GP), ventral striatum (VST), and thalamus (THA) was used to infer occupancy at D2 and D3 receptors. Results: ΔBPND following antipsychotic challenge is reported in Table 1. The regression model estimated D2:D3 selectivity as 5.25 for CLOZ and 2.38 for HAL. Conclusion: The selectivity was very similar to published in vitro values for HAL (3.03) but slightly larger for CLOZ (2.82). These data suggest that acute doses of CLOZ and HAL bind to D3 receptors in vivo, and that the lack of D3 occupancy by antipsychotics observed in some recent imaging studies may be due to other phenomena.
Mean ΔBPND +/- SD for acute-dose antipsychotic study. $N = 6$ for all results (3 subjects × 2 post-drug studies for each drug).

	−ΔBPND (%)	
Region	CLOZ	HAL
Putamen	43 +/− 11	70 +/− 14
Caudate	44 +/− 10	69 +/− 13
VST	24 +/− 17	66 +/− 18
GP	21 +/− 14	61 +/− 14
SN	7 +/− 12	39 +/− 50
Thalamus	14 +/− 10	31 +/− 75

ID: 975328

THE NEUROBIOLOGY OF COGNITIVE IMPAIRMENTS IN THE PRODROME TO SCHIZOPHRENIA

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Background: Alterations in both frontal and striatal functioning have been linked to the cognitive impairments seen in schizophrenia. However, it is not clear when these become apparent in the development of the disorder, or how they relate to each other. We sought to determine which is primary by studying people with prodromal signs of schizophrenia. Methods: We used PET and fMRI imaging in the same individuals to study both striatal dopamine synthesis capacity and the neural substrates of performance during tasks designed to index memory and frontal executive functions that are impaired in schizophrenia. Thirty subjects at high clinical risk of psychosis (all meeting the CAARMS criteria for an at risk mental state [ARMS]) who show prodromal signs of schizophrenia and twenty matched controls received the measures. The ARMS subjects received clinical follow-up to determine who developed psychosis. The striatal regions of interest were the whole striatum (S), and limbic (LS), associative (AST) and sensorimotor (SMST) striatal subdivisions. Results: Striatal dopamine synthesis capacity was significantly elevated in the associative striatum ($P < .05$) and was linked to poorer cognitive performance in the ARMS subjects. Furthermore it was also linked to alterations in brain activation during memory and executive tasks ($r = .732$, $P < .001$). The inter-relationship between striatal dopamine synthesis capacity and frontal activation was significantly different between ARMS and controls ($P < .0001$). Conclusion: These findings indicate that frontal and striatal abnormalities both predate the onset of schizophrenia in people with prodromal signs of schizophrenia, and that these show an altered inter-relationship to that seen in matched controls. This evidence suggests that fronto-striatal interactions play a role in the development of executive cognitive impairments, and that treatments targeting these circuits may thus be beneficial.
ID: 938758

USING MAGNETIC RESONANCE SPECTROSCOPY AND DIFFUSION TENSOR IMAGING AS BIOMARKERS OF THE PROCOGNITIVE POTENTIAL OF DAVUNETIDE IN SCHIZOPHRENIA

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Background: Schizophrenia is characterized in part by persistent neurocognitive deficits. *N*-acetylaspartate (NAA) is a putative marker of neuronal integrity and proton magnetic resonance spectroscopy (1H-MRS). Choline levels provide an index of membrane phospholipid turnover and elevated levels occur in several neurodegenerative disorders. Diffusion tensor imaging (DTI) provides complex measures of cortical connectivity. Furthermore, MRS and DTI measures are consistently altered in schizophrenia. Davunetide is a microtubule stabilizing peptide with neuroprotective properties. Our group recently found that adjunctive davunetide in schizophrenia produced improved cognitive functioning as measured by the UPSA. A subset of subjects had 1H-MRS and DTI to test the hypothesis that davunetide may exert procognitive effects through neuroprotective mechanisms. Methods: 12-week, randomized, double-blind, placebo-controlled multisite study of 2 doses of davunetide (5 and 30 mg/d i.n.) in 63 patients with schizophrenia on stable antipsychotic treatment. 18 subjects at 4 sites had 3T 1H-MRS and DTI performed at baseline and at 12 weeks. NAA/Cr and choline/Cr were measured in left DLPFC. DTI data were analyzed using FA, MD and EAR. Cognition was assessed using the MATRICS Consensus Cognitive Battery (MCCB). Results: NAA/Cr for davunetide produced a nominal 6.3% increase from baseline to Wk 12 vs placebo ($P = .122$). Baseline NAA/Cr correlated with multiple cognitive domains. Choline/Cr for davunetide suggested a 6.4% increase vs placebo ($P = .069$). DTI revealed several areas of anterior and posterior parietal cortex with altered FA and EAR following 12 weeks of davunetide vs placebo and these areas showed partial correlation with tests of spatial memory and processing speed. Conclusion: Davunetide represents a potentially useful procognitive agent for clinically stable patients with schizophrenia. Although the MRS and DTI studies were only powered to detect large effect sizes, the results are consistent in demonstrating modest increases for NAA and choline measures after 12 weeks of davunetide. As a marker of neuronal integrity, increased NAA is consistent with the putative neuroprotective properties of davunetide. The DTI data is also suggestive of robust effects on cortical connectivity in this small sample size. Larger studies are needed to better understand the mechanisms that contribute to the cognitive and functional effects of davunetide.
ID: 978935

FRONTAL CORTEX GABA, OSCILLATIONS, AND WORKING MEMORY IN SCHIZOPHRENIA

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Background: Cognitive deficits in schizophrenia (SCH) are a major source of disability in the illness but show only a limited response to currently available treatments. Disturbances in cortical GABAergic interneurons and neuronal synchrony are thought to underlie these deficits. We acquired MRS measures of GABA together with high-density electroencephalograms (EEGs) during a working memory (WM) task to help clarify the pathophysiology of WM deficits in SCH. Methods: Twenty-three participants (11 patients and 12 healthy volunteers) enrolled in the study. Baseline resting-state EEGs of all 23 participants were recorded for at least 3 minutes with eyes open. These were followed by 34-minute EEGs during a modified Sternberg WM task, yielding high quality recordings for eight healthy volunteers and six patients. GABA levels in a left DLPFC voxel were measured for all 23 participants on a separate day with a 3.0 T GE MR system. We used the volume-selective PRESS J-editing difference method with an 8-channel phased-array head coil and quantified levels relative to the simultaneously acquired internal water signal of the voxel. Results: WM performance was lower in patients than healthy volunteers (hit rate, two-tailed *t* test, $P = .026$). In the resting state, GABA levels in the DLPFC and power of gamma frequency band (30–56 Hz) for the corresponding scalp electrode (F3) were related ($r = .472$, $n = 23$, $P = .023$). This relationship was also examined in the encoding, retention, and probe stages of the WM task. All stages showed a significant correlation between GABA and gamma power ($n = 14$: encoding, $r = .739$, $P = .003$; retention, $r = .688$, $P = .007$; probe, $r = .802$, $P = .001$). Patients had lower gamma power than controls in every stage (two-tailed *t* test, $n = 14$: encoding, $P = .022$; retention, $P = .024$; probe, $P = .024$). GABA was also correlated with the peak gamma frequency of the encoding stage ($n = 14$, $r = .546$, $P = .043$). Conclusion: The role of DLPFC GABA in subserving gamma band power both in the resting state and during a WM task is supported by these data. GABA levels and gamma band power remain strongly correlated in SCH, although WM performance and gamma power are at lower levels in the illness. Studies of additional cognitive functions in relation to GABA and neuronal synchrony in other brain regions might further our understanding of cognitive impairment in SCH, potentially informing the development of more specific treatments for this disabling aspect of the illness.
ID: 978832

ABNORMAL IN VIVO DOPAMINE RELEASE IN CORTICO-PREFRONTAL AND SUBCORTICAL BRAIN REGIONS OF FIRST DEGREE RELATIVES OF

SCHIZOPHRENIC PATIENTS IN RESPONSE TO PSYCHOSOCIAL STRESS: A POSITRON EMISSION TOMOGRAPHY STUDY USING [^{18}F]FALLYPRIDE

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Background: Patients with a diagnosis of schizophrenia, as well as their first degree relatives, display increased sensitivity to stress. Although this has been hypothesized to be related to dopamine system abnormalities, evidence in the form of in vivo human imaging studies is currently scarce. Furthermore, the few studies that have investigated stress-induced changes in dopamine levels have focused solely on striatal dopamine transmission, whereas rodent studies suggest an equally important role for prefrontal dopamine projections in the neural processing of stress. We, therefore, aimed at investigating in vivo dopamine release in cortico-prefrontal and subcortical brain regions of first degree relatives of schizophrenic patients in response to a psychosocial stressor, using the highly selective dopamine $D_{2/3}$ PET radioligand [^{18}F]fallypride. Methods: 14 healthy volunteers and 15 first degree relatives of patients with a diagnosis of schizophrenia underwent a single dynamic PET scanning session after intravenous administration of 186.0 (±10.2) MBq [^{18}F]fallypride. Psychosocial stress was initiated at 100 minutes postinjection. PET data were analyzed using the linearized simplified reference region model (LSRRM), accounting for time-dependent changes in [^{18}F]fallypride displacement. Voxel-based statistical maps were computed to localize areas with increased ligand displacement after task initiation, reflecting dopamine release. Finally, regression analyses were performed to compare the amount of task-related ligand displacement between healthy volunteers and relatives. Results: Results are preliminary, since only 12 healthy volunteers and 13 relatives have been analyzed, thus far. Relatives showed decreased task-initiated ligand displacement in the left inferior frontal gyrus ($R^2_{(df=24)}$ = .28; P = .016; corrected for age and gender) and increased task-related ligand displacement in the globus pallidus (Left: $R^2_{(df=24)}$=.29; P = .013; Right: $R^2_{(df=24)}$ = .22; P = .042; corrected for age and gender), reflecting decreased and increased dopamine transmission in these regions, respectively. Conclusion: Although preliminary, our findings suggest that genetic vulnerability for psychosis is associated with abnormal processing of psychosocial stress, with observed dopamine "*hypo*activity" in the left inferior frontal gyrus and possible dopamine "*hyper*activity" in the globus pallidus. These findings add to the suggested disbalance of the dopamine system underlying stress-sensitivity in persons at risk for psychosis.
ID: 979212

RELATIONSHIP OF BRAIN METABOLITE ABNORMALITIES WITH WHITE MATTER INTEGRITY IN SCHIZOPHRENIA

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Background: Brain metabolite abnormalities have been described in schizophrenia (SZ). *N*-acetyl aspartate (NAA) is of interest as a marker of neuronal health and integrity. Glutamate has been implicated in both the pathophysiology of schizophrenia as well as a possible mechanism for neuronal toxicity. Diffusion tensor imaging (DTI) has found reduced white matter (WM) integrity in SZ. In this study we wanted to examine metabolite levels in different disease stages and their relationship to white matter integrity. Methods: Subjects included 14 young SZ subjects (<2 years psychosis), 13 young controls, 22 older SZ subjects, 13 older controls. Short echo spectroscopic imaging, anatomical imaging and diffusion tensor imaging data were collected on a 3T Siemens Trio scanner at three sites. The spectroscopy slice was collected from a 10 mm slice aligned with the AC-PC plane and above the corpus callosum. Linear regression methods of voxel tissue composition were used to estimate pure white matter and gray matter metabolite levels. Measures of the white matter fractional anisotropy(FA) were computed from the spectroscopy slice location. Results: In young patients, glutamate/glutamine(Glx) was found to be elevated in gray matter. In older patients, NAA was found to be lower in WM. Collapsing the young and older groups, there was a significant correlation of WM NAA with age in only the SZ. Controlling for age, there was a positive correlation of WM NAA with FA in controls but not in SZ. Conclusion: abnormally high early in the illness and WM NAA is only abnormally low later in the illness. The negative correlation of WM NAA with age in SZ points to a degenerative process not present in the controls. The lack of a correlation of WM NAA and FA in SZ may suggest a disruption between metabolic and structural properties in WM. In summary, this study suggests that there are events in gray matter Glx early in the disease, perhaps neurotoxic, that are followed by reduced WM NAA in older subjects perhaps due to the loss of dendritic connections in gray matter. A neurodegenerative process is further supported by the negative effect of aging in WM NAA present only in the SZ and the disturbed NAA/FA relationship in SZ. These data provide potential new insights into the pathophysiology of schizophrenia, the usefulness of multimodal approaches and the importance of verifying these findings in longitudinal studies.
ID: 979798

GLUTAMATE IN THE EARLY PHASE OF PSYCHOSIS

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Background: There is increasing evidence that altered glutamate function plays a critical role in the onset of psychosis. We investigated this in vivo, using multi-modal neuroimaging in subjects at Ultra High Risk (UHR) for psychosis. Methods: Subjects meeting PACE criteria for the At Risk Mental State were studied at first clinical presentation using MR spectroscopy and compared with healthy controls. Glutamate levels were assessed in thalamic and medial temporal regions. In a series of studies, MR spectroscopy was combined with either structural MRI, functional MRI, or F-dopa PET. Finally, UHR subjects who had been examined with MR spectroscopy at presentation were re-scanned using after 24 months of clinical follow up, by which time a proportion of the original sample had developed a first episode of psychosis. Results: At baseline, UHR subjects showed significantly reduced thalamic glutamate levels compared to controls. The magnitude of the reduction in thalamic glutamate was correlated with the degree to which graygray matter volume in prefrontal and medial temporal cortex was reduced, and that activation in the prefrontal cortex during a verbal fluency task was increased. The UHR group also showed increased striatal dopamine function relative to controls. Within the UHR sample, there was a correlation between medial temporal glutamate levels and striatal dopamine function that was not evident in controls. In controls, medial temporal glutamate levels were correlated with medial temporal activation during an

episodic memory task, but this was not evident in the UHR group. Comparison of data from follow up and baseline assessments indicated that there was a longitudinal reduction in thalamic glutamate levels in the subgroup of UHR subjects who later developed psychosis. Conclusion: These data suggest that there are significant abnormalities in central glutamate levels in people at ultra high risk of psychosis, and that these are related to abnormalities in brain structure, neurocognitive function, and dopamine activity that are also present in this group. The subsequent onset of psychosis in a subgroup of high risk subjects may be associated with progression of glutamatergic abnormalities evident at presentation. These findings provide a rationale for the evaluation of novel treatments that target glutamate dysfunction in the early phase of psychosis.
ID: 979283

METHAMPHETAMINE INDUCES MILD PSYCHOTIC SYMPTOMS AND MODULATES MESOSTRIATAL FUNCTION DURING REWARD ANTICIPATION IN HEALTHY VOLUNTEERS

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Background: It is well known that administration of amphetamines can induce positive psychotic symptoms; the mechanisms through which this occurs are still unknown though it is thought to relate to the ability of amphetamines to cause cortical or subcortical dopamine release. One candidate mechanism is through disruption of a dopamine-mediated frontal and subcortical reward and motivational salience processing network. We used intravenous methamphetamine infusions in healthy volunteers as a model of prodromal psychosis and examined behavioral and brain responses during a reward anticipation task. Methods: We recruited 17 healthy volunteers to perform a reward anticipation task within the functional magnetic resonance imaging scanner after methamphetamine challenge. Methamphetamine or saline was administered in an intravenous infusion at .3 mg/kg over ten minutes in a randomized controlled crossover design. We then collected fMRI data during a novel reward anticipation task in a 3T magnet. Following the MRI session, we measured psychopathology with the Comprehensive Assessment of At-Risk Mental States rating scale (CAARMS), a widely used instrument in clinical practice and research into prodromal psychosis. fMRI data was processed in FSL, with statistical analysis implemented using the non-parametric permutation based tool Randomise and correction for multiple comparisons using Threshold-Free Cluster Enhancement. Results: Under placebo, consistent with previous studies, we observed stronger activation of the ventral tegmental area/substantia nigra and ventral striatum during the anticipation of the reward compared with receipt of reward ($P < .05$). After methamphetamine challenge, the ability of this network to discriminate between reward anticipation and outcome was disrupted ($P < .05$). Methamphetamine induced mild psychotic symptoms as measured by the CAARMS. Conclusion: Methamphetamine induces mild psychotic symptoms after a single dose, and can be a useful model of prodromal psychosis. Methamphetamine impairs the ability of a mesostriatal network to discriminate reward anticipation and outcome. The results are consistent with theories postulating that disruptions of dopamine's role in motivational processing are implicated in the pathogenesis of psychotic symptoms.
ID: 954516

IN VIVO GABA, GLUTAMATE, AND NAAG MEASUREMENTS IN SCHIZOPHRENIA

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Background: The major excitatory and inhibitory neurotransmitter systems, glutamate and gamma-aminobutyric acid (GABA) respectively, are implicated in the pathophysiology of schizophrenia. Also, *N*-acetylaspartylglutamate (NAAG), a glutamate mGluR3 agonist and weak NMDAR antagonist, may be altered in schizophrenia. This study used specific proton magnetic resonance spectroscopy (1H-MRS) techniques, to measure these chemicals from medial prefrontal (MF) and centrum semiovale (CS) of subjects with and without schizophrenia. Methods: 14 subjects with chronic schizophrenia and 14 healthy subjects participated in this study. General cognitive function was assessed with the RBANS, and psychiatric symptom severity was assessed with the BPRS. MR scanning was conducted on a 3T Philips Intera at the FM Kirby Imaging Center, KKI, JHMI. For detection of glutamate and glutamine, spectra were acquired with a PRESS sequence (TR =2000 ms, TE = 35 ms, 2048 points, 2000 HZ, 128 averages). For detection of GABA, spectra were acquired with a MEGA-PRESS sequence (TR = 2000 ms; TE = 68 ms; 14 ms editing pulse applied at 1.9 ppm; 256 averages). For detection of NAAG, spectra were acquired with a MEGA-PRESS sequence (TR = 2000 ms; TE = 140 ms; 40 ms editing pulse applied at 2.6 ppm; 256 averages). Press spectra were analyzed using fully automated, standard curve fitting software, LCModel. MEGA-PRESS spectra were analyzed using the spectral analysis program CSX. Results: There were no statistically significant differences in NAAG and GABA levels between groups. Higher levels of CS NAAG were associated with greater negative symptom severity. Lower levels of CS GABA were associated with greater positive symptom severity. MF Glutamate/GABA ratios were positively correlated with performance on RBANS attention tests in healthy subjects but negatively correlated with performance on RBANS attention tests in patients. There was a trend for decreased MF glutamate+glutamine in schizophrenia, consistent with prior 1H-MRS studies. Conclusion: The association between higher NAAG and greater negative symptoms is consistent with NMDAR hypofunction in schizophrenia. The association between lower GABA and greater positive symptoms is consistent with altered inhibitory function in schizophrenia. Altered MF glutamate/GABA tone may be related to attention processing impairments in schizophrenia. This ongoing study illustrates the feasibility of in vivo measurements of GABA, glutamate, and NAAG in a single MR scan session.
ID: 979880

HERV-W RELATED RNA IN CEREBROSPINAL FLUID AND KYNURENIC ACID LEVELS IN PATIENTS WITH FIRST-EPISODE SCHIZOPHRENIA SPECTRUM DISORDER - IMPACT ON BRAIN CHANGES

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Background: Several studies identified transcripts containing retroviral sequences of endogenous origin, including those related to the W family of human endogenous retroviruses (ie HERV-W), in cerebrospinal fluids

(CSF) and sera samples of patients with first-episode schizophrenia-related psychosis. The aim of the present study was to investigate how the presence of HERV-W transcripts in CSF relates to CSF-levels of the neuroprotective compound kynurenic acid and to structural gray and white matter changes. Methods: In CSF samples from 49 patients with first episode schizophrenia spectrum disorder and 16 comparison subjects, HERV-W gag transcripts and levels of the neuroprotective tryptophan metabolite, kynurenic acid were analyzed by PCR and HPLC, respectively. Gray and white matter densities in patients were investigated by magnetic resonance imaging. Results: HERV-W gag transcripts were detected in the CSFs of 27 patients, but only in a single comparison subject. HERV-W positive patients showed significantly lower CSF-levels of kynurenic acid than HERV-W negative patients and controls. HERV-W positive patients exhibited significantly reduced densities in the right temporal lobe, hippocampus, internal capsule, cerebellum and tegmentum as compared to HERV-W negative patients. Conclusion: Our findings confirm aberrant transcription of genomic regions harboring HERV-W in first-episode schizophrenia. The association between detection of such transcripts in CSF and discrete density reductions suggest a relation to pathological mechanisms involved in density loss. The present findings suggest that kynurenic acid contributes to protection from such loss and are, thus, in line with hypotheses implicating glutamate-mediated processes in density loss during the early stages of schizophrenia.
ID: 983955

STRIATAL DOPAMINE SYNTHESIS CAPACITY IN NON-PSYCHOTIC INDIVIDUALS WITH AUDITORY VERBAL HALLUCINATIONS

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Background: Elevated striatal dopamine synthesis capacity is thought to be fundamental to the pathophysiology of schizophrenia, and has been linked to delusion formation in the form of the aberrant salience hypothesis. Psychosis, however, consists of several symptoms: delusions, auditory verbal hallucinations (AVH), catatonia and formal thought disorder. While the aberrant salience model provides an excellent explanation of how a hyperdopaminergic state can lead to delusions, it is less able to explain the occurrence of AVH. It is currently unclear if AVH are associated with increased dopamine metabolism. As very few patients experience AVH in the absence of other psychotic symptoms, the specific association between dopamine hyperactivity and AVH has never been assessed. Although AVH are characteristic of psychotic disorders, they are not specific for these disorders. Approximately 4% of otherwise healthy subjects also experience regular AVH. These healthy subjects experience similar AVH to psychotic patients, although the frequency is generally lower and the content more positive. The fact that they have never used antipsychotic medication makes them an ideal subgroup to investigate the isolated form of AVH. In this study we measured the synthesis of dopamine (as indexed by 18F-DOPA uptake) in the striatum of healthy subjects with AVH. Methods: Subjects were recruited from a cohort of healthy subjects with isolated AVH. The subjects were free of psychiatric and somatic pathology and experienced AVH at least once a week. In vivo striatal dopamine synthesis capacity was examined using [18F]-DOPA positron emission tomography scans. Striatal dopamine synthesis capacity in hallucinating subjects, as indexed by Ki value, was compared with matched control subjects of equal age and sex who had already been scanned with the 18F-DOPA protocol. Results: In an analysis of preliminary data, we found Ki values were higher in the AVH subjects compared with age-matched controls in whole striatum and for its associative, limbic and sensorimotor subdivisions (see table). Conclusion: Our current sample of healthy subjects with AVH show increased striatal dopamine synthesis capacity in a manner analogous to the increases found in patients with schizophrenia. AVH may to be related to, and are possibly the result of, increased dopamine metabolism.

	Whole striatum Ki value min-1 (mean ± SD)	Associative striatum Ki value min-1 (mean ± SD)	Limbic striatum Ki value min-1 (mean ± SD)	Sensorimotor striatum Ki value min-1 (mean ± SD)
Hallucinators $n = 4$	.013 ± .001	.013 ± .001	.013 ± .001	.015 ± .002
Controls $n = 3$	.011 ± .001	.011 ± .001	.011 ± .001	.013 ± .001

ID: 978423

PREDICTING DOPAMINE D2 RECEPTOR OCCUPANCY FOLLOWING ANTIPSYCHOTIC DOSE REDUCTION: A PILOT PET STUDY

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Background: Population pharmacokinetics can predict antipsychotic plasma concentration at a given time point prior to an actual dosage change. This in turn can be used to estimate a corresponding dopamine D2 receptor occupancy, using a close link between peripheral and central pharmacokinetics. However, this two-step prediction has never been tested. Methods: Eight subjects with schizophrenia (DSM-IV) (mean ± SD age = 58 ± 8) participated in the study. Two plasma samples for the measurement of risperidone and 9-hydroxyrisperidone concentrations were collected at separate given time points. Following a dose reduction of risperidone, subjects received a [11C]raclopride positron emission tomography scan for the calculation of D2 receptor occupancy. A plasma concentration associated with the dosage change was predicted, using the two samples with a population pharmacokinetic model, using NONMEM. D2 occupancy level was then estimated, by incorporating the predicted plasma concentration into a hyperbole saturation model. Accuracy of the predictions was then evaluated. Results: The mean (95% CI) prediction error and root squared prediction error (%) for the prediction of D2 receptor occupancy were as low as −4.6 (−13.5–4.4) and 9.9 (3.9–15.8), respectively. The observed and predicted dopamine D2 receptor occupancy levels were highly correlated ($r = .71$, $P = .047$). Conclusion: Our preliminary data suggest that D2 occupancy at a given time, following a dosage change, can be predicted from plasma concentrations collected at different time points in advance. In turn, these results may be used to predict the oral dose to achieve the target D2 receptor occupancy in the treatment of schizophrenia.
ID: 977515

FOCAL MICROGLIAL ACTIVATION IN SCHIZOPHRENIA

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Background: The pathophysiology of gray matter loss in schizophrenia has not been clarified, but it is thought to be secondary to neuronal damage, which in turn is closely associated with microglial activation. Recently, microglial activation has been reported in schizophrenia using (*R*)-[^{11}C]PK11195 and positron emission tomography (PET) (van Berckel et al 2008; Doorduin et al 2009). The purpose of this study was to compare the regional distribution of (*R*)-[^{11}C]PK11195 binding in schizophrenia patients with that in healthy controls. Methods: Binding potential (BP_{ND}) of (*R*)-[^{11}C]PK11195 was assessed in ten recent onset schizophrenia patients (age: 24 ± 2 years) and ten age and sex matched controls (age: 23 ± 4 years). Psychopathology was measured using the Positive and Negative Syndrome Scale (PANSS). Dynamic (*R*)-[^{11}C]PK11195 scans were acquired using an ECAT EXACT HR+ scanner. Parametric BP_{ND} maps were generated using receptor parametric mapping and the reference tissue was extracted using supervised cluster analysis. Subsequently, gray matter regions of interest (ROIs) were delineated on a T1-weighted structural MRI scan using an automatic procedure, resulting in the following regions: frontal, temporal, parietal and occipital cortex, and cerebellum. Statistical analysis was performed with SPSS General Linear Model multivariate design with ROIs as dependent variables and age as covariate. In addition, Pearson product-moment correlation coefficient was used to assess the correlation between age and regional BP_{ND}. Results: Schizophrenia patients showed increased (*R*)-[^{11}C]PK11195 BP_{ND} in temporal cortex only (table 1). There was a significant correlation between age and BP_{ND} in temporal and occipital cortex, and cerebellum (table 1). Conclusion: These results support the presence of microglial activation in temporal cortex of schizophrenia patients. This finding is in agreement with MRI studies indicating profound gray matter loss in the temporal cortex of schizophrenia patients.

Table 1. Regional (*R*)-[^{11}C]PK11195 BP_{ND} values and Pearson product-moment correlations

Region	Controls	Schizophrenia	General Linear Model		Pearson correlation	
	Mean BP_{ND} ± SD	Mean BP_{ND} ± SD	*F*	*P*	*r*	*P*
Frontal	.124 ± .066	.102 ± .057	.871	.364	.318	.172
Temporal	.087 ± .062	.147 ± .044	6.924	.018*	.540	.014*
Parietal	.139 ± .080	.129 ± .048	.360	.556	.348	.132
Occipital	.269 ± .083	.253 ± .080	.327	.575	.548	.012*
Cerebellum	.190 ± .066	.191 ± .119	.030	.864	.492	.028*

*$P = <.05$

ID: 979188

DISTURBANCES IN THE REWARD PROCESSES IN SCHIZOPHRENIA AND ITS RELATION TO DOPAMINE ACTIVITY: A LONGITUDINAL STUDY IN ANTIPSYCHOTIC-NAIVE FIRST-EPISODE SCHIZOPHRENIA PATIENTS

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Background: We plan to examine how reward processing abnormalities are related to striatal dopamine D_2/D_3 binding potentials (BP_p) and psychopathology in antipsychotic-naïve first-episode schizophrenia patients. Furthermore, we will explore how these disturbances are modulated by interventions with the D_2/D_3 antagonist amisulpride. Methods: The study is designed as a 6 week case-control follow-up study of 30 antipsychotic-naïve patients with schizophrenia and 30 matched healthy controls. The participants are examined at baseline and at 6 weeks follow up with an extensive battery of assessments, including Single Photon Emission Computed Tomography (SPECT), structural and functional Magnetic Resonance Imaging (fMRI), and neurocognitive- and psychophysiological testing. Patients are further examined with clinical rating scales to measure psychopathology, the level of function and subjective well-being. After baseline examinations the patients are treated with flexible doses of amisulpride according to their clinical condition. In order to examine the reward disturbances, fMRI is performed with a variant of the monetary incentive delay task. We use SPECT and ^{123}IBZM (123 labeled iodbenzamid) as radioligand to examine the BP of dopamine D_2/D_3 receptors in the striatum. 175 MBq ^{123}IBZM is administered over 4 hours using a steady state bolus-infusions-paradigm, and the participants are scanned for 2 × 30 minutes in a two headed Siemens Symbia-scanner. Plasma parent compound is determined by equilibrium dialysis and the BioTrap method. Matlab is used for the co-registration between MRI and SPECT images. Predefined volumes of interest (VOIs) will subsequently be identified automatically on the MRI image and directly transferred to the co-registered SPECT image. Results: Data collecting and analyses are ongoing. Currently we have fMRI and SPECT data from 9 patients at baseline, 7 at follow-up and 6 healthy controls. We find a decrease in the total PANSS scores and a decrease in striatal dopamine D_2/D_3BP_p after treatment. Conclusion: Our preliminary data suggest that blockade of striatal D_2/D_3 receptors with amisulpride has a positive correlation with treatment effect on positive psychotic symptoms. We further expect to find a decrease in salience abnormality and an individual narrow therapeutic window of D_2/D_3 blockade with a therapeutic effect on the positive symptoms without additional development of negative symptoms.

ID: 976446

14. Neuroimaging, Functional

BRAIN ASYMMETRY FOR EMOTIONAL PROSODY IN SCHIZOPHRENIA: CAUSAL RELATIONS INVESTIGATED WITH TMS

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Background: Emotional prosody (EP) is a key factor of social cognition, which is often impaired in schizophrenia patients. Previous studies revealed impaired processing of EP in schizophrenia patients. Further, less lateralization in schizophrenia has been demonstrated. This has been associated with impaired task performance, but also with compensatory mechanisms. We investigated whether schizophrenia patients as compared to controls demonstrated a difference in performance on an EP-task, using fMRI-guided Transcranial Magnetic Stimulation (TMS). Methods: Nine schizophrenia patients and ten controls performed an EP-task during fMRI. Subjects attended to the affective intonation and had to ignore the neutral content of the sentences. TMS with BrainVoyager neuronavigation was applied to reduce excitability of areas that were active during EP processing in fMRI (left and right superior temporal gyrus (STG)). TMS was performed for 20 minutes on 1 Hz. After stimulation, the subjects performed the EP-task again. In addition, a baseline measurement without TMS was included. Results (reaction time (RT) and accuracy) were analyzed with repeated measures analysis of variance (ANOVA). Results: For the emotion sad a trend for stimulation site (left, right or baseline) ($P = .09$) was found. Post-hoc analysis showed that RT for patients was higher during baseline. After TMS (left and right), RT was similar for patients and controls, while accuracy only improved in patients after TMS left ($P = .09$). Controls were more accurate after TMS on the right STG. For the accuracy of the emotion happy, there was a trend for stimulation site ($P = .09$), caused by less accurate responding during baseline measurement compared to the improved accuracy after left stimulation ($P = .01$), both in patients and controls. Conclusion: For the emotion happy, TMS on the left STG was related to improved task performance on the EP task in patients. This might be due to calosal disinhibition of the right hemisphere by the left hemisphere, since EP is hypothesized to be primarily processed in the right hemisphere. For the emotion sad, TMS caused opposing effects on accuracy in patients and controls depending on stimulation site. These preliminary findings support the theory that a different lateralization pattern may contribute to symptomatology in schizophrenia.
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ID: 979513

EMOTION, PLEASURE AND REWARD IN SCHIZOPHRENIA: RELATIONSHIPS TO INDIVIDUAL DIFFERENCES IN ANHEDONIA

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Background: Theories on the mechanisms that convey risk for the development of schizophrenia have frequently focused on a key role for anhedonia - the putative inability to experience pleasure. Clinical experience supports the centrality of ''anhedonia'' in the phenomenology of schizophrenia, as many patients have difficulty describing pleasures that they experience in their lives. However, a growing body of empirical research suggests that some components of ''in-the-moment'' emotional experience in schizophrenia are surprisingly intact, even those associated with positive stimuli. However, recent advances in neurobiological and computational theories of pleasure and reward processing provides a framework in which to understand disassociations among different components of hedonic capacity, including important distinctions between the neural systems that support the experience of pleasure (ie, ''consummatory pleasure'') and those that support the anticipation of pleasure. Methods: We overview data from a series of new behavioral and imaging studies designed to examine the integrity of both self-reports and neural correlates of the experience of positive events and/or rewarding stimuli in schizophrenia, as well as the anticipation of such events when they are not present in the current environment. Results: This research has shown that as a group, individuals with schizophrenia show relatively intact self reports of consummatory pleasure and intact modulation of the neural systems thought to support the experience of emotion and reward, including amygdala, insula, medial prefrontal cortex, and orbital frontal cortex. However, the responsivity of these neural systems varies as a function of the severity of anhedonia symptoms in individuals with schizophrenia, suggesting that group level analyses may not always provide an accurate or comprehensive picture of the neurobiological deficits associated with reduced hedonic capacity in this illness. Further, our work suggests that there may be important distinctions between deficits in the experience and anticipation of primary reinforcers in schizophrenia (eg, juice) vs secondary reinforcers (eg, money) that require the maintenance of more abstract representations. Conclusion: Taken together, these results suggest the need for a greater emphasis on understanding the heterogeneity of schizophrenia symptoms in research on the psychological and neural mechanisms of pleasure and motivation in this illness.
ID: 951747

MULTISCALE STATISTICAL ANALYSIS OF RESTING STATE BOLD TIME SERIES IN SCHIZOPHRENIA

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Background: Brain function in schizophrenia is characterized by a complex combination of abnormal activity and connectivity. Spontaneous low frequency fluctuations in brain activity can be measured at rest using fMRI. Disease-related changes in BOLD time series derived from sets of functional brain regions can be characterized using univariate, bivariate, and multivariate or network-based methods. To date it has remained unclear to what degree these three approaches provide independent or redundant information. Methods: Here we study functional activity and connectivity in a group of 29 patients and 29 controls who underwent a 6-minutes resting-fMRI scan at 3T with eyes closed. To reduce data dimensionality, we parcellated the brain into 90 anatomical regions (AAL atlas) from which regional mean time series were extracted and wavelet transformed (.06–.125Hz). Results: Univariate measures of brain activity, including range, variance, and entropy, calculated on regional wavelet time series, were unaltered in the schizophrenia population ($P > .26$). In contrast, average functional association between regions (based on bivariate 90 × 90 correlation or spectral coherence matrices) was significantly decreased in the patient cohort ($P < 9e\text{-}6$). To investigate specific patterns of functional connectivity that were independent of the mean, we used multivariate methods based on graph theory. We thresholded the correlation over the full range of correlation values to create networks of varying densities: sparse networks were created by using a high threshold and dense networks using a low threshold. Graph metrics were computed at all connection densities, and the subsequent curves (graph metric vs. connection density) were evaluated using functional data analysis (FDA). FDA provides a principled statistical

framework in which to compare two groups of curves, and has several advantages over recently proposed methods: it retains the information from the full network-density curve and does not require the choice of an arbitrary threshold or small range of thresholds over which to assess network characteristics. Using FDA, we found that several network properties including percolation ($P = .03$), clustering and local efficiency ($P = 5e\text{-}4$), and global efficiency ($P = .01$) significantly differed between patients and controls. Conclusion: In combination, our work indicates that univariate, bivariate, and multivariate approaches can each be used to assess distinct alterations in brain activity and connectivity in schizophrenia.
ID: 995672

BEHAVIORAL ADJUSTMENTS IN RESPONSE TO ERROR COMMISSION AND TO CUES PREDICTING ERROR LIKELIHOOD: DACC ACTIVITY MODULATION IN SCHIZOPHRENIA

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Background: Individuals with schizophrenia (SCZ) show deficits adjusting their performance to changing demands. Detecting an error in performance is critical for evaluative functions that allow adjusting behavior to optimize outcomes. Previous research shows activity in the dorsal anterior cingulate cortex (dACC) signals error commission, and that the magnitude of this response predicts behavioral adjustments (ie posterror slowing). A large body of literature suggests dACC response to error-commission is diminished in SCZ compared to healthy controls (HC). However, evidence regarding behavioral adjustments is mixed. It is unclear whether deficits adjusting performance can be directly traced to impairments detecting an error, or to more subtle alterations in self-regulation. Methods: We examined error-related behavioral adjustments (posterror slowing) and brain activity (using fMRI) during a change-signal task in SCZ and HC. By using two difficulty conditions, we were able to compare behavioral adjustments and patterns of brain activity not only in response to error commission, but also to cues that predict the likelihood of committing an error. We estimated BOLD responses using a general linear model including accuracy and error-likelihood (high, low) as regressors. To test the hypothesis that SCZ will show diminished brain activation responses to error-commission, we conducted ANOVAs using accuracy and error-likelihood as within-subject factors and group as a between-subject factor. To test the hypothesis that SCZ will fail to show a modulation of brain activation according to implicit cues that predict error-likelihood, we focused on correct Go-trials to eliminate signals associated with error-commission or with the need to modify action plans. To examine behavioral effects of accuracy on subsequent trials, we compared reaction times in correct trials following an error in change trial or a correct response. Results: Compromises in error-based behavioral adjustments are indicated by deficits slowing responses after incorrect trials. Diminished error related responses in dACC suggest alterations in the proper signaling of error commission. A negative correlation between dACC activity modulation between conditions and behavioral adjustments suggest alterations in self regulation involving the ability to increase cognitive control in demanding tasks. Conclusion: Alterations in the modulation of dACC responses to implicit environmental contingencies may relate to deficits adjusting behavior in SCZ.
ID: 979074

EFFECTS OF CANNABIDIOL AND DELTA-9-TETRAHYDROCANNABINOL DURING VISUAL ODDBALL SALIENCE PROCESSING: IMPLICATIONS FOR PSYCHOSIS AND ITS TREATMENT

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Background: There is increasing interest in the potential antipsychotic effect of Cannabidiol (CBD), one of the main ingredients in Cannabis. But, how CBD may act in the brain to exert its antipsychotic effect is unclear. Psychotic symptoms have been hypothesized to be related to the aberrant attribution of salience to what would otherwise be insignificant experiences or stimuli. Recent evidence suggests that CBD can attenuate the incentive salience of drug and food cues under the influence of delta-9-tetrahydrocannabinol (delta-9-THC), the other main psychoactive ingredient of cannabis, by reducing the attentional bias to these stimuli in man, complementing evidence from animal studies. However, whether cannabidiol modulates the neural correlates of salience has not been examined in man. Methods: Employing a double-blind, repeated measures, within subject design and oral challenge with 10 mg of delta-9-THC, 600 mg of CBD or placebo in 15 healthy volunteers, we first examined whether delta-9-THC modulates the neural correlates of visual oddball salience detection in man. We then examined the effects of CBD on the salience detection network and tested whether these effects were opposite to the effects of delta-9-THC. Results: During the processing of oddball stimuli, delta-9-THC attenuated the BOLD response in the dorsal striatum and hippocampus, but augmented it in the prefrontal cortex, relative to the placebo condition. Effect of delta-9-THC in the dorsal striatum was negatively correlated with the severity of the psychotic symptoms it induced as well as its effect on aberrant attribution of salience, as indicated by a stronger effect on response latency to standard stimuli relative to oddball stimuli. In contrast, CBD augmented striatal and hippocampal activation but attenuated prefrontal activation, relative to the placebo condition and this was associated with faster response latency to both oddball and standard stimuli. Delta-9-THC and CBD also had opposite effects on the functional connectivity between these brain regions. Conclusion: The effects of delta-9-THC on prefrontal, striatal and medial temporal activity and connectivity during salience processing may underlie its effects on psychotic symptoms and the risk of psychotic disorders. The antipsychotic effects of CBD may be related to its effects on striatal, medial temporal and prefrontal cortical activation that are opposite to that of delta-9-THC.
ID: 979607

IMPAIRMENT OF WORKING MEMORY SYSTEM CAPACITY BY Δ9-TETRAHYDROCANNABINOL (THC): TOWARDS A CANNABINOID TREATMENT OF COGNITIVE DEFICITS IN SCHIZOPHRENIA?

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Background: Cannabis use increases the risk for developing schizophrenia. This suggests that abnormal neurotransmission of the endocannabinoid system may be involved in the pathophysiology of this psychiatric disorder. Acute effects of cannabis and the cognitive phenotype of schizophrenia are strikingly similar regarding working memory (WM) impairment. WM in schizophrenia is thought to be compromised due to neuronal inefficiency, but the role of the endocannabinoid system in WM brain function is currently unknown. To elucidate this, we investigated the effect of an acute challenge with the cannabinoid agonist Δ9-THC on WM performance

and brain function. Methods: Nineteen healthy volunteers underwent two functional MRI sessions receiving THC or placebo using a Volcano vaporizer. WM was assessed with a parametric Sternberg item-recognition task consisting of letter sets with 1, 3, 5, 7 and 9 consonants. In SPM5, brain activation was compared between placebo and THC challenge. Regions of interest were defined based on pooled group activation maps for the load 7 minus load 1 contrast. Data were corrected for THC-induced effects on perfusion as measured with Arterial Spin Labeling. Results: Performance accuracy on the WM task decreased with load in both conditions, but was significantly reduced after THC administration compared to placebo ($P < .001$). Pooled group activation maps yielded a commonly found network of activated regions, including bilateral insula, left dorsolateral prefrontal cortex, left inferior parietal gyrus, left precentral gyrus, right cerebellum and anterior cingulate cortex. This network showed higher levels of brain activation with rising WM loads ($P < .001$). Compared to placebo, however, THC attenuated the load-dependent increase in activity in the left dorsolateral prefrontal cortex for the higher WM loads ($P < .05$). Conclusion: In conclusion, THC affected the response to increasing WM load in terms of performance and of frontal brain activity which is critically involved in WM-related processes such as maintenance of information. These results suggest that THC compromises WM system capacity. This is in line with reports on WM deficits in schizophrenia which state that either efficiency or capacity of the WM system is reduced (Jansma J. M. et al, 2004, Schizophr Res., 68, 159–171). Thus, acute effects of the cannabinoid agonist Δ9-THC may mimic the WM impairment observed in schizophrenia patients. Would a cannabinoid antagonist alleviate WM deficits of schizophrenia patients?
ID: 946362

NEURAL CORRELATES OF DELUSION-PRONENESS DURING REFLECTION ON SELF AND OTHERS

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Background: Delusions are one of the most common symptoms of schizophrenia. It has been hypothesized that delusions are associated with abnormalities in social cognitive processes such as thinking about the self and others (''social reflection''). Consistent with this, recent studies have found associations between delusional beliefs and impaired social reflection (eg, theory of mind deficits). Studies in healthy controls have found that tasks requiring social reflection engage midline cortical brain areas (medial prefrontal cortex (mPFC), posterior cingulate cortex (pCC)), and lateral temporal cortical areas (superior temporal sulcus/middle temporal gyrus). Functional MRI (fMRI) studies have found evidence for aberrant activation of lateral temporal and midline cortical areas during social reflection in schizophrenia. In the current study, we used fMRI to test whether subclinical delusional ideation (''delusion proneness'') in healthy subjects is associated with abnormal midline or temporal cortical function during social reflection. Methods: Sixteen nonclinical subjects were studied. During scanning, subjects viewed single words and performed four tasks: (1) Self Reflection (SR) (does this word describe you or not?); (2) Other Reflection (OR) (does this word describe your mother or not?); (3) Affect Labeling (AL) (is this trait desirable or not?) 4) Perceptual (P) (is this word in upper or lower case?). We examined the contrast SR+OR vs. AL+P to measure activation related to social reflection using FreeSurfer software in four a priori, anatomically-defined regions of interest (ROIs): (1) mPFC, (2) pCC), (3) superior/middle temporal gyrus (s/mTG), (4) inferior parietal cortex. Delusional beliefs were assessed using the Peters et al Delusions Inventory (PDI). Results: We found significant activation during social reflection in all 4 anatomically defined ROIs in the left hemisphere. A significant inverse correlation between activation to social reflection of the left s/mTG and PDI scores was found. There were no correlations between brain activity during ''social reflection'' in the mPFC, pCC, or IPT and PDI delusion ratings. Conclusion: This finding suggests that dysfunction of neural circuitry supporting social reflection, particularly the lateral temporal cortex, is associated with subclinical delusions. Future longitudinal studies will determine whether there is a relationship between this finding and the emergence of delusions in individuals at risk for schizophrenia.
ID: 979527

CHARACTERIZATION OF EARLY POSTNATAL PHENCYCLIDINE TREATMENT AS AN ANIMAL MODEL OF SCHIZOPHRENIA BY PHARMACOLOGICAL MAGNETIC RESONANCE IMAGING.

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Background: Schizophrenia is characterized by positive and negative symptoms, and cognitive deficits. Current available treatment is successful in treating only to some degree the positive symptoms, but has limited effect on the negative symptoms and cognitive deficits. To develop novel and more effective treatment approaches, the use of valid animal disease models is essential. Growing evidence suggests that neurodevelopmental insults as well as disturbances in NMDA receptor signaling may be a predisposing or even causative factor in schizophrenia. Acute administration of phencyclidine (PCP) induces symptoms that closely resemble those of schizophrenia in healthy humans and exacerbates symptoms in patients with schizophrenia. Methods: The hypothesis for the current study was to find differences in brain activation patterns between rats treated with either vehicle or PCP (20 mg/kg, s.c.) on postnatal day 7, 9, and 11, when given an acute dose of PCP (.5 mg/kg, i.v.) after reaching adulthood. To this end, we applied pharmacological MRI (phMRI) to examine the brain circuitry underlying the psychotomimetic action of PCP in the isoflurane anesthetized rat, and investigated how these functional changes might differ between "schizophrenic" ($n = 9$) and control ($n = 9$) male rats. Results: Acute administration of PCP (.5 mg/kg i.v.) produced robust and sustained positive relative cerebral blood volume (rCBV) changes in discrete frontal, cortical, hippocampal, and limbic brain regions in both groups of rats compared to acute treatment with vehicle ($n = 6$). Preliminary analysis suggests that animals previously exposed to early postnatal PCP treatment, compared to vehicle treatment, are hypersensitive to acute PCP exposure after reaching adulthood. Specifically, in brain regions associated with schizophrenia, namely the medial prefrontal cortex, nucleus accumbens and hippocampus these rats showed a tendency towards hypersensitivity compared to the controls. Importantly, the acute treatment did not have any significant effect on physiological parameters such as respiration and blood pressure. Conclusion: The present results from the ongoing data analysis suggest that early postnatal PCP treatment induces enduring deficits in the neural circuitry pathways involving NMDA receptor signaling in rats.
ID: 978206

ALTERED FUNCTIONAL AND STRUCTURAL BRAIN DEVELOPMENTAL TRAJECTORIES IN YOUTH AT CLINICAL RISK FOR PSYCHOSIS

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Background: Schizophrenia is associated with abnormalities in several key brain systems, including prefrontal and medial temporal lobe regions involved in working memory and declarative memory, respectively. Imaging techniques can help to clarify the timing and course of these changes across stages of the disorder and in relation to critical periods of brain development. Methods: Adolescents and young adults (aged 12–32) who met criteria for a prodromal risk syndrome, along with age- and gender-matched controls, were evaluated with fMRI, MRI and DTI at baseline assessment. BOLD signal was acquired during a verbal working memory task with varying degrees of memory load. Analyses focused on the relationships of imaging parameters with age, contrasting the age regressions between cases and controls. Results: While both patients and controls showed significant negative correlations between cortical gray matter density and age, this relationship was significantly more pronounced among patients, specifically in prefrontal cortex. Further, whereas controls showed increases in fractional anisotropy (FA) with age in several white matter tracts, including the medial temporal lobe, patients showed an absence of age-related increases in FA in these regions, which predicted a worsening clinical course. In fMRI analyses, both patients and controls activated a distributed set of brain areas during the working memory task. However, the slopes of the age-activation relationship differed significantly between patients and controls, specifically in prefrontal and parietal regions. Controls showed the predicted negative association between activation and age, while patients showed increasing activation with age. This pattern was accentuated in the prefrontal region among subjects who ultimately converted to psychosis. Conclusion: High-risk subjects show an abnormal pattern of age-related variation in functional and structural brain parameters. Although these findings must be confirmed by tracking change within subjects over time, the overall pattern of results is consistent with the view that altered adolescent neurodevelopmental processes, including synaptic pruning and myelination, may play a role in the pathophysiology of schizophrenia. The anatomical changes may reflect disruptions in the fine-tuning and connectivity of cortical networks, leading to more diffuse physiological activity in these brain systems, perhaps reflecting less functional specialization and integration.
ID: 978598

COGNITIVE AND IMAGING BIOMARKERS FOR PRO-COGNITIVE THERAPY DEVELOPMENT: CNTRICS II

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Background: Translating methods from basic cognitive neuroscience into tools to help focus and accelerate treatment development for cognitive and emotional processing deficits in schizophrenia and other disorders has become a high priority, and has been the focus on the CNTRICS initiative. During the first phase of this effort a series of consensus based meetings focused on identifying cognitive systems to be targeted, identified valid tasks for measuring the function of these systems and layed out a pathway for optimizing these measures for use in treatment development. Subsequent NIMH supported studies have pursued this agenda aggressively with a set of behavioral measures. One focus of the present round of CNTRICS is to develop a set of Imaging and related physiological correlates of impaired cognitive and emotional processing that may be used as biomarkers for treatment development and other purposes including risk prediction and personalized medicine. Methods: Two consensus based meetings and a series of web based surveys were held in which (1) the state of the art of understanding of the physiological basis of fMRI, EEG, MEG and TMS based measures was explored together with issues of robustness, reliability and practicality of administration were discussed in detail and an agenda for future development in these methods laid out, and (2) a set of Imaging Biomarkers measuring the function of neural systems supporting the core cognitive systems previously identified by CNTRICS were identified and recommended for further development. Results: A set of EEG, rTMS and fMRI paradigms that tap a range of cognitive and emotional systems impaired in schizophrenia, from visual perceptual processing, attention and memory to emotion identification and regulation will be described, along with technical and statistical approaches that will need to be pursued to validate and optimize these measures, as has been done for some CNTRICS behavioral measures. Initial empirical data on sensitivity and reliability for three measures that are in the processing of being developed into imaging biomarkers will be presented. Conclusion: The results of this effort suggest that valid, practical and reliable imaging based measures of neural activity are feasible and in some cases close to being ready for use in focusing and accelerating the process of treatment development for impaired cognitive and emotional processing in common mental disorders such as schizophrenia.
ID: 977375

THE NEUROFUNCTIONAL SUBSTRATES OF IMPAIRED HIGHER COGNITION IN SCHIZOPHRENIA

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Background: People with schizophrenia have a range of higher cognitive and emotional deficits which contribute to a substantial degree to the functional deficits and disability that they experience in their lives. Since this aspect of schizophrenia is entirely refractory to presently available treatments, understanding the neurobiology of impaired cognition and emotion in schizophrenia has become a critical imperative. Methods: In this talk I will present new data from a mulit-investigator collaborative study using functional MRI and ERP's in a sample of 30 early-course-of-illness schizophrenia patients and 30 control subjects. The study was designed to clarify the contributions of altered interactions between prefrontal cortical cognitive control related circuitry and posterior regions involved in attentional selection, memory encoding and language comprehension abnormalities in schizophrenia. Each subject completed two ERP studies (measuring response selection via the lateralized readiness potential and local and global context effects during language comprehension via the N400) and two fMRI paradigms (a rule-based memory encoding paradigm and an emotional interference task). Behavioral and brain activity were examined within and between groups and across paradigms. Results: ERP and behavioral data are consistent with the notion that patients have normal local level priming effects and impaired controlled response selection as well as reduced sentence level (more global) context effects. Furthermore fMRI results suggest specific impairments in PFC activity related to maintaining and using rules to support strategic encoding into long term memory, and managing interference from competing emotional information in working memory. Conclusion: These data are consistent with an important role for deficits in a range of functional neural circuits, which intersect in the

PFC, underlying higher cognitive dysfunction across the range of cognitive and emotional functions investigated. The implications of this circuit based result for our understanding of cellular and molecular processes contributing to impaired cognition and emotion in schizophrenia will be discussed.
ID: 956754

EFFECTS OF MINOCYCLINE ON REGIONAL CEREBRAL BLOOD FLOW IN SCHIZOPHRENIA

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Background: Minocycline is a broad spectrum tetracycline antibiotic with growing evidence of neuroprotective effects in neurological diseases and in schizophrenia. Three recent trials reported a broad symptomatic improvement when minocycline was added to usual antipsychotic treatment in schizophrenia (Levkovitz et al, 2008; Miyaoka et al, 2007; 2008). However, the effects of minocycline in the central nervous system remain obscure and have not been systematically studied using neuroimaging techniques. We report here the effects of minocycline on regional cerebral blood flow (rCBF) in patients with schizophrenia after twelve months of a double-blind, placebo-controlled trial of minocycline added to treatment as usual. Methods: A total of 24 patients with recent-onset schizophrenia were studied. Patients were stable on medication four weeks prior to baseline and were blinded to the medication they received. They were randomized to one of two groups (minocycline 200 mg/day or placebo). Brain SPECT scans were acquired 20 minutes after the injection of 99mTc-ECD. Results: Minocycline augmentation of antipsychotic treatment significantly reduced positive and negative symptoms when compared to placebo. Significantly decreased ECD uptake in the minocycline relative to the placebo condition was evident in the right parahippocampal gyrus (Brodmann area - BA30), right frontal superior gyrus (BA11), right orbitofrontal gyrus (BA11), right frontal inferior gyrus (BA45), right temporal inferior gyrus (BA37), left orbitofrontal gyrus (BA47) and left temporal inferior gyrus (BA20). Conclusion: Although the exact mechanism of minocycline's neuroprotective action remains unclear, it may involve several different actions, including anti-inflammatory effects, anti-apoptotic properties and effects on signaling pathways. The improvement on positive and negative symptoms, simultaneously with reduced perfusion in the above mentioned brain areas, compared to placebo, may have been mediated by modulation of glutamatergic transmission after minocycline treatment. Minocycline was shown to be effective in improving symptoms in schizophrenic patients, and these effects seemed to be related to changes in perfusion in limbic regions directly affected in schizophrenia.
ID: 986885

FROM PREDICTION ERROR TO DELUSIONS

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Background: Delusions are the false and often incorrigible beliefs that can cause severe suffering in mental illness. We cannot yet explain them in terms of underlying neurobiological abnormalities. However, by drawing on recent advances in the biological, computational and psychological processes of reinforcement learning, memory, and perception it may be feasible to account for delusions in terms of cognition and brain function. Methods: A functional neuroimaging study with a follow up behavioral pharmacology investigation involving ketamine and placebo administration to healthy volunteers. Results: Prediction error brain signals in frontal cortex and striatum were predictive of the subjective effects of ketamine infusion in healthy volunteers(delusion-like ideas and perceptual aberrations)as well as the cognitive effects of ketamine on perceptual inference and memory maintenance. Conclusion: These data support the notion of an overlap between perception and belief mediated by prediction error, suggesting a framework through which we can build a mechanistic and translational understanding of these puzzling symptoms.
ID: 980015

COMT VAL158MET, HIPPOCAMPAL FUNCTION AND GENETIC RISK FOR SCHIZOPHRENIA

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Background: Abnormalities of hippocampal- parahippocampal(H-PH) physiology are prominent features of schizophrenia and have been associated with genetic risk, suggesting that susceptibility genes for schizophrenia may impact on the molecular mechanisms of H-PH function. A potential mechanism involves dopamine genetic variation, which modulates the response of H-PH neurons during episodic memory. Methods: In the present study we evaluated the potential association of Cathecol-O-Methyltransferase (COMT) Val158Met with both H-PH mediated behavior (Weschler Memory Scale, WMS) and physiology (as assessed with functional magnetic resonance imaging, fMRI) during episodic memory in patients with schizophrenia, unaffected siblings, and healthy subjects. Results: In a cohort (N = 165) of 64 patients with schizophrenia, 48 healthy siblings and 53 healthy subjects we found a main effect of diagnosis on behavioral performance at the WMS (P = .00001). Siblings had intermediate performance (mean ± SD, 91.89 ± 13.83) compared with patients (78.71 ± 15.56) and healthy subjects (105.33 ± 11.65). No effect of COMT genotype or interaction with diagnosis was observed. We then examined the effect of COMT genotype on H-HP physiology (fMRI) in another cohort (N = 108) of 39 patients with schizophrenia, 15 healthy siblings and 54 healthy subjects during performance of a task of encoding in recognition memory. We found no differences in behavioral performance at this task between siblings and healthy subjects, while patients had reduced performance compared with both groups. The fMRI data demonstrated a main effect of diagnosis on H and PH activity (healthy subjects>siblings>patients - FWE corrected P = .0001) as well as an interaction with COMT genotype in right PH activity (FWE corrected P = .05) indicating that the predicted COMT Met allele dose-effect had an opposite direction in controls compared to siblings or patients. Conclusion: Our results provide direct evidence that COMT Val158Met may impact on the molecular mechanisms of H-PH function in individuals at greater genetic risk for schizophrenia and that this effect is more penetrant at the level of intermediate phenotypes with functional imaging.
ID: 979666

INCREASED RESTING STATE CONNECTIVITY OF THE HALLUCINATION-NETWORK IN NON-PSYCHOTIC INDIVIDUALS WITH AUDITORY HALLUCINATIONS

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Background: Activation in a network of bilateral frontal and temporoparietal language-related regions has consistently been reported during the experience of auditory verbal hallucinations (AVH). At present, it is unclear whether dysfunctional activation of this network is also present in the absence of AVH, ie during resting state. To elucidate this, resting state connectivity within frontal and temporoparietal language-related regions was investigated in a group of non-psychotic individuals with AVH, as these individuals experience AVH in the absence of delusions, disorganization and medication use. Methods: Twenty-five non-psychotic subjects with AVH and 25 matched control subjects participated in this study. Resting state fMRI scans were acquired while participants kept their eyes closed but stayed awake. Scans in which AVH occurred were excluded from analysis. A separate fMRI experiment in which an independent group of non-psychotic individuals indicated the presence of AVH was conducted to identify seeds for seed regression analysis. Seeds were selected from four regions significantly activated during AVH, ie the left (1) and right (2) inferior frontal gyrus and left (3) and right (4) superior temporal gyrus. Heartbeat and respiration were measured and corrected for to minimize the influence of cardio-respiratory processes. Regression coefficients were subsequently converted to Z-transformed correlation coefficients and entered in four separate (ie one for each seed) two-sample *T* tests to enable comparisons between the groups. Results: Increased correlation between the left superior temporal gyrus and the right inferior frontal gyrus was observed in the non-psychotic individuals with AVH. No significant differences in correlations between the two groups were found for the other seed regions. Conclusion: Increased resting state connectivity between the left superior temporal and the right inferior frontal gyrus might result from sustained activation of these regions after the occurrence of a hallucination. However, since these non-psychotic individuals experience AVH with an average frequency of once every week, these results are more likely to indicate that the observed increase in resting state connectivity represents a predisposition for AVH.
ID: 949954

PROBABILISTIC REINFORCEMENT LEARNING IN SCHIZOPHRENIA: RELATIONSHIP TO AMOTIVATION

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Background: Motivational impairments are critical features of schizophrenia (SZ) that significantly impact functional capacity and are resistant to treatment. Here, we use a reinforcement learning (RL) task to examine whether impairments in using rewarding outcomes to guide future choices may contribute to amotivation in SZ. Methods: 15 individuals with SZ and 15 controls underwent two sessions of a RL task. In this task, three stimulus pairs with different probabilistic reinforcement ratios were presented, and participants learned by trial-and-error to choose the more frequently reinforced member of each pair. Correct responses earned monetary rewards. All participants completed 6 blocks of 60 learning trials, followed by a test phase in which the pairs were recombined and no feedback was given. Results: Accuracy was examined with reinforcement ratio X block X session X group ANOVAs, which revealed significant main effects of ratio ($P < .001$) and block ($P < .001$), reflecting better performance for higher reinforcement ratios and an improvement in performance over time. There was also a significant blockXsession interaction ($P < .04$), and a trend-level block × session × group interaction ($P < .1$). On post-hoc analysis, patients showed an effect of block within Session 2 ($P < .02$), but not Session 1 ($P > .3$), indicating a significant learning slope over time only in the second session. In contrast, controls showed a significant effect of block in Session 1 ($P < .001$), but not Session 2 ($P > .5$) due to ceiling performance. On the test phase, patients performed more poorly than controls overall ($P < .001$), with no main effect of session or group × session interaction. In addition, on transfer measures of positive RL (frequency of choosing the most reinforced stimulus) and negative RL (frequency of avoiding the least reinforced stimulus), patients showed impaired performance on both measures ($P < .001$), with no main effects or interactions with RL type or session. These group differences persisted even when control performance at session 1 was compared to patient performance at session 2 ($P < .002$). fMRI results and relationships to amotivation will also be presented. Conclusion: Together, these results indicate that patients showed significant learning during session 2, but not session 1, suggesting that additional practice with the task may aid in their ability to acquire probabilistic contingencies. However, even with additional practice, patients showed deficits in reinforcement learning performance as compared to controls.
ID: 979878

FUNCTIONAL CONNECTIVITY IN SCHIZOPHRENIA

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Background: Some authors have suggested the emotional disturbances as a crucial factor in the pathogenesis of AH. ICA approach is a driven-data methodology that doesn't impose a design matrix but looks for grouping voxels according their similar temporal behavior. Activated areas could be obtained selecting those ICA components related to the task. Functional connectivity looks for statistical dependence between these activated areas by comparing their time-courses. Directional effects are implicitly pointed by the asynchronism of the obtained signals. We used intra-group ICA TC correlation matrix obtained for all pair wise combination of ICA time-course and fingerprints graphics to show functional connectivity. Methods: 31 controls and 27 patients with schizophrenia and AH underwent fMRI while listened an auditory paradigm. ICA analysis was performed using Group ICA approach fMRI Toolbox, GIFT. Infomax algorithm was used to extract 21 Independent Components for controls and patients, consisting of group and individual spatial independent maps and the related time courses for both. The beta values were computed by means of multiple regression sorting criteria selecting all data-sets and correlated with box-car paradigm model. Only the task related Component of Interest by means one Sample t-test with p-value were selected. It was measured the synchronization between pairs of the ICA time-courses by means of the correlation coefficient. Hence, the correlation coefficient between two ICA time-courses i, j is defined by formula where is the position i,j of the covariance matrix for the time-courses, taking the time-courses as variables and the sampled values as independent observations of the variables. Results: Correlation analysis in the controls' group revealed a high correlation between temporal component and the other components of interest. In the patients' group we observed a low correlation between temporal component and

limbic and cerebelar component. Conclusion: Healthy subjects' task activation was characterized by high synchronization between different networks. Schizophrenic patients shown less synchronization between those networks, mainly temporal and cerebellar networks.
These between-groups connectivity differences suggest that emotional auditory processing may be disrupted in patients with schizophrenia.
ID: 978266

FMRI REVEALS DECREASED PREFRONTAL CORTICAL ENGAGEMENT DURING RESPONSE INHIBITION IN YOUTH AT CLINICAL RISK FOR DEVELOPING SCHIZOPHRENIA

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Background: Response inhibition is an important component of the cognitive control systems that support optimal cognition. Though inhibitory deficits have previously been associated with full-blown schizophrenia, the degree to which these abnormalities are present in the disease's prodrome is less well characterized. Methods: Youth with ($n = 34$) and without ($n = 73$) prodromal signs of schizophrenia (mean age = 18 years; range = 11–30 years) were included in the study. Participants underwent functional magnetic resonance imaging (fMRI), while performing a go/no-go task, a classic response inhibition paradigm (nogo event $P = .16$). Correct no-go events (correct rejections) were contrasted with correct go events (hits), in order to isolate fMRI signal reflecting response inhibition. Changes in the neurofunctional organization of inhibition across typical development were taken into account by creating age-corrected voxelwise z-scores for the prodromal group, using healthy comparison subjects as a reference. Thus, final voxelwise nogo-go maps reflect deviation from normative age expectation in prodromal youth. Results: Prodromal participants had slower reaction times to go trials ($P = .03$), and also made more omission errors, though this difference did not reach statistical significance. There were no between-group differences on either error reaction times or percent errors to nogo trials ($P > .05$). Age-corrected voxelwise between-group comparisons of nogo-go events revealed a large, mostly right hemispheric, prefrontal region in which prodomal participants showed less activation while inhibiting prepotent motor response, than their typically developing peers. The area of significant group difference ($P < .05$, corrected), comprised medial prefrontal cortex encompassing bilateral anterior cingulate gyrus, extending laterally to include portions of dorsalateral prefrontal cortex, and also extending inferiorly to include inferior frontal gyrus, insula, and striatum (BA 9/10, 32, 47). Conclusion: These data provide an account of response inhibition-related brain functioning in youth at high risk for developing schizophrenia. Decreased engagement of prefrontal regions typically expected to subserve response inhibition (eg, right inferior frontal gyrus), suggests that compromised inhibitory control in schizophrenia may predate psychosis onset.
ID: 979888

NEURAL SUBSTRATES OF EMOTION PROCESSING IN ADOLESCENTS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Emotion processing abnormalities are core features of schizophrenia, with patients demonstrating particular deficits in emotion perception (Kohler et al, 2009). However, the extent to which such deficits are present prior to the onset of overt psychosis, and the role that they might play in its development, remain unclear. Methods: The present study uses functional magnetic resonance imaging (fMRI) to compare brain activations associated with emotion processing between healthy adolescents and adolescents at clinical high risk (CHR) for psychosis. We report on preliminary results as data collection is ongoing. Participants performed an affective labeling fMRI task (Lieberman et al, 2007), during which they judged which of two linguistic labels best identified a target facial expression (Affect Labeling) or which of two faces expressed the same emotion as a target face (Affect Matching). Additional control conditions included Gender Labeling, Gender Matching, and Shape Matching and allowed for isolation of unique effects of emotion processing. In addition to whole brain activation analyses, region-of-interest (ROI) analyses focus on amygdala and ventrolateral prefrontal cortical (vlPFC) activity. Results: Whole brain group analyses revealed that, compared with controls, CHR adolescents exhibited decreased activation in lateral occipital cortex and fusiform gyrus during emotion matching relative to baseline, while they showed increased activation in middle temporal gyrus and superior parietal lobule during emotion matching relative to shape matching. ROI analyses revealed a trend toward decreased amygdala activation during emotion processing vs control (gender) conditions in CHR adolescents. Conclusion: Our findings suggest that the high-risk syndrome is characterized by patterns of abnormal neural activity during emotion processing. In particular, adolescents at CHR for psychosis showed reduced activation in regions related to holistic face processing. These findings are in line with those observed in patients with schizophrenia (Fakra et al, 2008) and may suggest that adolescents at CHR for psychosis adopt a more cognitive, feature-based approach to affect processing. We conclude that altered patterns of neural activity during facial affect processing are present prior to illness onset and that longitudinal data are needed to see whether these abnormalities are predictive of conversion to psychosis.
ID: 978604

STRESS RESPONSE CIRCUITRY DEFICITS IN SCHIZOPHRENIA: IMPACT OF NEUROENDOCRINE AND SEX EFFECTS

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Background: Arousal deficits are prominent in schizophrenia (SCZ), with a hyper-response to stress. Brain regions implicated in stress circuitry also regulate the hypothalamic-pituitary-adrenal and -gonadal systems and are sexually dimorphic brain regions [anterior cingulate gyrus (ACG), amygdala (AMG), hippocampus (HIPP), hypothalamus (HYP), medial and

orbital prefrontal cortex (mPFC and OFC)]. We provide evidence here that understanding the etiology of stress response circuitry deficits in SCZ is intimately connected with characterizing the role of neuroendocrine dysfunction and sex effects. Methods: Sample from an ongoing community population study includes 24 patients with SCZ (54% male) comparable to 31 controls (55% males) on age, handedness, parental SES, and premorbid IQ. Mood and arousal were assessed and blood collected prior and during fMRI scanning, timed to pituitary and steroid hormone responses. Subjects viewed images from the International Affective Picture System while undergoing fMRI in a 3.0T Siemens scanner. SPM8 was used to test for group by sex differences in signal intensity changes and the impact of hormones. Females were scanned timed to menstrual cycle phases. Hormones assayed included estradiol, progesterone, testosterone, cortisol, and DHEAS. Results: Males and females with SCZ exhibited significantly increased brain activity in stress response circuitry compared to sex-matched counterparts in HIPP, ACG, AMG, with males exhibiting larger effect sizes (ES) compared to male controls than among females [ES = .13–.44]. Males also exhibited significantly increased prefrontal brain activity and hypoactivation of the HYP [ES = .34–.55]. Increased brain activity in stress response circuitry, in males with SCZ, was significantly associated with a high cortisol:DHEAS ratio and testosterone levels, and in females, with gonadal hormone abnormalities. Conclusion: Stress response circuitry activation is disrupted in SCZ in men and women, with men exhibiting greater deficits. Stress response circuitry deficits are significantly associated with hormonal dysregulation and vary by sex. Given that deficits in stress response have been found prior to psychosis onset, studying the links between deficits in neuroendocrine systems, stress response circuitry, and sex effects in SCZ will provide a clearer understanding of the development of brain abnormalities in this circuitry and implications for understanding the nature of the illness.
ID: 979245

AN INVESTIGATION OF THE NEURAL CORRELATES OF IMPAIRED OLFACTORY IDENTIFICATION ABILITY IN MICROSMIC AND NORMOSMIC PATIENTS WITH FIRST EPISODE PSYCHOSIS

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Background: While it is known that a proportion of patients with psychotic disorders is impaired on tests of olfactory processing, the neural underpinnings of these deficits have not been delineated. The purpose of this study was to use BOLD FMRI to compare the functional topography of the olfactory system in healthy control subjects to two groups of patients with first episode psychosis: those with olfactory identification deficits (microsmic) and those whose olfactory status was normal (normosmic). Methods: Twenty seven subjects participated in this study (15 healthy control subjects and 12 patients). All were between the ages of 19 and 26 years of age, had no contraindications to MRI scanning and no history of facial fracture or nasal injury. Olfactory functioning was measured using the University of Pennsylvania Smell Identification Test (UPSIT) and patients were stratified into olfactory subgroups based on available norms. The subjects were presented with five different odorants and were asked to rate these for hedonicity and familiarity using 10cm visual analogue scales (VAS). Those same 5 odorants were delivered to the subjects by way of an olfactometer while they underwent an FMRI scan. Results: No differences were noted between patients and controls on any of the VAS measures. FMRI Analysis was carried out using a region of interest (ROI) approach on brain regions known to underlie olfactory processing. On odors that were rated as ''pleasant'', patients and control subjects engaged similar brain regions. When presented with odorants rated ''unpleasant'', different patterns of brain activation were noted between diagnostic groups. When comparing the normosmic (n = 7) and microsmic (n = 5) patient groups, similar patterns of olfactory brain region activation were observed during the presentation of the odorant rated as most ''pleasant'' whereas different patterns were noted for all other odorants. Conclusion: While small sample size limits the conclusions drawn by this study, the data suggest that patients with first episode psychosis engage alternate cortical and subcortical regions for olfactory processing of unpleasant odorants in comparison to control subjects. This difference is most obvious in those patients who have objective olfactory deficits. These findings are consistent with prior investigations of the neural basis of pleasant and unpleasant odorant processing in schizophrenia, but provide further evidence of regional functional brain abnormalities in microsmic patients.
ID: 979415

''BRAIN ACTIVITY DURING SOCIAL COGNITION TASKS IN INDIVIDUALS WITH SCHIZOPHRENIA, THEIR UNAFFECTED SIBLINGS, AND HEALTHY CONTROLS.''

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Background: Several studies have shown that patients with schizophrenia have impaired performance in various aspects of social cognition including emotion processing and theory of mind. Most available neuroimaging studies have compared patients and healthy controls during such mental activity because the understanding of the neural basis of social cognition might help to explain some deficits in social functioning in this group of patients. The present study examined brain activation patterns during diverse social cognition tasks in patients with schizophrenia and their nonpsychotic siblings, trying to determine whether alterations in social cognition reflect a heritable trait. Methods: Twelve patients with schizophrenia (age 31.3 ± 6.5, 1 woman), twelve non-psychotic relatives (age 31.8 ± 3.5, 6 women) and twelve matched comparison subjects (age 30.1 ± 9.2, 6 women) underwent blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging during visual presentation of different social cognition paradigms. Emotion processing was assessed with Ekman Faces Test using a target (basic emotions) and a control (gender) condition. Theory of Mind (ToM) paradigms were focused on the ability to discriminate complex mental states in Faces and Reading the Mind in the Eyes task, with a target (complex mental states) and a control (gender) condition as well. Random effects analysis was done for each task within groups, measuring signal changes between the target and control conditions of each paradigm, and later a group analysis was done. Results: Apart from activation of brain areas associated with emotional response, social cognition tasks brought about activations in language areas (left inferior frontal gyrus and structures near tempo parietal junction). The intensity of these activations was minimum in the emotional processing task and maximum in the detection of complex mental states in eyes. Activation was predominantly left and unilateral in patients. Healthy controls also activated symmetric brain structures on the right side. Unaffected siblings also showed bilateral activation in the same brain structures but with left > right structures. Conclusion: These results support the idea the schizophrenia is an illness characterized by abnormalities in the process of brain lateralization, with failure to activate right structures possibly involved in processing of emotional aspects of language.
ID: 978713

ALTERED DYNAMIC COUPLING OF LATERAL OCCIPITAL COMPLEX DURING VISUAL PERCEPTION IN SCHIZOPHRENIA

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Background: There is mounting evidence that visual perception abnormalities in schizophrenia are partly explained by a dysfunction of the lateral occipital complex (LO). We previously demonstrated that schizophrenia patients had broader topography and reduced magnitude of activity of LO. However, the functional connectivity of LO with other brain regions during visual perception has not been directly investigated in schizophrenia. Methods: Eighteen patients with schizophrenia and eighteen matched controls performed a backward masking task during functional magnetic resonance imaging (fMRI). Stimulus onset asynchronies (SOAs) were manipulated to change the level of target visibility. To examine connectivity with LO function we conducted psychophysiological interactions (PPI) analyses using a region of interest (ROI) approach. ROIs were selected from the contrast between all SOAs vs a null condition for all 36 participants. Results: The groups did not differ in overall coupling with LO. However, while healthy controls showed clear changes in coupling between LO and prefrontal and parietal regions as a function of target visibility, patients showed significantly reduced dynamic coupling with LO in the left precuneus (P = .01), left inferior frontal (P = .02), and right superior frontal gyri (P = .007). Conclusion: The increased coupling between LO and higher-level parietal and prefrontal regions during visual awareness in healthy controls likely reflects visual reentrant processing. The lack of modulation of coupling between LO and key prefrontal and parietal regions found in patients may contribute to visual perception abnormalities in schizophrenia.

Regions-of-interest selected for analysis

ROI	Size (Voxels)	Hemisphere	MNI Coordinate of Peak Voxel	Brain Regions Included in ROI
Inf parietal	5115	Left	$x = -42$ $y = -30$ $z = 44$	Inf and Sup parietal gyri (BA 7 and 40)
Lingual 1	1421	Left	$x = -4$ $y = -80$ $z = -12$	Lingual gyrus (BA 18), Cerebellum
Lingual 2	56	Left	$x = -14$ $y = -78$ $z = 4$	Lingual gyrus (BA 18)
Precuneus	52	Left	$x = -22$ $y = -66$ $z = 36$	Precuneus (BA 7)
Insula	356	Left	$x = -44$ $y = 2$ $z = -4$	Insula (BA 13)
Thalamus	303	Left	$x = -16$ $y = -18$ $z = 10$	Thalamus
Inf frontal	149	Left	$x = -52$ $y = 8$ $z = 28$	Inf frontal (BA 9)
Sup parietal	2062	Right	$x = 14$ $y = -64$ $z = 64$	Inf and Sup parietal gyri (BA 7 and 40)
Middle frontal	223	Right	$x = 34$ $y = -4$ $z = 64$	Middle frontal gyrus (BA 6)
Sup frontal	31	Right	$x = 44$ $y = 38$ $z = 30$	Sup frontal gyrus (BA 9)
Medial frontal	106	Right/Left	$x = 0$ $y = -6$ $z = 54$	Medial frontal gyrus (BA 6)

ID: 977245

USING MULTIVARIATE PATTERN ANALYSIS OF FUNCTIONAL MRI DATA AT ENCODING TO PREDICT SUBSEQUENT MEMORY IN PATIENTS AT RISK FOR PSYCHOSIS

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Background: Patients with schizophrenia and individuals at risk for schizophrenia exhibit a range of impairments in cognitive functions, including deficits in learning and memory. Research suggests that patients with schizophrenia show greater impairment in recollection of learned information than in familiarity recognition. This pattern suggests that patients may have more difficulty encoding relational information during the learning phase and may show different brain activation. Although this question has previously been investigated using traditional statistical parametric mapping approaches, a newer statistical technique - multi-voxel pattern analysis (MVPA) - is now available that may help to shed light on the neural mechanisms underlying memory disturbances in patients with and at risk for schizophrenia. Methods: This study used MVPA to evaluate patterns of functional activation during encoding in relation to subsequent memory judgments in individuals at risk of developing schizophrenia and matched healthy controls. Functional neuroimaging of 13 prodromal individuals and 18 healthy controls was acquired during the learning and recall phases of an episodic memory task. MVPA was then used to examine the neural correlates of subsequent recall during the encoding phase for each individual. Results: Initial results suggest functional activity at encoding showed a variable ability to predict subsequent memory performance for the items. Prodromal patients demonstrated an average area under the curve (AUC) of .63 (ranging from .54 to .74). Controls demonstrated an average AUC of .66 (ranging from .55 to .76). In addition, importance maps were generated for each individual to identify the voxels that contributed most strongly to prediction accuracy. Brain regions found to be involved in the prediction of subsequent memory include the left middle frontal gyrus and the parahippocampal gyrus, both of which have been implicated in memory formation. Conclusion: These results suggest that with further refinement, functional activity during encoding in conjunction with techniques such as MVPA may be useful for studying memory impairment in patients with and at risk for schizophrenia. Differences in activation as well as differential conditional predication accuracy may help to clarify functional networks underlying memory in patients at risk for schizophrenia. Future analyses will compare subjective judgments (such as remember vs know) to additionally assess memory strength.

ID: 979997

BRAIN ACTIVITY IN MEDIAL TEMPORAL REGIONS DURING ENCODING OF EMOTIONAL IMAGES IS POSITIVELY ASSOCIATED WITH MEMORY PERFORMANCE IN HEALTHY SUBJECTS, BUT NOT FOR INDIVIDUALS WITH SCHIZOPHRENIA

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Background: There has been recent increased interest in evaluating the integrity of emotion-cognition interactions in schizophrenia, with a goal of

understanding the contribution of these processes to symptoms (amotivation, anhedonia) and functional impairment. Many studies have now documented the impact of glucocorticoids, or dopamine release as a response to stimulus salience, in modulating late LTP (the proposed biological substrate for long-term memory). Research has also suggested that some of these modulatory effects are primarily seen following a period of sleep. In the current study we assessed the relationship between brain activity during encoding of emotional and neutral stimuli and memory performance following a 24-hour delay in healthy (HC) and schizophrenia (SZ) subjects. Methods: 10 SZ participants and 10 demographically matched HC subjects completed an incidental encoding task in the MR scanner on day one, and returned to complete a recognition task on day 2. Stimuli presented were positive, negative, and neutral images from the International Affective Picture System. During the recognition task subjects indicated whether they had seen the presented image previously. Brain activity during the encoding task in anatomically defined regions of interest in medial temporal lobe and inferior prefrontal cortex were correlated with later memory performance indexed by Discrimination Index Pr. Results: The relationship between brain activity during encoding and memory performance differed by diagnosis, and emotion type. For positive images, brain activity in the amygdala and parahippocampal gyri during encoding was associated with better memory performance for HC subjects, but negatively correlated for SZ subjects. For negative images, brain activity in amygdala, parahippocampal gyri, and hippocampus, as well as in frontal regions (OFC, SFG, IFG) during encoding was positively associated with memory performance in HC subjects, but negatively with memory performance in SZ subjects. For neutral stimuli, activity in the OFC, hippocampus and right PHG during encoding were positively associated with memory in performance in both HC and SZ subjects. Conclusion: These data indicate that brain activity during encoding of stimuli is associated with different performance outcomes in HC and SZ subjects, and suggest that different biological mechanisms may contribute to long-term memory performance in these populations.
ID: 979847

ELEVATED FUNCTIONAL COUPLING ALONG A CORTICOSTRIATAL LOOP AND THE MECHANISM OF AUDITORY/VERBAL HALLUCINATIONS IN PATIENTS WITH SCHIZOPHRENIA

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Background: The pathophysiology of auditory/verbal hallucinations (AVHs) remains poorly understood. Higher levels of inter-region functional coordination can facilitate emergence of neural activity as conscious percepts. We consequently tested the hypothesis that AVHs arise from elevated functional coordination across a speech processing network. Methods: Two fMRI studies will be described. The first study considered BOLD activity time-course associated with AVHs signaled via button-presses by 11 patients with schizophrenia. These data were contrasted with corresponding BOLD activity time-course due to random button pressing by 10 similarly diagnosed, nonhallucinating patients. In the second study, functional coordination was assessed as resting state functional connectivity (FC) between cortical and subcortical region computed from BOLD inter-region correlations. Thirty-two patients with schizophrenia reporting AVHs, 24 similarly diagnosed patients without AVHs, and 23 healthy controls were studied. FC was computed relative to a bilateral Wernicke's seed region and a secondary seed region within the left inferior frontal gyrus (IFG). Results: For the activity time-course study, an elevated between-subject correlation ($R = .78$) linking BOLD activity in the left IFG and right posterior temporal regions were detected a full 9 seconds prior to motorically signaled events for hallucinators when BOLD activity was at baseline. These inter-region BOLD correlations were negative ($R = -.25$) at the same time-interval when assessed relative to random button press behavior by nonhallucinating patients. These two regions subsequently expressed the earliest evidence of frank BOLD activation as hallucination experience emerged. In the second study, robustly elevated resting FC differentiated patients with active AVHs from patients without AVHs and healthy controls when summed along a loop incorporating the left IFG and posterior temporal areas – two regions critical to speech perception – and the putamen, which plays a central role in initiating language generation. These group differences remained even when the analysis was limited to hallucinators who experienced AVHs minimally during scanning. Conclusion: These studies suggest a synergistic process, where baseline elevations in functional coupling along a corticostriatal loop episodically spike upwards to produce conscious percepts of hallucinated speech.
ID: 977183

REWARD AND PUNISHMENT EXPECTATIONS MODIFY BEHAVIOR AND BRAIN ACTIVITY PATTERNS ASSOCIATED WITH VISUAL DISCRIMINATION

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Background: Difficult judgments made in association with an expectation of reward are likely to be faster but less accurate than those made in association with an expectation of punishment, if the punishment and reward are both contingent on accuracy. Most healthy subjects will work harder to avoid punishment than to gain reward if the subject is confronted with a trial that can be missed without ill effect and rewarded if guessed correctly; and if punishment trials guarantee a loss if in error and no gain if guessed correctly. This enhanced effort is reflected in longer response times by the subject when error likelihood is high in conjunction with threat. This study examined the response times, accuracy and fMRI BOLD responses in a pilot study to determine how error likelihood interacts with reward and punishment expectations. Methods: In this pilot study of six healthy subjects participants were presented with trials cued to indicate positive or negative outcomes. On positively cued trials subjects gained additional funds if they guessed correctly and were treated neutrally if they guessed wrong. But on negatively cued trials subjects lost funds if they guessed wrong and were treated neutrally if they guessed correctly. Two hundred trials were presented while subjects were scanned in a 3Tesla Philips Intera magnet (FM Kirby Research Center, JHMI). Results: Negative expectation trials were associated with higher accuracies on all three levels of task difficulty than positive expectation. The negative (threat) trials were also associated with a robust tendency to slow response times in conjunction with the hardest perceptual task, but the positive (reward) trials showed no shift from one level of difficulty to another. With respect to BOLD response correct trials generated by negative and positive expectations differed primarily in amygdala and anterior hippocampal regions. Negative expectations prompted larger BOLD responses in the amygdala than positive. Conclusion: This pilot study demonstrates a method for studying an individual's response to threat and reward. The marked response time slowing associated with threat is particularly relevant in light of the amplified activity responses observed in the amygdala on the negatively cued trials. This experimental design approach may be useful in studying physiological and behavioral correlates of stress.
ID: 979968

RESTING-STATE FUNCTIONAL CONNECTIVITY OF THE MEDIAL PREFRONTAL CORTEX IN SCHIZOPHRENIA AND THE DELUSION-PRONE

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Background: Functional and structural changes of the medial prefrontal cortex (mPFC), including abnormalities in mPFC functional connectivity, have been reported in schizophrenia patients and in individuals at risk for the disorder. Recent studies conducted in healthy subjects have revealed that the intrinsic functional connectivity network of the mPFC is comprised of several subsystems within the default network, including a dorsal mPFC and a ventral mPFC -based system. However, it is not yet known whether the functional coupling of each of these mPFC networks is abnormal in schizophrenia. Addressing this question involves accurately measuring functional connectivity differences as well as image characteristics in schizophrenia patients that may confound the analyses. Methods: In the current study, we examined the resting-state functional connectivity network of the mPFC in 34 DSM-IV diagnosed patients with schizophrenia and 39 demographically-matched healthy control subjects. In addition, because subclinical delusional ideation is relatively common in the general population, we assessed the frequency and intensity of delusional beliefs of the control subjects, using the Peters et al Delusions Inventory (PDI), to test whether "delusion-proneness" is associated with changes in mPFC functional connectivity similar to those seen in schizophrenia. For each subject, one 6-minute-20-second resting BOLD scans (TR = 5000 ms; TE = 30 ms; flip angle = 90; 55 × 2 mm slices/3T Tim Trio) was acquired and processed and low-frequency (<.08 Hz) fluctuations in the BOLD signal were extracted. Then within and between -group comparisons of mPFC connectivity were conducted using mPFC seed regions in whole brain analyses. Results: These comparisons revealed that functional coupling of both the dorsal and ventral mPFC with other regions of the default network was significantly greater in the controls in comparison to the schizophrenia patients. Moreover, delusion-proneness in the controls was inversely correlated with the magnitude of mPFC functional connectivity with other regions of the default network. Conclusion: Ongoing analyses will determine the relative contributions of the pathophysiology of psychosis and the potential confounds of scanning-related between-group differences to these results. If confirmed, these findings suggest that disruption of functional connections of the mPFC is associated with schizophrenia and subclinical psychosis.
ID: 979918

THE INFLUENCE OF COMBINED COGNITIVE AND SOCIAL-COGNITIVE TRAINING ON AMYGDALA RESPONSE DURING FACE EMOTION PROCESSING IN SCHIZOPHRENIA

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Background: Initial research on cognitive remediation in schizophrenia suggests that targeted cognitive and/or social-cognitive training improves behavioral performance on trained skills. However, questions remain regarding how behavioral improvement is achieved and whether these behavioral improvements can support long-lasting functional benefits. Neural plasticity models suggest that remediation techniques which restore the underlying neural mechanisms supporting cognitive and social-cognitive skills are most likely to produce optimal benefits, yet the impact of cognitive remediation on neural mechanisms is largely unknown. Methods: Here we tested whether a cognitive remediation intervention which included both cognitive and social-cognitive training would impact neural mechanisms that support social-cognition skills. Social cognition training focused on facial emotion recognition skills. It is well known that the amygdala and associated medial temporal lobe structures support emotion recognition skills. We predicted that after completion of the social cognition training, schizophrenia participants would show an increase in amygdala activity during face emotion processing. Schizophrenia participants (N = 22) were randomized to a treatment condition consisting of auditory training (AT) [Brain Fitness Program, Posit Science] plus social-cognition training (SCT) [including MindReading and Subtle Emotion Training Tool (SETT) software programs] or a placebo condition of non-specific computer games (CG). Each group completed their computer-based intervention approximately 60 minutes per day, 5 days a week for 8 weeks. Pre and post intervention assessments included two fMRI tasks of face emotion processing - a facial emotion recognition task and an automatic face emotion processing task (1-back with emotional faces) - as well as standardized behavioral tests of emotion processing (MSCEIT Perceiving Emotions). Results: FMRI results showed the predicted group by session interaction: AT+SCT participants had an increase in amygdala activity from pre to post training on both facial emotion processing tasks, whereas CG participants did not. Furthermore, among AT+SCT participants, the increase in amygdala activity when correctly identifying facial emotion, predicted behavioral improvement on the standardized behavioral test of emotion processing. Conclusion: Results indicate that social cognition training impacts neural mechanisms that support social cognition performance.
ID: 979383

DECREASED RESTING STATE CONNECTIVITY IN LIMBIC-SUBCORTICAL NETWORKS IN SCHIZOPHRENIA

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Background: Low frequency fluctuations in the blood oxygenation level dependent (BOLD) signal have provided an important new window on brain function, reflecting patterns of connectivity of putative brain networks. In previous work, we have demonstrated impaired connectivity of thalamo-cortical connectivity with the medial frontal cortex (Welsh et al, Schiz Bull, 36:713 2010). Here we extend this work in a larger cohort of patients, investigating resting state connectivity of limbic-subcortical regions. We hypothesized that schizophrenia patients would show reduced connectivity of regions involved in the integration of affect and dopamine neurotransmission. Methods: Twenty-nine adult chronic medicated schizophrenic patients (SCZ; 39.8 ± 10.5 years, M:F 21:7) and 18 healthy controls (HC; 36.7 ± 10.4 years, M:F 11:8) underwent 6 minutes of T2* sensitive BOLD imaging, with simultaneous physiology measurement for correction. Subjects were instructed to rest quietly and maintain fixation on a crosshair. Seed voxels were placed in the ventral tegmental area (VTA), caudate nucleus head (caud), nucleus accumbens (NA) and amygdala. Regional correlations were calculated using published methods. Results: SCZ showed less positive connectivity than HC in the left posterior thalamus with the following seeds: R VTA (Z = 3.88 k = 10), L VTA (Z = 3.96 k = 27), R caud (Z = 4.51 k = 56) and L Caud (Z = 3.87 k = 35). Caudate seeds

also demonstrated less connectivity with R and L frontal poles. The R amygdala seed showed reduced connectivity with the R anterior insula (Z = 4.7 k = 288), whereas L amygdala showed reduced connectivity with R post-central gyrus (Z = 4.5 k = 114). Schizophrenia patients did not show significantly greater connectivity than controls in any region. Conclusion: These findings provide additional evidence for impaired connectivity of the thalamus in schizophrenia, a key integrative node for brain dynamics. Impaired thalamic connectivity with regions involved in dopamine transmission (VTA, caudate) may have implications for dopaminergic dysregulation. The lack of connectivity between the amygdala and insula may reflect impairments in emotional regulation known to characterize schizophrenia.
Supported by: R01-MH64148 and the Boledovich Schizophrenia Research Fund.
ID: 979886

DOPAMINERGIC DYSFUNCTION: ITS POTENTIAL AS A BIOMARKER FOR SCHIZOPHRENIA RISK AND LINKS TO SALIENCE DYSREGULATION

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Background: The revised dopamine hypothesis proposes that dopamine dysfunction leads to the aberrant attribution of salience to stimuli, which in turn underlies the development of psychosis in schizophrenia. Supporting this, abnormal indices of presynaptic dopaminergic function are a consistent finding in schizophrenia, and have been linked to symptom severity-suggesting that they could be a biomarker for schizophrenia risk. We have previously found that striatal dopamine dysfunction predates the onset of schizophrenia. Here we report how it relates to the attribution of salience and how it changes with the subsequent development of psychosis. Methods: We measured presynaptic dopamine synthesis capacity in two cohorts of patients with prodromal signs of schizophrenia (meeting CAARMS criteria for an at risk mental state, ARMS) and matched controls using 18-F DOPA PET imaging. The ARMS subjects have received clinical follow-up and repeat PET imaging to determine changes in dopamine synthesis capacity with the development of psychosis. Additionally a sub-group (18 ARMS and 18 controls) have received additional fMRI imaging using the Salience Attribution Test (SAT). The SAT is a reward-learning task where subjects' speeded responses in the presence of cues earn money. The cues have both relevant and irrelevant stimulus dimensions to index the attribution of salience, and patients with schizophrenia have been previously show greater misattribution of salience to the irrelevant dimension. Results: Striatal dopamine synthesis capacity was significantly elevated in the ARMS group compared to controls (P <.05). Analysis of new data in ARMS subjects who have completed follow-up showed that striatal dopamine synthesis capacity was elevated at baseline in those who went on to develop psychosis, and increased further with the development of psychosis (P = .03). This contrasts with the findings in those who did not go on to psychosis who did not show a baseline elevation or longitudinal change (P >.1). Additionally, the ARMS showed greater misattribution of salience to irrelevant stimuli than controls, and activation during this task was related to striatal dopamine dysfunction. Conclusion: These data indicate that dopaminergic dysfunction might serve as a biomarker for the development of psychosis in schizophrenia, and link it to aberrant salience processing in people with prodromal signs of the disorder.
ID: 950649

REDUCED TEMPORO-LIMBIC ENGAGEMENT DURING ENCODING OF WORD PAIRS IN AN ASSOCIATIVE MEMORY TASK IN THE PSYCHOSIS PRODROME: BASELINE FMRI FINDINGS FROM THE NORTH AMERICAN PRODROME LONGITUDINAL STUDY (NAPLS)

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Background: In addition to the well-replicated finding of generalized memory impairments in schizophrenia, recent evidence additionally suggests a specific deficit in associative memory formation. This deficit represents an underlying psychological process that disturbs the ability to carry out integrative higher-order cognitive functions that are important in everyday life. The neural mechanisms underlying associative memory formation have thus far not been examined prospectively in individuals who are at risk for developing psychosis. Methods: In this study thirty-eight individuals identified as being at clinical high-risk (CHR) for psychosis (M = 19.9 ± 3.8 years; 22 males and 16 females) and eleven normal comparison participants [M = 19.1 ± 3.2 years; 3 males and 8 females) participated in an fMRI scan to assess neural functioning during a paired associative memory (PAM) task. During encoding, participants studied pairs of words and corresponding images; they were told to memorize the pairs by bridging a salient association between the two unrelated words to facilitate remembering the word pairs later. In a subsequent recognition task, participants performed a pair recognition test (intact/rearranged pairs). Results: Group comparisons of the encoding phase fMRI data revealed reduced neural signal in the right parahippocampus and cingulate in the CHR group, regardless of retrieval fate. During the encoding of pairs that were subsequently successfully remembered, controls increased activation in bilateral middle temporal gyri and the right inferior parietal lobe, whereas the CHR group recruited the right cerebellum during these trials. For pairs that were subsequently forgotten, unlike the pattern of activity seen in the controls the CHR group engaged posterior brain regions, including the left inferior occipital lobe and right cerebellum. Conclusion: These current findings reveal a disruption in the interconnected network of temporo-limbic regions that may serve as a putative antecedent to uncovering the specific neural contributions responsible for disrupted associative memory processing in schizophrenia, which are possibly identifiable during the risk phase of the illness. Further longitudinal work is currently being carried out to explore these findings in the context of the progression to developing schizophrenia.
ID: 979777

EVIDENCE FOR POOR FUNCTIONAL CONNECTIVITY IN SCHIZOPHRENIA: INTERREGIONAL CORTICAL PHASE-SYNCHRONY OF GAMMA ACTIVITY DURING OBJECT PERCEPTION IN SCHIZOPHRENIA

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Background: Recent studies have revealed that individuals with schizophrenia have deficits in visual processing involving visual and prefrontal brain areas that support perception of objects when only partial information is available. Electroencephalography (EEG) studies have shown that schizophrenia is associated with poor synchronization of high-frequency neural activity between brain regions suggesting that deficient functional connectivity may characterize the disorder. The perceptual abnormalities of schizophrenia have been associated with deficient phase synchrony (PS) between anterior and posterior brain regions. However, due to the low spatial resolution and volume conduction, scalp EEG PS measures are unlikely to elucidate the locus of abnormal brain dynamics during object perception. Methods: Ten schizophrenia patients and 10 healthy controls completed a continuous performance task, requiring identification of target objects within a sequence of visually degraded stimuli. Magnetoencephalography (MEG) and structural magnetic resonance imaging (MRI) data were gathered to reconstruct cortical source signals using a source localization technique. Novel measures of neural PS (Avyente et al, 2010) were computed between10 cortical regions of interests (ROIs) where increased high-frequency oscillations were observed for target identification. Results: Patients tended to have lower accuracy and had significantly longer reaction time than controls. Patients had reduced PS in various gamma frequency range (40 ~ 120 Hz) in multiple pairs of ROIs, including between visual and prefrontal ROIs as well as between those in visual and prefrontal areas. In early period (80 ~ 300 ms), patients had reduced PS of left middle frontal gyrus (MFG) with left fusiform gyrus (FG) and left lateral occipital cortex (LOC), and reduced PS of left superior frontal gyrus with left FG and right ligual gyrus (LG) compared to controls. In similar period (150 ~ 250 ms), patients also had reduced PS of left LOC with left FG and right LG. For a long period of time (0 ~ 900 ms), patients had reduced PS of left lateral orbitofrontal cortex with left MFG and right anterior cingulate cortex, and reduced PS of cingulate with right inferior temporal gyrus. Conclusion: In addition to deficits in early phasic PS between visual areas and prefrontal-posterior PS, tonic PS between prefrontal areas might contribute perceptual deficits in schizophrenia, suggesting both top-down attentional and bottom-up visual processing deficits in this disorder.
ID: 980099

FUNCTIONAL ACTIVATION CHANGES ACROSS ADOLESCENCE IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Schizophrenia is considered to have a strong developmental component, with symptoms emerging across adolescence and young adulthood. The ongoing developmental changes observed during adolescence may thus be key for understanding psychosis onset. While there are indications that trajectories of brain development in schizophrenia patients and those at risk may differ from typically developing controls, it is unknown whether there are age-associated changes in functional MRI (fMRI) activation during this period. Methods: We assessed 19 typically developing controls, and 20 patients at clinical high risk (CHR) for developing psychosis (UCLA CAPPS clinic). Our subjects ranged from 14 to 21 years old and we employed a cross-sectional analysis to investigate age-related changes. We administered a verbal working memory task during fMRI. To control for performance, we calculated each subject's working memory capacity and analyzed the data for each subject only at the load closest to their own capacity. To test for an interaction between the relationship of age and activation, we modeled age for each group, and tested the relationship between the slopes for each group. Results: Our voxel-wise analysis indicates that the slopes of the age-activation relationship significantly differ between CHR participants and controls in frontal and parietal regions, key components of the working memory circuitry. Specifically, controls showed a predicted negative association between activation and age, while CHR participants showed a significantly different pattern of positive association between activation and age. Preliminary analyses focused on conversion to psychosis indicate that subjects who ultimately convert to psychotic illness may have a different, more frontally based pattern of disrupted development than do those who did not convert during follow up. Conclusion: The prodromal period may be associated with a deviation from the normal developmental trajectory in the ability to recruit cortical regions for use in working memory tasks. To our knowledge this is the first investigation of fMRI changes with age in CHR adolescents. Understanding how such changes emerge over time may provide a better basis for interpreting functional neuroanatomic differences seen in adult patients with schizophrenia and other psychoses, as well as helping to identify potential points for later intervention.
ID: 978583

DOES COMPUTERIZED COGNITIVE REMEDIATION CHANGE BRAIN ACTIVATION PATTERNS IN SCHIZOPHRENIA: FMRI PILOT DATA

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Background: Attention, memory, especially working memory (WM) and information processing deficits are important features of schizophrenia. WM functions appear to be mediated by neural networks involving the dorsolateral prefrontal cortex (DLPFC). The aim of this study is to determine whether there are brain activation changes in the DLPFC after stimulation with a neurocognitive task as a result of engaging in a 12 week course of cognitive remediation therapy (CRT) in patients with chronic schizophrenia. Methods: Pilot data is presented of 5 patients with DSM IV schizophrenia who were randomized to a 12 week trial of CRT using a Computerized CR program COGPACK or to a 12-week control condition. Patients in the CR group complete a total of 36 one-hour sessions. Patients received at baseline and endpoint an fMRI scan with a cognitive task (N-back task), a neuropsychological test battery (MATRICS), functional and symptom assessments. fMRI acquisition was done using a 1.5T MRI scanner at the Center for Advanced Brain Imaging at the Nathan Kline Institute, Rockland, NY. A Visual-letter n-back WM task was used in the scanner. Data was analyzed using FSL 3.3 available from FMRIB, Oxford, UK. Results: All 5 subjects showed improvement in the WM composite T-score and vigilance T-score of the MATRICS after CRT. Post minus Pre intervention scans averaged across patients showed increased activation in the DLPFC [Brodmann Area (BA) 46 and 9] in the 2-back task as compared to the 0-back task, at the threshold of $z > 2.3$ and $P < .05$. In addition, in the averaged post minus pre CRT scans there were significantly increased activations in the anterior cingulate [BA 32, 33], medial frontal gyrus [BA 10, 11], and parietal areas [BA 40]. Conclusion: Activation in BA 46 and 9 is seen during working memory tasks. The increased activation in these areas was parallel to the improvements seen in working memory tests on the MATRICS after CRT. BA 32 (anterior cingulate gyrus) is activated in tasks involving decision making including attentional control, error detection and conflict monitoring and correlated well with improvement in vigilance scores of the MATRICS. Area 40 (the supramarginal gyrus) of the parietal lobe is associated with verbal short term memory, which may have been activated as the letter N-back task was used. We plan to add diffusion tensor imaging to this study to see if there are any corresponding neuroanatomical white matter changes in response to CRT.
ID: 979715

FMRI STUDY OF TREATMENT EFFECTS ON EXTERNALLY-ELICITED AND INTERNALLY-GENERATED RESPONSES IN FIRST EPISODE SCHIZOPHRENIA

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Background: Little systematic work has been done to assess how antipsychotic medication impacts functional brain systems that support cognition and behavior. Methods: Unmedicated first episode schizophrenia patients participated in functional magnetic resonance imaging studies before and after 5 weeks of second generation antipsychotic treatment. During scanning they performed a visually-guided saccade task and a predictive saccade task, translational paradigms for assessing neural systems that support, respectively, externally-elicited sensorimotor responses (saccades to an unpredictably moving target) and learned, internally-driven responses (saccades to a temporally and spatially predictable target). In contrast to traditional neuropsychological tests, both tasks have been shown in prior laboratory studies to be more sensitive to treatment effects. Demographically matched healthy controls also performed the tasks twice about 5 weeks apart. Results: For the visually guided saccade task, schizophrenia patients displayed normalization of pretreatment activation deficits in frontal and parietal attentional cortex and in higher order visual information processing cortex. By comparison, healthy subjects displayed no increases in these areas. For the predictive saccade task, schizophrenia patients displayed increased activation in parietal cortex and in visual information processing cortex after treatment, suggesting improved visual attention. No increase was seen in these regions in healthy subjects at retest. Behaviorally in the predictive task, posttreatment response latencies remained speeded (~100ms) for patients, consistent with primary reliance on internal mechanisms to execute responses. Conclusion: Externally-guided saccades were performed with normalized engagement of visual attentional systems after antipsychotic treatment in first episode schizophrenia patients, replicating prior work. For internally-generated saccades, treatment was associated with activation patterns suggesting increased spatial and visual processing. Taken together, results from both saccade tasks suggest schizophrenia patients had enhanced attentional, spatial, and visual processing after treatment.
ID: 978410

AN FMRI STUDY OF EMOTIONAL AMBIVALENCE TOWARD PARENTS IN SCHIZOPHRENIA

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Background: Emotional conflict toward parents in patients with schizophrenia is one of the important environmental factors of long-term course, but its neural base has not been studied yet. This study was done to explore the characteristics of the neural basis of emotional response to parents in patients with schizophrenia. Methods: Fourteen outpatients with schizophrenia and 15 healthy volunteers who have parents were scanned using functional MRI while performing the imaginary sentence completion task in the father, mother and neutral conditions. Results: In the behavioral response, patients with schizophrenia showed increased response missing percentage and response time (P = .036 and P = .037, respectively). When compared with the control group, the patient group showed the significant brain responses in the posterior cingulate cortex, left insula and right thalamus in the father condition, and the anterior cingulate cortex and left superior temporal gyrus in the mother condition. The patient group showed significant correlations between the percent signal changes of the left insula in the father condition and Parents Adolescent Communication Inventory scores and between the percent signal changes of the right anterior cingulate cortex in the mother condition and ambivalence scale scores. Conclusion: The behavioral results from this study suggest patients' emotional conflict and ambivalence toward their parents. These behavioral responses may be connected to potential exacerbation of psychotic symptoms in patients with schizophrenia via the paralimbic network including the insula and anterior cingulate cortex.
ID: 978223

AN FMRI INVESTIGATION OF PREDICTION ERROR AND TEMPORAL DISCOUNTING IN SCHIZOPHRENIA

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Background: The aim of this study was to evaluate elements of reward processing in schizophrenia (SZ), and more specifically, whether the neural correlates of prediction error and temporal discounting are impaired in the illness. Prediction errors generated when there is a mismatch between reward value predicted and received are thought to be modulated by the midbrain dopaminergic system. On the other hand temporal discounting or the decreased valuation of a reward as the delay of the reward delivery increases, relates to elements of value-information integration thought to be subserved by prefrontal neuronal networks. Methods: Stable, medicated SZ (n = 21) and matched healthy controls (HC) (n = 13) were scanned during performance of (1) a probabilistic decision task where prediction errors (PE) were generated when the expected value (EV) of a monetary reward conflicted with the reward magnitude (RM) obtained, and (2) a delayed discounting (DD) task where subjects had to choose between an immediate smaller monetary reward and a larger, delayed reward. Data were acquired on a 3 T Siemens Allegra magnet (TR = 2.2 sec, TE = 30 ms, Flip angle = 70 degrees, slice thickness = 4 mm, 1mm gap, 30 slices). Data were preprocessed and analyzed using SPM8. The time course of activation in response to each of the experimental conditions was modeled using an HRF with a temporal derivative within the context of the General Linear Model. Several conditions (PE: EV, RM, and the parametric modulation of RM by PE; DD: delayed vs. immediate choices) were modeled. The statistical threshold was set at $P < .005$ with a minimum of eight contiguous voxels. Results: Preliminary analyses of the data indicate that SZ showed an abnormal modulation of the BOLD signal in the ventral striatum when the value of the reward received was less than expected (negative PE). In addition, relative to HC, SZ showed decreased BOLD response in the anterior cingulate and the dorsolateral prefrontal cortices when they made delayed rather than immediate choices. Conclusion: These preliminary data demonstrate differences in BOLD signal between the SZ and the HC in a network encompassing the ventral striatum, and the prefrontal cortex. Studying differences in the neural correlates of prediction error and temporal discounting in schizophrenia could lead to a better understanding of the impairments in drive and goal-directed behaviors associated with the illness.
ID: 978720

DECREASED PREFRONTAL ACTIVATION IN PATIENTS WITH SCHIZOPHRENIA PERFORMING THE TOWER OF LONDON TASK

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Background: Negative symptoms and cognitive impairments are often persistent in patients with schizophrenia. They have been related to decreased prefrontal activation, also called hypofrontality. It is unclear whether hypofrontality is caused by decreased task-related activation or by high activation during baseline. In this study, we investigated whether prefrontal activation in schizophrenia patients is impaired during a planning task or overactive during baseline conditions. Methods: Fifteen schizophrenia patients and healthy eleven controls did the Tower of London task during fMRI. In this task, three colored beads on vertical rods have to be mentally moved to another position. The minimal number of steps from a starting to a target configuration has to be indicated. As baseline, red and blue beads had to be counted. Stimuli were presented on a screen via a mirror on top of the head coil Responses were given by an MR-compatible button box. A pseudocontinious arterial spin labeling (ASL) sequence was acquired on a Philips 3 T scanner. Perfusion images were entered in a GLM analysis, contrasting task with control condition. Contrast maps were entered in a random effects analysis comparing patients with healthy controls. Results: The task activated prefrontal, parietal and striatal regions. Patients showed less activation in the L and R medial frontal gyrus (MFG), L & R anterior cingulate (ACC; BA 32), L & R cingulate gyrus (BA 31), L & R insula (BA 13), L & R superior temporal gyrus (STG), L & R caudate body and L middle frontal gyrus (MiFG) compared to controls. Patients showed small areas of increased activation in the L MiFG and R amygdala. Moreover patients had shorter reaction times but a lower accuracy. Conclusion: Patients showed decreased activation in medial and lateral prefrontal regions. Decreased medial prefrontal activation as shown by additional analysis was presumably caused by baseline overactivation. High activity in this region has been related to mind wandering, which may explain the lower accuracy of patients. In contrast, lateral frontal regions, ACC, striatal regions and insula, activated less during task performance. Decreased activation in the ACC has been related to conflicting possible solutions of the task and decreased attention, while striatal activation has been related to disturbed dopamine transmission. We conclude that the decreased activation in the PFC in SCH patient reflects a combination of increased activation during rest and lower performance during task.
ID: 978222

OVERLAPPING FUNCTIONAL AND STRUCTURAL NETWORK DIFFERENCES IN SCHIZOPHRENIA

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Background: Schizophrenia is considered to involve dysconnection within distributed neural networks. Methods are available to quantify this dysconnection. Diffusion tensor imaging (DTI) tractography provide a measure of structural connectivity between regions, most likely related to structure and organization of white matter tracts. Resting state fMRI (rsfMRI) allows assessment of the strength of functional connectivity between brain regions. Both methods have provided evidence of functional and structural dysconnectivity, however, no studies have combined the two approaches. The Network Based Statistics (NBS)(Zalesky et al Neuroimage 2010) provides an approach for identifying network connectivity group differences while avoiding confounds due to multiple comparisons. We sought to identify differences in functional and structural networks and their overlap in schizophrenia using NBS. Methods: 29 patients and 29 controls underwent a 6-min resting-fMRI scan at 3T with eyes closed. DTI data was collected in 11 minutes with 30 noncollinear directions. The AAL atlas was used to identify 90 anatomical regions of interest (nodes) from which average time-courses were extracted, wavelet transformed (.06–.125Hz), and a 90 × 90 correlation matrix formed. Streamlines were calculated with a FACT-based algorithm with custom software used to calculate the number of streamlines connecting each of the nodes. The number of connections that link a node to another was computed to create a 90 × 90 matrix. NBS was used to identify any component with pairwise associations that were significantly different between groups. Suprathresholds were selected to match number of nodes between functional and structural networks. Results: Significant components were identified for functional (nodes = 31, $P = .0001$) and structural (nodes = 30, $P = .006$) networks. Overlap of nodes between the networks was roughly a third, located in caudate, putamen, frontal, temporal(Heschl), parietal (precuneus) and occipital (cuneus) regions. Conclusion: From functional and structural information, we were able to identify network components that differed between patients and controls as well as nodes in both networks that overlapped in regions of known importance in schizophrenia, including subcortical dopaminergic pathways and distributed cortical networks. These data further suggest that deficits in functional and structural networks may be closely linked, and support rsfMRI/DTI as complementary biomarkers of regional dysconnectivity in schizophrenia.
ID: 977413

CANNABIS USE AND BRAIN FUNCTIONING IN SCHIZOPHRENIA: AN FMRI STUDY

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Background: Cannabis may be a risk factor for developing schizophrenia, possibly mediated through effects on brain function and biochemistry. Thus, it is conceivable that cannabis may also influence cognitive functioning in this patient group. Data and a literature review from our laboratory have previously shown paradoxical positive effects of previous cannabis use on cognition. The aim of the present study was to explore possible neurobiological correlates to these effects through functional neuroimaging. We used an fMRI paradigm together with a dichotic speech perception task to tap both verbal processing and attention. We hypothesized that the patients with schizophrenia and a history of cannabis abuse would show more normalized brain functioning as compared to patients with schizophrenia alone. Methods: Thirty-one patients with a DSM-IV and ICD-10 diagnosis of schizophrenia were grouped into a previous cannabis user group ($n = 13$) and a schizophrenia only group ($n = 18$). Information on the history of cannabis use was based on the clinical records, therapist questionnaires, and SCID-interviews. Exclusion criteria were neurological disease, history of head injury, and hearing impairment. The patients and a control group were scanned while listening to dichotic presentations of CV-syllables. The subjects were scanned with a GE Signa 3.0 T scanner, and the data were analyzed with the SPM8 software. Results: The patient group as whole showed overall reduced brain activation compared to the control group. As expected, the schizophrenia group with previous cannabis use showed a more normalized pattern, with stronger activation in prefrontal areas, including the anterior cingulate cortex, when listening to the speech sounds. This pattern of brain activation may correspond to an attentional/executive network. No significant clinical differences between the two schizophrenia sub-groups emerged that could have influenced the results. Conclusion: The

patients with schizophrenia and a history of cannabis abuse showed a more normalized brain functioning as compared to patients with schizophrenia alone. We suggest that cannabis causes a transient cognitive breakdown that may facilitate the development of psychosis and which imitates the typical cognitive vulnerability seen in schizophrenia. These transient cognitive deficits may improve after the cessation of cannabis abuse, thus creating a more normalized brain functioning in this schizophrenia sub-group.
ID: 979355

DIFFERENTIAL EFFECT OF CLOZAPINE AND RISPERIDONE ON CRAVING RELATED BRAIN ACTIVITY IN PATIENTS WITH SCHIZOPHRENIA AND CANNABIS USE DISORDER

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Background: Cannabis abuse and dependence in patients with schizophrenia occurs frequently and is associated with adverse outcome. Craving is regarded as a central phenomenon in cannabis dependence. It contributes to the continuation of cannabis use and to relapse after a period of abstinence. Antipsychotic medications with high affinity for the dopamine D2 receptor have been found to increase craving. Clozapine, with its low affinity for the dopamine D2 receptor, could reduce craving. Goal: To study differences in craving between clozapine-treated patients and risperidone treated patients. We hypothesize that the brain activity in areas associated with reward will increase and that activity in areas associated with attentional bias and cue elicited craving will decrease after treatment with clozapine. Methods: Randomized controlled trial. Functional MRI will be used to assess brain activity before and after 4 weeks of treatment. Three specific cognitive tasks, which are designed to assess non-drug reward, attentional bias and cue elicited craving are used. Results: 25 patients with schizophrenia and cannabis abuse disorder were included. Preliminary analysis showed significant differences in brain activation between the medication groups during the fMRI-tasks. Further analysis will be performed in the beginning of 2011, and will be presented. Conclusion: Preliminary results suggest a differential impact of treatment with clozapine and risperidone on brain activation during fMRI-tests of craving pathways in patients with schizophrenia and cannabis abuse.
ID: 978374

MOTION PROCESSING DEFICITS IN SCHIZOPHRENIA: EVIDENCE FROM FUNCTIONAL MRI

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Background: Several studies have shown that motion processing is significantly impaired in schizophrenia (SZ) patients [1, 2]. Though the exact relation of these deficits to the pathophysiology of SZ remain to be determined, it has been suggested that they are attributable to dysfunction along the magnocellular visual processing pathway [2]. The present study is based on the rationale that there are multiple processing stages in motion analysis and that dysfunction at an early stage of processing can lead to deficits at higher levels of analysis. In primates, motion processing is initiated subcortically in the retina and thalamus, continues into primary visual cortex (V1) and subsequently to various extrastriate cortical areas including the middle temporal area (MT). Methods: Twelve healthy control subjects and fourteen SZ patients participated in this functional MRI study. Stimuli were low contrast (12%) concentric rings extending from fixation and filling a circular region approximately 10 in diameter. Stimuli were delivered in 20-seconds epochs, alternating between stationary rings and rings expanding/contracting at a rate of 7/seconds. The fMRI signal during epochs in which the rings moved was statistically compared to the signal elicited by stationary rings. The resulting activations were localized with respect to the boundaries of retinotopically organized visual areas. Prior to fMRI, contrast sensitivity (CS) functions were derived for all subjects. Linear regression between CS and fMRI signal strength in motion sensitive areas was performed. Results: Control subjects showed robust activations in motion area MT as well as significant, though less pronounced, activations in area V1. Schizophrenia patients, on the other hand, had significantly reduced activations in both area MT and V1. Across both groups, the strength of these fMRI activations significantly predicted CS at low, but not high, spatial frequency. Conclusion: Overall, these results are consistent with previous physiological and psychophysical reports of a hypoactive magnocellular pathway in SZ. Furthermore, they provide neurophysiological evidence of impairments in the motion processing pathway of SZ patients starting at the initial stages of analysis, suggesting that the cortical deficits in MT and other areas may be secondary to impairments at lower levels of the magnocellular pathway.
1. Chen, et al, Schizophr Res, 2003. 61(2-3)
2. Kim, et. al., Schizophr Res, 2006. 82(1)
3. Martinez, et . al., . J Neurosci, 2008. 28(30)
ID: 979501

ABERRANT DEFAULT MODE NETWORK CONNECTIVITY DURING REST IN EARLY SCHIZOPHRENIA AND IN PATIENTS AT HIGH CLINICAL RISK FOR PSYCHOSIS

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Background: FMRI studies have identified a slowly oscillating ''default-mode'' network (DMN) of brain regions that is active during rest (ie, stimulus-independent thought), suppressed during goal directed tasks, and anti-correlated with a ''task-mode'' network (TMN) that includes the dorsolateral prefrontal cortex (DLPFC). While DMN hyperconnectivity and reduced anti-correlation with DLPFC have been reported in schizophrenia (SZ), it is unclear whether they predate psychosis onset. Accordingly, we examined DMN connectivity in individuals at clinical-high risk for psychosis (CHR), early SZ (ESZ) patients, and healthy controls (HC). Methods: Resting state fMRI data were acquired from ESZ (n = 34), CHR (n = 20), and HC (n = 35) participants. CHR patients met criteria for a prodromal psychosis syndrome. DMN connectivity was assessed using four separate seed regions known to be major nodes of the DMN: (1) Anterior Medial Prefrontal Cortex (aMPFC), (2) Posterior Cingulate Cortex (PCC), (3) left Lateral Parietal Cortex, and (4) right LPC (rLPC). For each subject, the four DMN-seeded connectivity maps were averaged to generate a single DMN map. Results: Within-group analyses revealed a robust DMN encompassing the four seed regions and other DMN regions including ventral MPFC (vMPFC), lateral temporal cortex, hippocampal formation (HF) and parahippocampal cortex (PHC). A TMN that was anti-correlated with the DMN was also identified, comprising DLPFC, supplementary motor area, superior parietal lobule, inferior frontal gyrus, and insula. Within DMN regions, both CHR and ESZ patients showed stronger DMN connectivity in vMPFC (BA 10, 11, 47) than HC. However, relative to HC, CHR patients showed weaker DMN connectivity in the HF/PHC, and ESZ patients showed weaker DMN connectivity in the PCC. Within the TMN, both CHR and ESZ patients showed attenuated DMN anti-correlations with DLPFC (BA 9, 10, 46), relative to HC. Conclusion: Our results suggest that both CHR and ESZ patients show DMN hyperconnectivity in vMPFC and attenuated DMN anti-correlations with the DLPFC. Deficient inverse coupling of the DMN with DLPFC may be related to difficulties with efficient DLPFC recruitment during cognitive tasks. Moreover,

reduced DMN connectivity with HF/PHC in CHR patients suggests that their stimulus-independent thought may be less influenced by long-term memory retrieval. Overall, aberrant DMN connectivity predates psychosis onset and may be a biomarker of risk for schizophrenia in CHR patients.
ID: 978877

NEUROIMAGING STUDIES IN SUBJECTS AT ULTRA HIGH RISK OF PSYCHOSIS

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Background: Neuroimaging studies in people at ultra high risk (UHR) of psychosis provide a powerful means of investigating the neural basis of psychotic disorders. Methods: In a series of studies, UHR subjects were studied at first clinical presentation using volumetric MRI; functional MRI, during verbal fluency, memory and salience processing tasks; Diffusion Tensor Imaging; MR spectroscopy for glutamate; and F-dopa PET. All studies involved multiple imaging techniques in the same subjects, most of whom were antipsychotic medication naïve. Subjects were followed clinically subsequent to scanning and re-scanned after 24 months. Data were also collected from healthy controls. Results: At baseline, compared to controls, UHR subjects showed reduced prefrontal volume; differential activation in prefrontal and medial temporal cortex; altered connectivity and reduced white matter integrity in fronto-temporal pathways; reduced thalamic glutamate levels; and elevated striatal dopamine function. There were correlations between: alterations in cortical activation and both dopamine and glutamate function; volume reductions and glutamate levels; and medial temporal glutamate levels and striatal dopamine function. Clinical follow up revealed that reduced medial temporal volume, increased prefrontal, medial temporal, and midbrain activation, and elevated dopamine function at baseline predicted later onset of illness. Comparison of baseline and follow up scans indicated that the onset of psychosis was associated with longitudinal decreases in medial temporal volume and in thalamic glutamate levels, and increases in striatal dopamine function. Conversely, symptomatic and functional improvement was associated with a longitudinal increase in anterior cingulate activation. Conclusion: These data suggest that an increased vulnerability to psychosis is associated with alterations in the structure, function, connectivity and chemistry of the brain. These findings are qualitatively similar to those seen in psychotic disorders, and appear to be inter-related. A subset of the findings evident at baseline are associated with the subsequent onset of psychosis, and certain abnormalities appear to progress as subjects make the transition to illness. These data may ultimately be useful to clinicians in helping to predict which individuals at high risk will later become psychotic, and in informing the development of new treatments for early intervention in psychosis.
ID: 979505

GENDER DIFFERENCES IN FIRST EPISODE PSYCHOSIS PATIENTS DURING THE N-BACK TASK

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Background: Research shows differences in brain activation for healthy male and female individuals during a working memory task prior to covarying for gender bias. In patients with schizophrenia working memory is consistently found as impaired, and even in this population gender differences in brain activation have been reported. However, the behavioral performance has been found to be similar for male and female patients. Unfortunately, patient studies to date are few, have used small sample sizes, and have investigated chronic populations. This study sought to clarify, in a large sample of first episode psychosis patients, whether gender differences in working memory are present in both brain activation and performance at illness onset. Methods: Sixty one (Male = 36, Female = 25) first episode psychosis patients were recruited at their first contact with mental-health services. A 3.0 Tesla scanner was used to acquire an MRI scan. 186 volumes were acquired with a slice thickness of 3.5 mm over 6 minutes and 40 seconds during the N-Back working memory task. The task consists of 4 parts - 0, 1, 2 and 3 back (0 back being the control condition, and 3 back the hardest condition). Results: Reaction time, correct responses and behavioral output was analysed over all trials and compared in males and females. Within the 3-back females performed significantly better than males on the total number of correct answers ($P = .01$), and at trend level in the 2-back. Males had higher activation ($P = <.015$) in the superior frontal gyrus, inferior temporal gyrus, cingulate gyrus and medial frontal gyrus compared to females. Whereas females showed higher cerebellar activation (P ranging from .03 to .005). The largest differences in activation occurred on the 3-back trial. Conclusion: Already at illness onset, there are gender differences in working memory performance and brain activation in individuals with psychosis. Females perform significantly better on more demanding working memory tasks, and have higher activation of posterior cerebellar areas, suggesting they may be performing better in detecting actual targets, rather than at simply retaining information.
ID: 979708

THE EFFECTS OF OXYTOCIN ON BRAIN ACTIVITY DURING A "TRUST GAME" IN SCHIZOPHRENIA

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Background: Recent evidence suggests that oxytocin, a hormone better known for its role in normal childbirth, may also be a promising candidate for treating treatment resistant positive and negative symptoms in schizophrenia. Recent research has found that healthy participants given oxytocin as a nasal spray experienced decreased anxiety and stress in social interactions, and increased "trust" in other people, and that increased trust related to changes in activity in the amygdala and striatum. Methods: In the current study, we examined the effects of a single intranasal dose of 40 IU oxytocin or placebo in individuals with a diagnosis of schizophrenia who carried out a "trust game" paradigm in the MRI scanner. Participants were told that they would be given $10, and (as the investor) could choose to share any part of that amount with another anonymous player. The amount given to the recipient is tripled by the experimenter. The recipient can return any part of that amount back to the investor. Thus it is in the subject's best interest (as the investor) to share a larger portion of the money, as it could potentially lead to gains for both parties. However, it does involve a risk for the investor, as the recipient may choose not to return any money to the investor. Participants carried out multiple trials of the game both as investor and recipient. On half the trials they were told that they were playing against other people and on the other trials, told they were playing against a computer (which would respond based on a random number generator). They were told that the results of one of the trials would determine the bonus they received for participation. Participants carried out the experiment twice (four weeks apart), after an intranasal spray of oxytocin or placebo (administered in a double blind manner). Results: Oxytocin increased generosity of participants (as the recipients), but did not significantly influence the amount shared as the investor (against people or

the computer). However, despite similar behavioral results, the BOLD response on trials as the investor showed a drug x recipient interaction in the amygdala, ventral striatum/ nucleus accumbens, caudate, and parts of the medial prefrontal cortex. Conclusion: Oxytocin's modulation of activity in limbic and striatal regions might provide a mechanistic explanation of its antipsychotic effects.
ID: 980209

NEURAL MECHANISMS OF ENVIRONMENTAL RISK FACTORS FOR SCHIZOPHRENIA

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Background: Environmental risk factors such as urbanicity, migration, high expressed emotion and low socioeconomic status have been clearly implicated in schizophrenia but the underlying neural mechanisms are unknown Methods: Using functional magnetic imaging, we aim to identify neural mechanisms related to processing of social stimuli related to environmental risk. Results: With regard to social status, In both stable and unstable social hierarchies, viewing a superior individual differentially engaged perceptual-attentional, saliency, and cognitive systems, notably dorsolateral prefrontal cortex. In the unstable hierarchy setting, implicated in risk, additional regions related to emotional processing (amygdala), social cognition (medial prefrontal cortex), and behavioral readiness were recruited. Using a social stress paradigm, we provide evidence that urbanicity tunes key prefrontal regulatory regions of the extended limbic system implicated in the processing of negative affect. Conclusion: Our data support the hypothesis that neural mechanisms for environmental risk factors may, at least for some, be related to prefrontal regulation of negative emotion and social stress.
ID: 979086

GENOME-WIDE SIGNIFICANT RISK FACTORS FOR SCHIZOPHRENIA AND BRAIN CONNECTIVITY

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Background: In schizophrenia, abnormal connections have been hypothesized to play a role since Wernicke. Neuroimaging has clear identified "dysconnectivity" in the disorder, with both abnormal hyper- and hypoconnectivity (measured using functional coupling parameters such as functional connectivity) identified. Methods: In this talk we will relate this work to genetic risk, using imaging genetics in a large Caucasian sample, functional connectivity as a coupling marker, and general measures of brain topology such as small-worldness, hierarchy and modularity as measures. Results: Genome-wide significant variants in ZNF804A and CACNA1C, among others, have pronounced regionally specific impacts on brain connectivity that have discernible downstream effects relevant for clinical manifestations, for example on the theory of mind/mentalizing system in the case of ZNF804A (Walter et al Mol Psych 2010). Both cognitive task dependent and independent components can be identified (Esslinger et al in press). These data are discussed in the context of emerging work showing a reshaping of the entire topological configuration of the brain connectome in schizophrenia (Bassett et al J Neurosci 2008, PLoS Comp Neurosci 2010). Conclusion: Our data show pronounced impact of genetic risk factors on global and local brain connectivity, compatible with the neurodevelopmental hypothesis of schizophrenia.
ID: 979084

NEURAL CORRELATES OF COGNITIVE AND EMOTIONAL PROCESSING IN INDIVIDUALS AT-RISK FOR SCHIZOPHRENIA AND FIRST EPISODE PSYCHOSIS

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Background: Efforts to lessen the functional impact of the onset of schizophrenia can be informed by a better understanding of brain systems involved in cognitive and emotional processing at the earliest stages of the disorder. Understanding disruptions in the neural systems underlying cognitive and emotional processing at these earliest stages of psychosis will lead to more targeted efforts to prevent or minimize functional limitations among patients with psychosis. Methods: Using functional MRI, we compared brain functioning associated with emotional and cognitive processes in groups of individuals who exhibited prodromal symptoms of psychosis (P,10) to patients after their first psychotic episode (FE,12) and to healthy individuals (HC,12). We also explored to what extent the engagement of neural systems during these challenges is related to individual emotional and cognitive performance as well as global functioning along the psychosis spectrum. Results: Contrary to our expectations, load-related brain activation during the working memory challenge was similar among all three groups in a region of DLPFC that was task-responsive across the groups, although whole-brain analysis revealed group differences in other regions. Amygdalar brain activation during the emotional challenge, in contrast to our hypothesis, was not different between the HC and P groups and was increased in magnitude in the FE group. Neuropsychological performance was related to DLPFC brain activation in both FE and P groups, but in opposite directions. We also found associations between global functioning and magnitude of brain response during the emotional and cognitive challenges. Conclusion: Results suggest that both cognitive and emotional systems are implicated in the earliest stages of psychosis. Further analyses suggested that brain responses were associated with neuropsychological performance as well as overall global functioning scores. While behavioral performance on measures of cognition and emotion have been linked to global functioning before, our findings extend these associations and highlight that more basic neurobiological abnormalities likely account for overall global functioning early in the course of schizophrenia. Our results could be interpreted as supporting a dysregulation hypothesis of developing psychosis such that global functioning is compromised as a function of disruption in the regulatory mechanisms between cognitive and emotional systems.
ID: 979773

INSULA, DORSAL ANTERIOR CINGULATE AND VENTRAL STRIATUM RESTING STATE FUNCTIONAL CONNECTIVITY NETWORK IN NICOTINE ADMINISTRATION, NICOTINE ADDICTION AND SCHIZOPHRENIA

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Background: People with schizophrenia (SZ) have unusually high rates of smoking. Damage to the insula alters smoking behavior. Decreased resting state functional connectivity (rsFC) in a dorsal anterior cingulate (dACC) to ventral striatum (VS) circuit is associated with nicotine addiction. We hypothesized that insula and dACC circuits may jointly contribute to nic-

otine addiction in normal control smokers (NC) and smokers with SZ. Methods: Using a double-blind, placebo-control, cross-over design, 19 smokers with SZ and 19 NC underwent resting state fMRI during randomized placebo vs. nicotine patch conditions. We manually partitioned left and right insula (lIns, rIns) and dACC (ldACC, rdACC) as region of interest (ROI) "seeds" and generated whole-brain rsFC with each ROI. We studied the contribution of each ROI's rsFC circuit to nicotine addiction severity as measured by the Fagerstrom Test for Nicotine Dependence (FTND). Findings are based on $p_{corrected} < .05$ [$p_{uncorrected} < .001$; cluster >324 mm^3] for each seed-based rsFC whole brain analysis. Results: FTND scores did not differ between SZ and NC subjects ($P = .62$). Regression analysis identified 7 rsFC circuits that were significantly associated with FTND after Bonferroni correction ($P < .004$; see table). Mixed effect ANOVA revealed that more severe addiction was associated with reduced rsFC in all 7 circuits. We found no significant drug effect (nicotine vs. placebo). Furthermore, ldACC to right and left VS and rIns to left somatosensory cortex showed significantly reduced rsFC in SZ compared with NC. Stepwise regression revealed that 2 of the 7 circuits (ldACC-right VS and rIns-bilateral dACC) combined explained 43% of the variance in FTND ($P < .001$). Conclusion: Reduced rsFC in an insula-dACC-VS network model explains a substantial portion of the variance of nicotine addiction. Decreased rsFC in ldACC-VS and rIns-somatosensory cortex circuits may index an overlapping circuitry for smoking and SZ.
ID: 977243

IMPAIRED FLEXIBILITY IN THE ALLOCATION OF NEURAL RESOURCES IN ANTIPSYCHOTIC-NAÏVE PATIENTS WITH FIRST-EPISODE SCHIZOPHRENIA

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Background: Neuroimaging studies have shown abnormal task-related deactivations during working memory (WM) in schizophrenia patients with recent emphasis on brain regions within the default mode network. Using fMRI we tested whether first-episode schizophrenia patients, who were also antipsychotic-naïve, were impaired at deactivating brain regions that do not subserve WM. Methods: Twenty-three antipsychotic-naïve patients with first-episode schizophrenia (18M; mean age of 26 years, SD = 5.0) and 35 healthy individuals (24M; mean age of 27 years, SD = 5.8) underwent whole-brain 3T fMRI while performing a verbal N-back task which included 0-back (no WM load), 1-back (low WM load), and 2-back (high WM load) conditions. Neuroimaging findings are reported as significant if they reached a corrected cluster-level threshold of $P < .05$. Results: No WM performance difference was found between groups. Contrasting the 2-back and 0-back conditions revealed that patients deactivated default mode network regions to a similar degree as controls. However, with increasing WM load, patients were impaired in deactivating large bilateral clusters centered on the superior temporal gyrus. A greater proportion of this temporoparietal region activated with the no WM load condition (0-back) in both groups. Conclusion: We attribute the bilateral temporoparietal activation during 0-back to most likely underlie verbal attentional processing. Therefore, we argue that persistent activation in the 1-back and 2-back conditions reflects an inability in patients to shift cognitive strategy with onset, and increase, of WM demands. Since patients were naïve to antipsychotic drugs and task performance was equal to controls, we infer that this impaired reallocation of neuronal resources represents a primary dysfunction in schizophrenia.
ID: 977519

ALTERATIONS OF THE BRAIN REWARD SYSTEM IN ANTIPSYCHOTIC NAÏVE SCHIZOPHRENIA BEFORE AND AFTER ANTIPSYCHOTIC TREATMENT

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Background: During the recent years a few studies using functional Magnetic Resonance imaging (fMRI) have found disturbances in the Brain Reward System in medication free schizophrenic patients and in patients treated with typical antipsychotics, while patients receiving atypical antipsychotics show fewer alterations of the Brain Reward System. Most of the earlier studies have been cross-sectional and there are by now no longitudinal studies on antipsychotic naïve schizophrenic patients. In this study, we aim to look at disturbances in the Brain Reward System in antipsychotic naïve schizophrenic patients before and after antipsychotic monotherapy. Methods: 27 antipsychotic naïve schizophrenic patients and 27 age and gender matched healthy controls have been included. At baseline all participants have been examined with fMRI while playing a var-

	rsFC Circuits	FTND Main Effect	Diagnosis Main Effect[a]			Drug Main Effect[a]			Dx x FTND
Seed ROI	Co-activating cluster (Coordinate)	*t* value (*P*)	SZ Smokers	NC Smokers	*t* value (*P*)	Nicotine	Placebo	*t* value (*P*)	*t* value (*P*)
Left dACC	Right VS (−26, +20, +9)	**−4.1 (.0002)**	1.9 ± .4	3.1 ± .4	**−2.6 (.015)**	2.5 ± .4	2.5 ± .3	−.6 (.56)	2.0 (.051)
	Left VS (+32, +17, +6)	**−3.9 (.0005)**	2.2 ± .5	3.3 ± .5	**−2.5 (.017)**	2.8 ± .6	2.7 ± .4	−.8 (.45)	**2.1 (.048)**
	Pons (+11, +38, −31)	**−3.7 (.0008)**	.3 ± .3	.4 ± .3	−.8 (.428)	.7 ± .3	−.02 ± .4	−.5 (.62)	1.2 (.26)
Right insula	Right VS (−23, +14, +9)	**−3.1 (.0044)**	2.9 ± .4	4.0 ± .4	−.7 (.510)	3.3 ± .3	3.5 ± .3	.9 (.37)	.4 (.73)
	Bilateral dACC (+2, +8, +27)	**−3.2 (.0033)**	.5 ± .4	1.1 ± .4	−1.4 (.161)	.9 ± .3	.7 ± .4	−.6 (.53)	1.0 (.32)
	Left premotor (+20, +11, +60)	**−3.7 (.0008)**	.9 ± .3	1.7 ± .3	−1.4 (.164)	1.5 ± .3	1.0 ± .3	−.1 (.95)	1.2 (.24)
	Left somato-sensory (+23, +35, +54)	**-3.3 (.0026)**	.5 ± .4	2.7 ± .4	**-2.1 (.048)**	2.0 ± .4	1.3 ± .4	.3 (.79)	1.2 (.24)

***P* <.05**.
[a]Mean ± SE of mean z scores (functional connectivity) in Dx and drug conditions.

iant of the Monetary Incentive Delay task in a 3 Tesla Philips scanner. After a six week period where the patients have been treated with individual doses of the dopamine $D_{2/3}$ blocker, Amisulpride, the participants have been rescanned. The psychopathology of the patients has been evaluated with several clinical rating scales before and after treatment. Results: The fMRI data are currently being analysed, thus the following results are preliminary. Regarding the baseline data, we did not find any significant group differences in the whole brain comparison during either the anticipatory or the outcome phase. Looking at the ventral striatum as a predefined Region of Interest, preliminary results suggest that salient cues elicit a smaller increase of the BOLD response in the patients during the anticipation phase. Similar, the data suggest a smaller increase of the BOLD response in the ventral striatum of the patients during the outcome phase. The follow up data are still undergoing analyses, but will be presented at the conference. Conclusion: This is the first longitudinal study looking at medication effect on reward disturbances in antipsychotic naïve schizophrenic patients. The preliminary baseline results are in line with earlier studies on medication free patients, suggesting that in a hyperactive dopaminergic state, the chaotic activity of the dopaminergic neurons in the patients drowns out the otherwise rapid changes of the BOLD response seen in the healthy controls. We expect these alterations to be improved by dopamine $D_{2/3}$ blockade at follow up.
ID: 974898

THE DIFFERENCE IN BRAIN ACTIVATION RELATED TO THE DIRECTIONALITY OF AFFECTIVE REVERSAL ASSOCIATION BETWEEN PATIENTS WITH SCHIZOPHRENIA AND HEALTHY CONTROLS

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Background: The dopaminergic mesolimbic pathway, a classical neural system involved in the pathophysiology of schizophrenia, has been implicated as a core neural system for processing motivationally salient information that is either rewarding or aversive. Affective bias in reversal learning, where reattributing appropriate rewarding values is difficult and false aversive values easy, may underlie clinical manifestations of schizophrenia, such as paranoid delusions and avolition. The present study investigated the affective bias in reversal learning and its underlying neural process in the cortico-striato-limbic network in patients with schizophrenia. Methods: Fifteen healthy participants and 14 outpatients with schizophrenia underwent an event-related functional magnetic resonance imaging scanning while performing a monetary incentive contingency reversal task. Results: Patients had higher physical and social anhedonia scale score than healthy controls. Both groups showed greater accuracy when reversing from punishment-to-reward contingency than vice versa without group differences. While healthy controls showed unidirectional acceleration in reaction time when reversing from punishment-to-reward contingency, patients showed significantly diminished punishment-to-reward reversal acceleration. In healthy controls, the anterior cingulate cortex was significantly activated and the amygdala, putamen, and the lateral orbitofrontal cortex activations were also identified during reversal response. In patients with schizophrenia only reversal response-related lateral orbitofrontal cortex activations were identified. Unidirectional punishment-to-reward reversal activations were observed in the lateral orbitofrontal cortex in both groups and in the anterior cingulate gyrus in healthy controls only. Physical anhedonia score correlated with reversal response-related anterior cingulate activity changes in healthy controls, whereas physical and social anhednoia scale scores and PANSS negative symptom scores correlated with the lateral orbitofrontal cortex in the patients. Conclusion: These finding suggest that deficiency in anticipation and engagement in reversing instrumental behavior to obtain reward reflected in the blunted anterior cingulate and compensatory lateral orbitofrontal activity may underlie the neural pathophysiology of anhedonia/avolition in schizophrenia.
ID: 979235

EXPLORING CONNECTIVITY DIFFERENCES AMONG LOW-FREQUENCY RESTING-STATE FMRI NETWORKS BETWEEN SCHIZOPHRENIA AND PSYCHOTIC BIPOLAR SUBJECTS AND THEIR UNAFFECTED FIRST-DEGREE RELATIVES

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Background: Long considered independent, schizophrenia and psychotic bipolar disorder share many clinical symptoms and some risk genes. An underlying functional disconnectivity hypothesis is proposed for the pathophsyiology of both disorders. We therefore used a functional network connectivity (FNC) approach to measure differential interactions across independent resting state circuits in schizophrenia, bipolar, their respective unaffected first-degree relatives and healthy comparison subjects derived from B-SNIP. Methods: We assessed age, sex & ethnicity-matched groups of psychotic bipolar (BP, N = 63) & schizophrenia (SZ, N = 71) patients, unaffected SZ relatives (SZR, N = 74), unaffected BP relatives (BPR, N = 52) & healthy controls (HC, N = 116). Functional MRI scans were collected at 3T, as subjects rested quietly with eyes open. Preprocessed images were analyzed using independent component analysis (ICA). Data were decomposed into 15 networks and submitted to a FNC analysis. Resulting connectivity data were then analyzed in 2 stages. First, we examined potential resting state connectivity patterns that differed significantly between SZ and BP probands & controls. Next, we assessed these identified dysfunctional connections in relatives to detect potential endophenotypes. Results: A total of 3 different network pairs were identified as abnormal (FDR-corrected $q < .05$) in stage 1, involving 5 individual networks. Although networks contained multiple regions, for simplicity we designated these as (A) Dorsolateral/Occipital, (B) Prefrontal/ACC, (C) Temporal/Basal ganglia, (D) Paralimbic & (E) Sensory-Motor/oculomotor. One abnormal pair was unique to SZ, (C–E); one unique to BP, (C–D); one was shared between the two disorders (A–B). In the next step, we found that 1 of the above 3 combinations was also abnormal in SZR (C–E), but none in BPR (although close to significant for C–E). Conclusion: This study suggests that SZ and BP probands share several abnormal resting state network connections, but that there are also unique neural network underpinnings between the disorders. We also demonstrate that specific connections may also be candidate psychosis endophenotypes, although these do not straightforwardly segregate with conventional diagnoses. The Paralimbic circuit (D), (which in combination with circuit C uniquely distinguished BP probands) contains multiple mood-relevant regions, including amygdala, cingulum, temporal pole, insula, orbito-frontal cortex, hippocampus/parahippocampus and BA 24/25.
ID: 977875

EXPLORING GENETIC AND ENVIRONMENTAL INFLUENCES ON BRAIN FUNCTION IN SCHIZOPHRENIA

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Background: Altered neurocognitive function in schizophrenia could reflect both genetic and environmental effects. Our aim was to use functional magnetic resonance imaging to discriminate between the influences of genetic and environmental factors on the neural substrate of verbal fluency, a candidate schizophrenia endophenotype. Methods: The total sample consisted of 206 subjects in an extended twin-sibling design. 163 twins varying in their zygosity and concordance for schizophrenia and 43 singletons from siblings clusters varying in their concordance for schizophrenia. Groups were matched for handedness, parental socio-economic status, and ethnicity. All subjects were scanned at 1.5T while performing a paced overt response phonological verbal fluency task. Results: Relative to the healthy control group, patients with schizophrenia and the non-psychotic co-twins from monozygotic discordant pairs produced fewer correct responses. Patients with schizophrenia and their unaffected relatives developed greater activation in the left inferior frontal and left superior temporal gyri and failed to activate in the left parahippocampal and middle temporal gyri bilaterally. These differences were manifest in a graduated manner across the groups, reflecting their hypothetical risk loads. In a subsequent contrast exploring genetic and shared environmental risk, non-psychotic co-twins and siblings showed greater activation than the controls in inferior frontal gyrus bilaterally and left superior temporal gyrus. Finally exploring unique environmental effects, monozygotic twins with schizophrenia showed greater activation than their genetically identical but non-psychotic co-twins in medial frontal gyri bilaterally and the right middle and superior frontal gyri. Subsequent genetic modelling demonstrated evidence of a moderate phenotypic correlation between schizophrenia and neural activity in the inferior frontal gyrus/insula on the left, due in part to familial factors. Conclusion: Both genetic vulnerability to schizophrenia and schizophrenia itself were associated with impaired verbal fluency performance and functional deficits in the temporal region, with possible compensatory, or inefficiency driven, increases in the inferior frontal regions. This regional inefficiency, was due in part to the familial risk of the disorder. There was evidence of further unique environmental effects in the medial frontal gyrus.
ID: 979608

NEURAL CORRELATES OF METONYMY COMPREHENSION IN SCHIZOPHRENIA

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Background: Comprehension of nonliteral language (like proverbs, metaphors, metonymies or ironic expressions) is impaired in schizophrenia. So far, only a very small number of studies investigated the neural correlates and of this deficit. However, several authors claimed a right hemisphere language deficit plays a key role in the pathophysiology of nonliteral language. Whereas the evidence for reduced language lateralization in literal language is increasing, this is much less clear for nonliteral language. The aim of this work was to investigate the laterality and functional anatomy of metonymy comprehension in schizophrenia. Metonymies are speech forms/tropes in which one entity is used to stand for another associated entity (for example "Kremlin" for "the Russian government"). Metonymies are very frequently used in everyday language and exemplary models for complex semantic association processes on sentence level. Methods: 15 probands with DSM-IV Schizophrenia (10 female) and 15 healthy control subjects (10 female), matched for age and education, completed a self-developed metonymy resolution test whilst functional magnetic resonance imaging data were acquired. Subjects read 123 short German sentences with either metonymic, literal or nonsense content silently and judged by button press whether the sentence has a meaningful content. Metonymic and literal sentences are matched for occurrence in a large corpus. As well, all patients completed neuropsychology and psychopathology (PANSS). Imaging was performed using a 3T Siemens TRIO scanner. Slices covered the whole brain. Data were analysed using SPM5 software. Results: Congruent with a previous off-line study, patients made more errors in the metonymy comprehension test relative to control subjects. Relative to literal sentences, metonymies activated a bilateral, predominantly left lateralised network with maxima in the lateral prefrontal cortex. Patients showed attenuated activation in the left lateral prefrontal cortex. Language lateralization was significantly reduced in parietal brain regions. Severity of PANSS positive symptoms was significantly correlated with medial prefrontal BOLD response in the patient group. Conclusion: The results provide further evidence for abnormalities in the brains fronto-temporal language network in schizophrenia. Reduced language lateralization was present. Results are discussed in the context of studies on language lateralization and psychopathology of nonliteral language in schizophrenia.
ID: 979852

AN FMRI STUDY OF REDUCED NEURAL ACTIVATION DURING WORKING MEMORY MAINTENANCE IN UNMEDICATED FIRST-EPISODE SCHIZOPHRENIA AND PSYCHOTIC BIPOLAR DISORDER PATIENTS

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Background: The reduced ability to maintain information in working memory to guide future behavioral responses in schizophrenia implicates dysfunction of prefrontal and thalamocortical circuitry. Studies are needed to characterize the neural basis of this deficit, and to determine whether this dysfunction is specific to schizophrenia or shared across psychotic disorders including psychotic bipolar disorder. Methods: Unmedicated first-episode patients with schizophrenia (n = 19) or psychotic bipolar disorder (n = 11) and matched healthy controls (n = 20) performed an oculomotor delayed response task during event related fMRI studies. The task used was similar to those developed in studies of nonhuman primates to establish the rele-

vant cortical and subcortical circuitry for maintaining spatial information in working memory. This task requires subjects to hold spatial location information online over a brief delay period and then make a saccadic eye movement to a remembered spatial location. Activation during a 5 second delay period was contrasted with a passive central fixation period. Results: Compared to healthy individuals, patients with schizophrenia showed significantly reduced activation in several frontal regions including the dorsolateral prefrontal cortex, frontal eye fields, and anterior cingulate, whereas reduced frontal activation among bipolar patients was restricted to the anterior cingulate. Both patient groups demonstrated reduced activation in posterior parietal cortex and precuneus. Additionally, patients with schizophrenia demonstrated reduced activation in dorsomedial thalamus. Conclusion: Patients with schizophrenia and psychotic bipolar disorder both demonstrate reduced activation in frontal and posterior parietal regions while maintaining information in working memory. However, more brain regions showed reduced functional activation in schizophrenia, including dorsolateral prefrontal cortex, frontal eye fields, and dorsomedial thalamus. This suggests that broader dysfunction of the anterior thalamocortical circuitry relevant to spatial working memory circuit is affected in schizophrenia.
ID: 977645

EFFECTS OF MTHFR 677C>T GENOTYPE ON DORSAL ANTERIOR CINGULATE ACTIVATION DURING RESPONSE MONITORING: A CASE-CONTROL FMRI STUDY

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Background: Patients with schizophrenia exhibit deficient response monitoring as indicated by blunted neural responses to errors. We previously found that patients who carry a hypofunctional variant in MTHFR, 677C>T, exhibit more pronounced dorsal anterior cingulate (dACC) blunting following error commission, suggesting that this folate- and dopamine-related gene contributes to altered executive function in schizophrenia. However, it remained unclear whether MTHFR 677C>T also affects error-related dACC activation in healthy individuals. Here, we examined effects of MTHFR 677C>T on error-related dACC activation in a new cohort of 28 chronic, medicated schizophrenia patients and 21 demographically matched healthy volunteers. Methods: All participants underwent functional magnetic resonance imaging (fMRI) while performing an antisaccade paradigm, which requires inhibition of a prepotent response and substitution of a novel behavior. Using an event-related design, we compared dACC activation for erroneous vs correct antisaccades in C/C homzygotes ($n = 14$ patients and 11 controls) and T allele carriers ($n = 14$ patients and 10 controls). Repeated measures analysis of variance included diagnosis and MTHFR genotype as between-subject factors and hemisphere and condition (error or correct) as within-subject factors. Results: A strongly significant condition x genotype interaction was observed, indicating greater error-related dACC activation in C/C subjects than in T allele carriers. This pattern did not differ significantly between patients and controls. Conclusion: These findings indicate that MTHFR 677C>T genotype influences the neural response to errors regardless of diagnosis. The 677T allele has been consistently associated with increased risk of schizophrenia, as well as with more pronounced negative symptoms and executive dysfunction within the disorder. It appears to exert a fundamental effect on dACC function irrespective of disease state or medication use, suggesting that 677T allele effects on clinical schizophrenia phenotypes are not confounded by these factors. Rather, on the background of other schizophrenia risk genes, MTHFR 677T allele-related dACC dysfunction may contribute to deficient executive function, presenting a novel target for intervention.
ID: 979908

CA3 SUBFIELD-SPECIFIC INCREASES IN RCBV IN SCHIZOPHRENIA WHICH CORRELATE WITH PSYCHOSIS

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Background: We have developed a model of psychosis in schizophrenia which posits that neuronal activity is increased in CA3 due to reduced afferent innervation from DG and exaggerated plasticity responses within the CA3 recurrent collateral- and the direct perforant pathway- projections. We hypothesize that associational mistakes occur within this hyper-activated region, some bizarre or nonsensical, and then are laid down in memory albeit with a psychotic content. This model is supported by published literature (1), as well as by our own preliminary molecular (postmortem tissue) and MR (fMRI and perfusion) data. Methods: Perfusion studies in schizophrenia volunteers, both on and off medication, were completed and scan images were acquired under high resolution conditions where subfield-specific perfusion can be assessed. Up to 20 schizophrenia (SZ) volunteers with (SZ-ON) and without (SZ-OFF) antipsychotic medication have been contrasted with normal controls. Perfusion was assessed by regional cerebral blood volume (rCBV). We used Vascular-Space Occupancy (VASO) MRI technique [2] to measure rCBV at high resolution. The VASO scan method includes a pre-contrast scan, injection of contrast agent, and a post-contrast scan. rCBV is calculated from the pre- and post-contrast images. Coronal rCBV maps were acquired perpendicular to the hippocampus with an in-plane resolution of .8 mm × .8 mm and slice thickness of 4mm (no gap). A T2-weighted anatomical image was also acquired; subfields have been identified on this image and the corresponding ROIs were subsequently overlaid onto the VASO image. Results: These data so far have shown a selective increase in rCBV in CA3 especially in the SZ-OFF, without a change in other subfields. We will report results from a full study testing rCBV in SZ-ON vs SZ-OFF vs NC volunteers, assessing rCBV in hippocampal subfields and correlating the perfusion with functional activation to memory tasks. Conclusion: We predict that we will confirm the increase in CA3 perfusion, with a decrease in functional activation and an inverse correlation between the two. We propose that these changes will be greatest in SZ-OFF and blunted in SZ-ON, but still apparent; and, that perfusion will correlate with psychosis in the SZ-OFF.
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ID: 976382

NEUROIMAGING TECHNIQUES AND RESPONSE TO PSYCHOLOGICAL INTERVENTION IN PSYCHOTIC PATIENTS: A SYSTEMATIC REVIEW

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Background: Several studies suggested that neuroimaging techniques may be related with clinical response to psycho-social intervention in patients

with schizophrenia, but results are controversial. The aim of this review was to assess the heterogeneous findings and to investigate the principal variables related with clinical response and brain changes. Methods: A systematic review of the literature was conducted introducing a query of 5 items in PUBMED and PSYCHO-INFO data base. We selected the studies that fulfilled the following inclusion criteria: (1) longitudinal studies. (2) Implementation of some kind of psychological intervention. (3) Inclusion of a group or sub-group of patients diagnosed with schizophrenia or schizoaffective disorder. (4) Use of a technique of neuroimaging before and after psychological intervention Studies that fulfilled inclusion criteria were reviewed using a comprehensive battery of quality methodological assessment question. Results: Eight studies met the inclusion criteria. Six of them use rehabilitation techniques and 2 Cognitive Behaviour Therapy (CBT). Structural changes in the hippocampus and amygdale are the most relevant findings in relation with cognitive rehabilitation. Prefrontal activity at baseline may be a predictor of clinical response to psychosocial intervention. Conclusion: There are some evidence of a brain protective effect of psychosocial intervention in patients with psychosis . Nevertheless there are not enough evidence of specific changes related with these interventions. Different Neuroimaging techniques using new paradigms are suggested.
ID: 986865

EVOLUTION OF NEURAL CIRCUITRY ALTERATIONS IN MEMORY PROCESSING IN SCHIZOPHRENIA: IMPACT OF SEX

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Background: Primary deficits in schizophrenia (SCZ) include short and long term memory. It is critical to understand how the neural circuitry underlying these functions goes awry and at what point in the illness. We evaluate whether the primary brain regions implicated in memory functions (dorsolateral PFC (DLPFC), anterior cingulate gyrus (ACG), hippocampus (HIPP), and parietal cortex (PAR)) that are abnormal in chronic patients, are present at first episode (FE) and prior to psychosis onset (''prodrome''). Given that these brain regions are normally sexually dimorphic, we hypothesize that differential abnormalities in this circuitry will explain sex differences in memory dysfunction in SCZ. Methods: Subjects were 21 prodromal subjects (PRO; 52% male) and 14 healthy controls, 24 FE SCZ patients (70% male) and19 healthy controls, and 88 chronic patients with SCZ (67% male) and 48 healthy controls. Groups were comparable on sex, age, education, handedness, ethnicity and parental SES. Structural and functional MRI (fMRI) scans were acquired on a Siemens 3T magnet. Visual 2-back vs 0-back working memory tasks and a verbal encoding task were used in fMRI. SPM8 was used to analyze fMRI data, with a focus on the anatomically defined regions of interest (ROIs). Results: Chronic patients exhibited volumetric abnormalities in the ROIs, whose covariance differed by sex in the relationships between HIPP-ACG, DLPFC-iPAR, and iPAR-ACG. In FE subjects, there was significantly increased HIPP and paraHIPP activity in 2-back [FWE-corrected $P = .001$] and verbal encoding [$P = .06$] tasks, and increased ACG in verbal encoding [$P = .02$] that was associated with better performance among females. In PRO vs. controls, significant alterations in functional activity were observed in paraHIPP and DLPFC, as in FEs, and PAR in response to the 2-back task, while the verbal encoding task elicited alterations in paraHIPP, DLPFC, and ACG. Conclusion: Associations between brain volumes implicated in short and long term memory are abnormal in chronic patients, and are present in fMRI processing at FE and prodrome, indicating pre-illness developmental deficits. Women with SCZ exhibit better memory function than men and this is associated with a differential ability to activate brain regions within the memory circuitry. Thus, findings suggest the importance of understanding sex differences in brain development in regions associated with memory processing in SCZ.
ID: 979416

NEURAL CORRELATES OF EMPATHIC PERSPECTIVE-TAKING IN SCHIZOPHRENIA

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Background: Empathic Perspective-Taking (EPT) is a higher-order component of empathy, and requires an individual to appreciate the subjective view of others. Neural regions engaged during EPT include the insula, which is recruited to retrieve emotional memories, the temporoparietal junction (TPJ), which processes emotional memory, and the anterior cingulate cortex (ACC), involved in emotional decision-making. Behavioral studies have found deficits in EPT among individuals with schizophrenia (SCZ). However, the functional abnormalities that may accompany these deficits in SCZ are unknown. Methods: SCZ and healthy controls (CON) performed an EPT task during a fMRI scan. Subjects viewed a social scene involving two people, but with one of the faces covered. Subjects then chose which of two faces matched the expression of the covered face. Two fMRI runs were collected with a 3T Siemens TIM Trio (TR = 2.2 seconds; 1.7 × 1.7 × 3 mm; 360 volumes/run, total time = 26:24). fMRI data were analyzed with AFNI and slice time and motion corrected, spatially normalized and blurred (FWHM = 8 mm). Spherical regions of interest (ROI) with a 4 mm radius were defined bilaterally in the insula, TPJ, and ACC. A general linear model examined between-group differences in the blood-oxygen-level-dependent (BOLD) signal within each ROI. Results: SCZ had a lower performance accuracy than CON on the EPT task ($P = .024$). An ROI-based analysis revealed less BOLD activation in SCZ than CON in three ROIs (insula, TPJ, and ACC). When viewing the social scene, SCZ had less right TPJ activation than CON. When subjects had to decide which of two faces matched the covered face, SCZ had less activation than CON in the left insula, left TPJ, and right ACC. Conclusion: Our findings replicated previous studies which suggest that SCZ have impaired EPT performance and abnormalities when recruiting the neural regions involved in EPT, namely, reduced activation in the TPJ, insula, and anterior cingulate cortex. With the TPJ being crucial to empathic and theory of mind processes, our data suggest that SCZ have difficulty assessing the emotional and cognitive dynamics of social interactions. The inability to synchronize the functional networks necessary to make such decisions can then lead to incorrect attributions about a social situation. Further work is needed to elucidate

whether SCZ have neural dysfunction for specific emotional contexts and whether this network can be strengthened in a therapeutic setting.
ID: 976609

EFFECTS OF CANNABIS USE ON DEFAULT MODE NETWORK CONNECTIVITY AND COGNITION IN EARLY SCHIZOPHRENIA

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Background: The default mode network (DMN) is an emerging model of brain function at rest, based primarily on wave correlation analyses in task-free MRI. Although consensus is emerging about its overall structure, the exact nature of its possible dysfunction in schizophrenia remains unclear. Also unclear is the possible effect of environmental factors such as cannabis use on the DMN and its development, particularly in the at-risk developmental period of adolescence and early adulthood. Methods: The present study utilizes a hybrid analytic model, previously used by our group [1] to show decreased connectivity in the DMN of established schizophrenic subjects. The functional MRI method combines a data-driven independent component analysis followed by seed-based region-of-interest (ROI) connectivity analysis to characterize the DMN in this population. The structural method uses diffusion tensor imaging to assess white matter connectivity between ROIs, offering a more complete picture of the DMN. MRI was performed on 146 subjects, comprising 37 with schizophrenia, 20 with schizophrenia and cannabis use, 31 with cannabis use alone, and 58 healthy controls. These 146 subjects also underwent neurocognitive testing, aimed at assessing executive function, working memory, and verbal fluency. These areas were chosen for their known pattern of dysfunction in prodromal and early schizophrenic patients [2]. Results: Analysis of these data is ongoing. Conclusion: We hypothesize that cannabis use will be negatively correlated with DMN connectivity, both functional and structural, when compared with non-cannabis using subjects. We further hypothesize that this effect will be stronger in the schizophrenia group, reflecting an increased vulnerability to disruption of developing neural networks. Lastly, we hypothesize that this decreased connectivity in the DMN will be correlated with decreased performance on neurocognitive measures.
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ID: 985929

CAN THE N-BACK TASK HELP TO PREDICT FUTURE TREATMENT RESPONSE IN FIRST EPISODE PSYCHOSIS PATIENTS?

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Background: Treatment of psychotic disorders is currently conducted on a trial and error basis with antipsychotic medication. However, approximately a third of patients show no response. Previous research has shown that psychosis is associated with abnormalities in brain function, already at the early stages of illness, for example during the execution of working memory tasks. However, it remains unclear if brain functional alterations that accompany the performance of these cognitive tasks characterize a subgroup of individuals with a poor response to treatment with antipsychotics. The aim of this study was to explore the relationship between brain functional activation during a working memory task at onset of psychosis and treatment response at 3 months. Methods: 30 First episode psychosis patients were recruited at their first contact with services. Patients were scanned in a 3.0 Tesla scanner whilst completing the N-Back task. This task has 4 parts: 0, 1, 2 and 3 back. Clinical (PANSS, CGI and GAF) data was collected at MRI and 12 weeks later. Follow up PANSS scores categorized patients as responders (n = 17) or non-responders (n = 13). Results: At baseline no significant differences in PANSS or CGI scores between patient groups were seen. Baseline GAF showed patients who later did not respond to treatment scored significantly better those who later did. At 3 months a significant difference was seen in PANSS scores with non-responders being more symptomatic. Behavioral data for the N-Back was analysed. On 1 and 2 Back, responders showed significantly quicker response times and a higher percentage of correct responses than non-responders. Both patient groups performed equally poorer on the 3 Back. Functional MRI data was analysed using SPM5. Responders showed a trend for a higher activation than non-responders at whole brain level (p = .005) on the 2 Back condition in the precuneus and on the 3 Back in the middle frontal and precentral gyrus. Non-responders also showed an increase in activation on the 3 Back in the inferior frontal gyrus. Conclusion: These analyses show that patients who later respond to treatment have a higher activation at baseline compared with those who later do not respond to treatment. This was evident with the more difficult conditions of the N-back task. This could suggest that those patients who later respond to treatment have a better visual memory recall than those who later do not respond to treatment at baseline.
ID: 979679

ALTERED LANGUAGE NETWORK ACTIVITY AND VERBAL MEMORY DEFICITS IN YOUNG ADULT FIRST-DEGREE RELATIVES OF PERSONS WITH SCHIZOPHRENIA

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Background: Language and memory abnormalities are core features of schizophrenia (SZ). Abnormalities in brain regions subserving language processing are observed in SZ, and our preliminary work demonstrates similar abnormalities in first-degree relatives (RELs) of persons with SZ. Here, we extend this work, using an event-related semantic priming task to examine how the semantic relationship of prime and target words modulates hemodynamic activity during lexico-semantic processing in young adult RELs compared to healthy controls. Methods: Subjects were 22 non-psychotic RELs and 21 controls comparable in age, sex, ethnicity, handedness and IQ. Task-related hemodynamic response was estimated using functional magnetic resonance imaging (fMRI) scans collected on a Siemens 3.0 Tesla scanner. During fMRI, subjects viewed directly related, indirectly related, and unrelated prime-target word-pairs as they performed a lexical decision task, in which they decided whether each target was a real word or a nonword. fMRI data were analyzed in SPM8. Between-group differences were tested using two-group t tests or ANCOVA, and were corrected for multiple comparisons (1) across the whole-brain, or (2) using a priori, task-

specific anatomically-defined regions of interest. Results: While controls had a higher level of parental education, there were no group differences in other demographic variables, mood state or semantic priming, except RELs were impaired on a verbal memory story recall task. During lexical processing of directly related (relative to unrelated) word-pairs, RELs failed to activate left inferior temporal regions, suppressed activity in frontal regions (where controls activated), and enhanced activity (relative to controls) in the hippocampus and parahippocampus. During lexical processing of indirectly related (relative to unrelated) word-pairs, RELs suppressed activation in the same regions in which controls showed significant activation (the left inferior parietal lobule, the left inferior, middle and superior temporal gyrus and temporal pole, and the left insula and inferior frontal gyrus (BA 13/44/45/47) (all clusters corrected across the whole-brain). Conclusion: Familial risk for SZ may be associated with failure of left frontal- and temporal- activation (and hippocampal hyperactivity) in response to semantic associations. Future analyses will evaluate the relationship of brain activity during lexical decisions and verbal memory processing.
ID: 979488

NICOTINE ENHANCES CEREBELLAR RESPONSE DURING FINGER TAPPING

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Background: Dysfunction of nicotinic cholinergic systems is observed in schizophrenia. To determine how nicotine differentially affects cortical responses in patients with schizophrenia as compared to healthy controls, fMRI was used to study the effects of nicotine on neuronal responses during a finger tapping task. Results for healthy controls are reported here. Nicotine increases self-paced finger tapping (FT) rates. The neurobiological effects of nicotine on cortical activity during FT have not been studied in nonsmokers. We hypothesized that nicotine will not alter the primary motor cortex (PMC) activity patterns associated with finger tapping in healthy individuals when the behavioral rate of tapping was fixed. Methods: This is a single-blind crossover trial of nineteen non-smoking, right-handed subjects performing a paced FT task one hour after placement of a 7 mg nicotine or placebo patch. FT consisted of pressing a response box with the right index finger in response to auditory cues at rates of 1 hz, 2 hz and 4 hz during 20 second blocks. fMRI data were acquired using BOLD contrast technique in a 3T MR scanner. Images were processed and analyzed using an ANOVA in SPM2. Results: The FT task elicited contralateral primary motor cortex (PMC) response. PMC activity increased with increasing FT rate. Nicotine administration resulted in greater activity in the ventral tegmental area, the right cerebellar hemisphere, and vermis as compared to placebo during the FT task, but yielded no statistical difference in activation of the primary motor cortex. Conclusion: Our finding of increasing activity in the primary motor cortex with increasing FT rate is consistent with prior work and is a potential confounding factor in pharmacological studies of FT. As we hypothesized, nicotine did not affect the primary motor cortex activity when the FT rate was controlled; however, it did have an effect on the right cerebellar hemisphere and vermis, as well as the ventral tegmental area. Future studies will examine the effects of nicotine on FT in individuals with schizophrenia.
ID: 980058

LACK OF PERCEPTUAL COHERENCE IN SCHIZOPHRENIA: A FUNCTIONAL MRI STUDY OF VISUO-PERCEPTUAL ORGANIZATION IN A VISUAL SEARCH TASK

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Background: Patients with schizophrenia fail to integrate information in space, possibly explaining why the outer world is perceived as fragmented. Previous studies reported abnormal visual organization, but the origin of the deficits are unclear, since it involves several processes. Low-level mechanisms enable automatic structuring of information according to grouping principles. Re-grouping information differently can however be required when searching for specific targets. Flexibility in perceptual organization is thus needed to adapt to circumstances, but involves the risk of breaking perceptual coherence issued from automatic grouping. Methods: We used event-related fMRI to test the ability to maintain perceptual coherence while re-organizing information in chronic patients with mild symptoms. 16 outpatients and matched controls identified 2 targets in a 6 figures display. The targets were either grouped by a connector (automatic grouping) or located between 2 connectors (to be re-grouped). Automatic grouping efficiency was also tested by presenting targets within/across hemifields, since connectors reduce the inter-hemispheric transfer cost for targets across hemifields. To test for the stability of automatic grouping across time, the ratio of connected/unconnected targets varied in 4 blocks with this sequence: (1) majority of unconnected targets, (2) equal ratio, (3) majority of connected targets and (4) equal ratio. FMRI analyses were performed on blocks 2 and 4, which were identical except that they followed blocks 1 or 3, which drove subjects to focus on regions either between or within perceptual groups. Results: Patients showed a preserved benefit from connectors in all cases but block 1, when there was a majority of unconnected targets: they were then faster for unconnected targets but unusually slowed down for connected ones within hemifields. In block 2, whole brain analyses showed deficient activations in right inferior/middle frontal areas for unconnected vs connected targets ($P < .005$). In block 4, supplementary activations were observed for connected vs unconnected targets in the right dorsal anterior cingulate/superior frontal areas ($P < .005$). Conclusion: The results suggest an impaired ability to simultaneously reorganize information and maintain automatic grouping, causing patients to face conflicting perceptual organizations or even loose perceptual coherence, depending on the task conditions.
This research was supported by a PHRC grant (Hospital Project for Clinical Research)
ID: 979116

EMOTION REGULATION STRATEGIES IN SCHIZOPHRENIA PATIENTS: AN FMRI STUDY

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Background: Previous studies showed that schizophrenia patients experience emotion regulation difficulties. While healthy subjects prefer to reinterpret (reappraise) negative experiences and give it a positive connotation, schizophrenia patients show an increased preference for suppressing negative emotions. Suppression has been associated with lower levels of well-being and decreased social functioning. To date, the neural basis of emotion regulation has only been investigated in healthy subjects. Other studies did show structural and functional alterations in schizophrenia patients in the dorsolateral and medial PFC, ACC and amygdala, brain areas related to emotion regulation. This study aims to shed more light on the neural mechanisms of emotion regulation in schizophrenia. Methods: Eight schizophrenia patients and eight healthy controls completed a self-report measure of emotion regulation (Emotion Regulation Questionnaire). Furthermore, brain activation was measured by means of functional Magnetic Resonance Imaging (fMRI), an emotion regulation task with two experimental (1, 2) and two control (3 ,4) conditions was administered: (1) reappraise a picture scene, (2) suppress the negative emotion, (3) attend a negative picture and (4) attend a neutral picture. All pictures were accompanied by the instructions to either reappraise, suppress or attend. Then, subjects were asked to rate their current negative affect. All subjects were trained beforehand. Results: Schizophrenia patients reported more use of the suppression strategy than healthy controls and demonstrated less activation in superior, medial and middle frontal regions in the reappraisal condition. Suppressing negative stimuli did not reveal activation differences in the emotion regulation network between groups. Conclusion: The increased use of the suppression strategy may indicate that patients have more problems reappraising negative events and therefore have a tendency to suppress more often. This is reflected in the imaging results; less activation in the prefrontal areas during reappraisal may indicate that reappraising negative events requires resources that are less available to patients. Thus, increasing the use of the other emotion regulation strategy, suppression, seems a natural alternative. Training schizophrenia patients in the use of the reappraisal strategy may improve their handling of negative events and thus improve their quality of life.
ID: 979424

INHIBITION OF RESPONSE TO EMOTIONAL WORDS ELICITS ATTENUATED NEURAL RESPONSES IN SCHIZOPHRENIA

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Background: Disruptions of response inhibition constitute one of the most characteristic neurocognitive deficits associated with schizophrenia. In addition, patients with schizophrenia demonstrate impairments in emotion processing and identification. In the present study, we employed a verbal affective go/no-go paradigm in which response selection and inhibition must be guided by affective content, thus explicitly linking cognitive and affective processing. As patients with schizophrenia are impaired on both response inhibition and emotion processing, assessing this task in an fMRI setting could shed light on the neural processes underlying these deficits. Methods: fMRI scans were obtained in 13 people with schizophrenia and 16 healthy age matched adults. Four conditions were presented in a randomized block design: neutral targets, with negative or positive distracters, and negative or positive targets with neutral distracters. Blocks consisted of 10 word stimuli, and each condition was presented twice. Data were preprocessed and analyzed with SPM5. Within- and between-subject t-tests were conducted to assess task-related and group differences in brain activation respectively. Activation clusters were considered significant if they exceeded a threshold of $P < .001$, uncorrected, with an extent >20 voxels. Results: In healthy adults, inhibition of negative stimuli revealed activation in a predominantly right hemispheric network: middle and superior frontal gyrus, lateral inferior frontal gyrus, cingulate, insula, and angular gyrus, whereas inhibition of positive stimuli caused deactivation of the anterior cingulate. In people with schizophrenia, neither contrast revealed significant clusters, though at a lower threshold patients did show activity in portions of the network identified in healthy adults. Two sample T tests revealed significantly increased activation in the right superior/middle frontal region and left insula when inhibiting negative stimuli, and enhanced deactivation in the mid-cingulate gyrus when inhibiting positive stimuli in controls relative to schizophrenia. Conclusion: People with schizophrenia showed attenuated neural responses in the frontal cortex, a region contributing to response inhibition, and the insula, implicated in facilitating interference resolution for emotional information. These findings are suggestive of aberrant interactions between cognitive and affective processing streams in schizophrenia.
ID: 987271

SELF-RECOGNITION DEFICITS IN SCHIZOPHRENIA PATIENTS WITH AUDITORY HALLUCINATIONS: A META-ANALYSIS OF THE LITERATURE

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Background: Theories about auditory hallucinations in schizophrenia suggest that these experiences occur because patients fail to recognize thoughts and mental events as self-generated. Different theoretical models have been proposed about the cognitive mechanisms underlying auditory hallucinations. Regardless of the model being tested however, experimental designs are almost identical in that they require a judgment regarding whether an action was self-originated or not. The aim of the current study was to integrate all available literature for a meta-analysis on this topic, and reach conclusions about self-recognition performance in (i) patients with schizophrenia compared to healthy controls, and (ii) patients with auditory hallucinations compared to patients without these symptoms. Methods: The literature was systematically searched for suitable studies, as recommended in the Prisma statement. It identified 23 studies that contrasted the performance of schizophrenia patients with that of healthy controls (1370 participants), and 9 studies that directly compared patients with and without auditory hallucinations (315 participants). The results were quantitatively summarized in a series of meta-analyses to reach mean weighted effect sizes about differences in experimental groups. Results: We found significantly reduced self-recognition performance in schizophrenia patients, which was more pronounced in patients with auditory hallucinations compared to patients without. In patients with hallucinations, this pattern of performance was specific to self-recognition processes, and not to the recognition of external information. Conclusion: In summary, a striking finding from the results was the homogeneity in results across studies regardless of the action modality, timing delay, and design used to measure self-recognition. Additional important findings include the results that self-recognition def-

icits pertain more to attentional/perceptual than to later memory processes, and more to controlled than to automatic processes. Overall, this review of studies from the last 30 years has validated the presence of impaired self-recognition in schizophrenia, and particularly those with auditory hallucinations. This suggests an association, perhaps a causal one, between this cognitive deficit and hallucinatory experiences in schizophrenia.
ID: 977165

MAGNETIC RESONANCE IMAGING OF RESTING-STATE CEREBRAL BLOOD FLOW IN SCHIZOPHRENIC PATIENTS WITH PERSISTENT SUDITORY VERBAL HALLUCINATIONS

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Background: Abnormal regional cerebral blood flow (rCBF) in patients with schizophrenia experiencing auditory verbal hallucinations (AVH) has been shown by neuroimaging studies using positron emission tomography (PET) and single-photon emission computed tomography (SPECT). In contrast to PET and SPECT, continuous arterial spin labeling (cASL) is a non-invasive magnetic resonance imaging (MRI) method of high spatio-temporal resolution, which delivers a quantitative assessment of cerebral perfusion. Using resting-state cASL, the aims of this study were 1. to test the hypothesis that persistent AVH are associated with rCBF-changes in a speech-related brain network, and 2. to explore the relationship between cortical baseline perfusion and AVH phenomenology. Methods: Resting-state rCBF was studied in 14 healthy controls and 20 patients with schizophrenia according to DSM-IV criteria. 10 patients were classified as treatment resistant with regard to AVH and reported the occurrence of AVH during the MRI session. The clinical control group consisted of 10 clinically stable in-patients with schizophrenia without AVH. Group comparisons ($P < .05$, corrected) between controls, patients with and without AVH were conducted using an analysis of variance model. Results: Compared to healthy controls, patients with AVH exhibited increased rCBF in the bilateral superior temporal cortex, the left insula, the supplementary motor area, the left anterior cingulate cortex, the left inferior frontal gyrus and the right supramarginal gyrus. Patients without AVH showed increased rCBF in the left middle and superior temporal cortex, the left insula and the left supramarginal gyrus. Hallucinating patients showed increased rCBF in the left middle temporal cortex and the right supramarginal gyrus when compared to patients without AVH. A positive correlation ($P < .05$) was found between left inferior frontal, cingulate and right temporal rCBF and AVH scores, as assessed by the Psychotic Symptom Rating Scale. Distinct correlation patterns were found between regions exhibiting perfusion changes and AVH phenomenology within cognitive, physical and affective domains. Conclusion: These data indicate that perfusion abnormalities in brain regions associated with inner speech and auditory processing may underlie persistent AVH in patients with schizophrenia. Moreover, the relationship between indices of AVH severity and rCBF suggests that distinct cortical loci of dysfunction may contribute to the phenomenological diversity of AVH.
ID: 978515

NEUROIMAGING AND NEUROBEHAVIORAL ASSESSMENT OF REWARD PROCESSING IN SCHIZOPHRENIA

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Background: Progress in understanding the phenomenology and pathophysiology of reward-processing abnormalities in schizophrenia will require integrating subjective reports with objective neural and behavioral data. Ventral striatum (VS) plays a key role in normal reward processing, and VS hypofunction has been related to global negative symptom severity in schizophrenia. Further investigation of this relationship must focus in on specific negative symptom domains. Animal research indicates that ventral striatum dysfunction impairs motivation and anticipatory pleasure while sparing consummatory pleasure, a pattern also observed in schizophrenia. Methods: Ten patients with schizophrenia and ten controls have completed the study to date. 3T fMRI BOLD data is obtained during two guessing-game tasks, adapted from the Delgado Gambling Task. The tasks were designed to probe VS neural responses to positive and negative feedback; in one task feedback is provided through monetary gains and losses while the other task utilized photographs of facial emotions. After scanning, a neuroeconomic behavioral battery measures risk aversion, loss aversion, temporal discounting, probabilistic learning, and motivation. Negative symptoms are evaluated with self-report and interview scales, including the SANS and the Clinical Assessment Inventory for Negative Symptoms (CAINS, under development). Results: In both groups, peak activation across the brain occurred in VS for the positive feedback > negative feedback contrast. VS responded similarly to monetary and facial affective feedback; however fusiform and occipito-temporal cortex responded more strongly to facial feedback. Both patients and control groups showed similar levels of loss aversion, risk aversion, and similar progressive ratio response breakpoints; however patients showed greater temporal discounting of delayed rewards. Across groups, subjects with greater loss aversion showed greater VS activation to monetary feedback. Conclusion: In this preliminary analysis, control subjects showed expected findings, and schizophrenia subjects showed qualitatively normal neural and behavioral responses, although with greater temporal discounting. The current sample is underpowered for analysis of group differences or negative symptom correlations. As the sample size increases, such analyses may reveal related VS and behavioral abnormalities during reward processing in schizophrenia, particularly in those patients with prominent anticipatory anhedonia and avolition.
ID: 978350

RESTING-STATE NETWORKS ARE DIFFERENTIALLY AFFECTED IN SCHIZOPHRENIA

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Background: Neural dysconnectivity hypotheses of schizophrenia posit that symptoms result from abnormalities in brain circuits underlying cognition and emotion. However, it is unknown if dysconnectivity is a global phenomenon characterized by widespread alterations, or if specific brain networks are affected. To help address this question, we used resting-state fMRI and functional connectivity methods to examine the integrity of four intrinsic connectivity networks in schizophrenia. Methods: 42 patients with

schizophrenia/schizoaffective disorder and 61 matched control subjects underwent resting-state fMRI scanning. Seed-based functional connectivity analysis was used to identify the default mode, dorsal attention, executive control, and salience networks. Group differences in functional connectivity were analyzed on a voxel-wise and region-of-interest basis. Results: In schizophrenia patients we found increased functional connectivity in the default mode and decreased functional connectivity in the dorsal attention and executive control networks. The spatial topography of the default mode was expanded into prefrontal regions (inferior frontal gyrus/lateral orbitofrontal cortex and superior frontal gyrus) and lateral temporal cortex. These regions of increased connectivity in patients overlapped with the normal executive control network, suggesting that the process of network differentiation, occurring during adolescence, may be altered in schizophrenia. Conversely, patients demonstrated less connectivity in the executive control and dorsal attention networks. Region-of-interest analysis within these networks revealed that inter-hemispheric connectivity between homotopic brain regions was more affected than intra-hemispheric connections. This suggests disturbances in the integrity of trans-collosal white matter tracts connecting homotopic brain regions. Conclusion: Overall, our findings indicate that neural dysconnectivity in schizophrenia, inferred on the basis of temporal coherence in resting-state fMRI BOLD signals, is heterogeneous: connectivity is increased in some networks and reduced in others. Follow-up studies will be required to determine the functional relevance and mechanisms of these changes, including disturbances in white matter connectivity, abnormal neurodevelopment, and genetic risk for schizophrenia.
ID: 952040

BEHAVIORAL AND FMRI EVIDENCE FOR COGNITIVE UNDERPINNINGS OF VERBAL HALLUCINATIONS

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Background: Auditory verbal hallucinations (AVHs) require that an inner, self-generated event be experienced as not self-generated and possibly external. Dysfunction in the cognitive processes involved in the generation of private thoughts may contribute to externalization, through reduced salience of generating thoughts, and/or increased perceptual qualities associated with private thoughts. In the present study, we investigated the neural activity associated with generating private thoughts using two conditions: verbal thought generation (VTG) and speech perception (SP). Methods: Data collected to date consists of 11 each of schizophrenia patients, bipolar disorder, and healthy controls. For VTG, participants mentally generated a definition of a word. For SP, participants listened to a definition of a word. These condition were examined with functional magnetic resonance imaging (fMRI). Data analysis was performed using Constrained Principal Component Analysis (CPCA) with a Finite Impulse Response (FIR) model. Results: Component 1 was dominated by the dorsal anterior cingulate cortex, left prefrontal cortex, and the cerebellum, comprising aspects of the task-positive network. Component 2 was dominated by the visual cortex activations and reciprocal deactivations in the ventral anterior cingulate cortex, with the latter comprising aspects of the task-negative (default) network. Component 3 was dominated by deactivations in the posterior cingulate cortex, which is an aspect of the task-negative (default) network. Component 4 was dominated by in bilateral Heschel's gyrus, bilateral middle temporal cortex, and occipital cortical regions. The networks represented by Components 3 and 4 were significantly more activated in the SP relative to the VTG condition, suggesting that these were primarily involved in perception of speech. The schizophrenia group showed a higher activation peak relative to the other groups in the SP condition for Component 4, and in both the SP and VTG conditions for Component 3. Conclusion: This set of results suggests that hyper-reactivity in the neural networks involved in perceiving auditory verbal information may be characteristic of schizophrenia, and that this may extend to private thought generation for the default mode aspects of these networks. Hyperactivity of the neural networks involved in the perception of auditory stimuli may provide a biological basis for AVHs.
ID: 979393

NEURAL RESPONSE OF ANTICIPATORY AND CONSUMMATORY PLEASURE IN PSYCHOTIC DISORDERS: AN ACTIVATION LIKELIHOOD ESTIMATE META-ANALYSIS OF MONETARY INCENTIVE DELAY TASK

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Background: The neural response of anticipatory and consummatory affect can be separately identified by using monetary incentive delay (MID) task. In the past decade, cumulative evidences of sub-cortical (eg ventral striatum) and cortical (eg frontal gyrus) abnormalities have been reported in patients with schizophrenia and depression using the MID task. However, these studies have not been quantitatively reviewed. The current study aimed to conduct a meta-analysis to quantitatively review the impairments associating with neural activation of anticipatory and consummatory pleasure in patients with schizophrenia and depression compared with healthy controls. Methods: Activation likelihood estimation (ALE) meta-analysis was conducted using the GingerALE. Results: A systematic search of the literature indicated there were six studies fulfilled the criteria of inclusion for the meta-analysis. For anticipatory pleasure, it revealed a relative activation in right caudate head, left putamen, and right red nucleus in healthy controls. However, it revealed hypofunction of left putamen for anticipatory pleasure in patients with schizophrenia relative to healthy controls and hyperfunction of right middle frontal gyrus for patients with depression compared with healthy controls. For consummatory pleasure, healthy controls demonstrated a relative activation in left anterior cingulated. Compared with healthy controls, patients with depression deactivated caudate body. Conclusion: The results provide the first-hand data to demonstrate the robust findings of affective experience disturbance in psychotic disorders.
ID: 978173

15. Neuroimaging, Structural

COVARIANCE MODELING OF MRI BRAIN VOLUMES IN MEMORY CIRCUITRY IN SCHIZOPHRENIA: IMPACT OF GENDER

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Background: Brain regions subserving memory function have been found to be abnormal in schizophrenia (SCZ), including prefrontal cortex (PFC), inferior parietal lobule (iPAR), anterior cingulate gyrus (ACG), parahippocampus, and hippocampus (HIPP). Verbal memory processes that utilize these regions are disrupted, and more so in men with SCZ than women. Despite the importance of verbal memory dysfunction as a key deficit in SCZ, an understanding of the brain anatomy associated with the female advantage for verbal memory is still unclear. Methods: 29 females and 59 males with SCZ made comparable to 21 female and 27 male healthy volunteers were scanned using structural magnetic resonance imaging (sMRI) in order to assess volumes of regions across the entire brain. Sex differences within and between groups in the covariance structure of memory circuitry regions were evaluated using a novel approach to covariance analysis. Regions of interest were those listed above. Results: Findings showed a significant difference between the covariance matrices of females and males with SCZ [χ^2 (15) = 38.30, $P < .001$], driven by significant differences ($P < .05$ for post-hoc correlation z test) between the correlation of iPAR-PFC ($z = 2.54$), iPAR-ACG ($z = 2.16$), and HIPP-ACG ($z = 3.31$). Sex differences in the iPAR-PFC relationship were significantly associated with sex differences in verbal memory performance. In control women, but not in men, ACG volume correlated strongly with memory performance. In SCZ, ACG volume was reduced in females, but not in men, relative to controls. Conclusion: Findings suggest that the relationship between iPAR and PFC is particularly important for understanding the relative preservation of verbal memory processing in females with SCZ and may compensate for ACG volume reductions. Results illustrate the utility of a unique covariance structure modeling approach that yields important new knowledge for understanding the nature of SCZ and the importance of considering sex differences when studying cognitive symptoms and brain anatomy in SCZ.
ID: 976645

CANNABIS USE AND WHITE MATTER MICROSTRUCTURE IN ADULTS BORN VERY PRETERM

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Background: Preterm birth is a risk factors for psychosis. It is not known how (or whether) this interacts with other known risk factors - such as use of cannabis. Microstructural abnormalities of white matter are associated with preterm birth, and with cannabis use and have been implicated in the etiology of psychosis. We studied the effect of cannabis on white matter structure, indexed by Diffusion Tensor-MRI (DT-MRI), in individuals born very preterm (VPT: before 33 weeks' gestation) and term-born controls. Methods: 72 VPT and 42 term-born young adults were assessed with DT-MRI at a mean age of 19 years. Cannabis use data was recorded using the relevant fields of the Clinical Interview Schedule - Revised. DT-MRI data was analysed using SPM and XBAM, comparing group differences in Fractional Anisotropy (FA) at a voxel level between users and non-users of cannabis in Term and VPT groups. Results: Cannabis use was reported significantly less frequently in the VPT group ($chi^2 = 4.91$; $P = .027$). In the VPT group, cannabis users had lower FA than non-users in one cluster located in the anterior corpus callosum. In the Term group, there were no significant difference between cannabis users and abstainers. Conclusion: White matter in the VPT brain may be more vulnerable to the detrimental effects of cannabis. Further studies would be required to establish whether this has any clinical relevance. It is of interest that VPT young adults appear to be less likely to use cannabis.
ID: 978341

SCHIZOPHRENIA-LIKE ABNORMALITIES INDUCED BY IMMUNE ACTIVATION DURING PREGNANCY CAN BE PREVENTED IN THE FEMALE RAT OFFSPRING BY RISPERIDONE TREATMENT DURING ADOLESCENCE

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Background: Schizophrenia (SZ) is a neurodevelopmental disorder manifested symptomatically in late adolescence/early adulthood. Neuroimaging studies show that neuroanatomical aberrations precede onset of symptoms, raising a possibility that SZ can be prevented. We have recently shown, using in vivo structural MRI that treatment with the atypical antipsychotic risperidone (.45 and 1.2 mg/kg) during an asymptomatic period of adolescence prevents the emergence of SZ-like brain structural and behavioral abnormalities in adult male offspring of dams exposed to the synthetic double-stranded RNA polyriboinosinic-polyribocytidylic acid (poly-I:C) that mimics a viral infection, a well documented risk factor of SZ. Given that sex differences exist in response to anti-psychotic treatment, here the preventive capacity of risperidone was assessed in adult female offspring exposed prenatally to poly-I:C. Methods: Pregnant rats were injected on gestational day 15 with poly-I:C or saline. Their female offspring were injected daily for 14 days during adolescence (postnatal days [PND] 34–47) with .045 [RIS-.045] or 1.2 [RIS-1.2] mg/kg risperidone or saline. SZ-like structural brain changes and abnormal behaviors were assessed at adulthood (PND90+). Results: Adult offspring of poly-I:C-treated dams exhibited hallmark structural abnormalities associated with SZ: enlarged lateral ventricles (LV) and smaller hippocampus (HIP). Both volumetric abnormalities were prevented by RIS-.045 but only the reduction in HIP volume was prevented by RIS-1.2. Poly-I:C-exposure also resulted in loss of latent inhibition (LI) and increased amphetamine-induced hyperactivity. RIS-.045 again was superior to the higher dose as it prevented both behavioral abnormalities in poly-I:C-exposed offspring while having no deleterious effects in saline-exposed offspring. In contrast, RIS-1.2 prevented only the LI deficit in poly-I:C-exposed offspring and led to hypersensitivity to amphetamine in saline-exposed offspring. Conclusion: Thus, while in males both RIS doses were effective, in females only the low dose, which exerts potent 5HT2A receptor antagonism, was effective. Our results show that pharmacological intervention during adolescence can prevent the emergence of behavioral and brain structural abnormalities resulting from in utero insult in both sexes. Furthermore, our results reveal sex-specific efficacy of preventive treatments, underscoring the importance of investigating preventive treatments and their mechanisms in both sexes.
ID: 977411

FUNCTIONAL POLYMORPHISMS OF DGCR2 GENE MAY BE ASSOCIATED TO SCHIZOPHRENIA PATHOGENESIS AND PLAY A ROLE IN NEURO-DEVELOPMENT

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Background: Several studies have shown that 22q11 deletion is an important risk factor for schizophrenia. Genetic and functional evidence suggest an association between the DGCR2 gene, located at 22q11.2, and schizophrenia, although its role in the pathology is still not clear. The aim of this study was to investigate the association between functional DGCR2 gene polymorphisms and brain structure in patients with schizophrenia. Methods: A total of 193 patients with schizophrenia was selected from the Schizophrenia Program (PROESQ) and compared with 156 healthy controls recruited from the Interdisciplinary Laboratory of Clinical Neurosciences (LiNC), both at UNIFESP. The patients were genotyped for rs2073776 (T/C), rs807759 (A/G) and rs2072123 (A/G) DGCR2 gene polymorphisms using TaqMan® probe-based real-time PCR assay. In order to investigate the association between these polymorphisms and the disease, as well as to verify Hardy-Weinberg equilibrium, a chi-square test ($P < .05$) was applied. Among 193 genotyped patients, 139 were submitted to MRI scan in a 1.5T scanner. A whole-brain gray matter voxel-based morphometry (VBM) analysis was performed using SPM5. Smoothed images (FWHM = 10 mm) were analyzed through a factorial ANCOVA design using intracranial volume as a covariate. Small volume correction (SVC) was used for multiple comparisons at $P < .01$ (false discovery rate). Subjects were divided in groups according to their genotypes. Results: All allele polymorphisms were in Hardy-Weinberg equilibrium. It was found an association between rs2073776 T allele carriers and schizophrenia, but no association between rs2072123 and rs807759 polymorphisms and the disease was found. VBM analysis revealed a significant reduction of right insula ($Z = 3.33$, pFDR $< .01$) and of the bilateral temporal gyrus ($Z = 4.05$, pFDR $< .01$) volumes in subjects with GG genotype, when compared to AG and AA, assuming a recessive model for rs2072123. Similar results were found for rs2073776 polymorphism when comparing TT to CT and CC genotypes. Conclusion: In this study, it was shown that T allele (rs2073776) may be a risk factor for schizophrenia and, in addition, when present in homozygosis, this allele is related to insula and temporal gyrus volume reduction. Similarly, G allele homozygous for rs2072123 polymorphism presented a similar pattern of brain structural reduction. These findings, taken together, reinforce the idea that DGCR2 gene may be associated to schizophrenia pathogenesis and also, play a role in the neurodevelopment.
ID: 978437

THE NEURAL CORRELATES OF PERSISTENT NEGATIVE SYMPTOMS IN FIRST EPISODE SCHIZOPHRENIA: A MULTI-MODAL STRUCTURAL MRI INVESTIGATION

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Background: Persistent negative symptoms (PNS) are considered intrinsic to schizophrenia. However, clinically significant PNS represent an unmet therapeutic need in many cases. Thus, a better understanding of the pathophysiology of PNS in first-episode patients could help identify better or alternative treatments for those affected. Methods: The current neuroimaging study included 55 first-episode schizophrenia patients, treated in a specialized early intervention service, and 60 healthy controls; 12 patients displayed PNS (that is, at least 1 primary negative symptom at moderate or greater severity sustained for at least 6 months). We set out to determine if neuroanatomic volumetric differences were evident between PNS and non-PNS patients using fully-automated (voxel-based morphometry, whole-brain analysis), semi-automated (caudate, putamen, globus pallidus), and manual tracing (amygdala, segmented hippocampus, lateral ventricle) techniques. Results: The voxel-based morphometry analysis identified smaller graygray matter volumes in the frontal pole bilaterally and left inferior and right medial frontal gyri in PNS patients compared to non-PNS patients. In contrast, PNS patients displayed larger right and left amygdala volumes (significant on right, trend on the left) compared to non-PNS patients. There were no significant differences in caudate, putamen, globus pallidus, hippocampus, or ventricle volumes between patient groups. Conclusion: Neural markers (namely amygdala volume) of persistent negative symptoms are evident in first-episode patients. A better understanding of the neural etiology of schizophrenia and its relationship to PNS may encourage the search for new medications and/or alternative treatments to better help those affected.
ID: 947088

ANALYSIS OF DIFFUSION TENSOR IMAGING IN PATIENTS WITH SCHIZOPHRENIA AND THEIR NON-PSYCHOTIC SIBLINGS

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Background: Structural brain abnormalities have consistently been found in patients with schizophrenia. Diffusion tensor imaging (DTI) has been shown to be a useful method to measure white matter (WM) integrity in this illness, but findings of studies are inconclusive. As having a first-degree relative with schizophrenia is the strongest known risk factor for schizophrenia (Gottesman, 1991), differences in WM microstructure may also be present in these relatives. By examining a large group of patients with schizophrenia and their non-psychotic siblings at risk for developing the illness, it is possible to investigate whether differences in WM microstructure may be related to the (genetic) risk for developing schizophrenia. Methods: From 126 patients with schizophrenia, 123 of their non-psychotic siblings and 109 healthy control subjects, DTI images were acquired with a 1.5 Tesla scanner. Mean fractional anisotropy (FA) was compared along averaged WM tracts, computed for the genu, uncinate fasciculus, cingulum, inferior fronto-occipital fasciculus (IFO), fornix, arcuate fasciculus, inferior longitudinal fasciculus (ILF), and splenium. Results: After controlling for age, gender and handedness, patients and non-psychotic siblings did not differ from healthy control subjects in mean FA. In patients with schizophrenia, a significant decline in mean FA with age was found compared to siblings and healthy control subjects in the genu ($X^2 = 3.82$, $P = .05$), left uncinate fasciculus ($X^2 = 3.89$, $P = .05$), left inferior fronto-occipital fasciculus ($X^2 = 7.51$, $P = .01$), and left inferior longitudinal fasciculus ($X^2 = 8.28$, $P = .00$). Type of medication did not seem to effect on mean FA comparing the group of patients using atypical vs typical medication. In addition, the pronounced decrease that we found in mean FA with age, in patients did not seem not to be explained by the effect of duration of illness. Conclusion: No differences were found in mean FA between patients with schizophrenia, their non-psychotic siblings and healthy control subjects. That we found a stronger decline in FA with age in patients with schizophrenia com-

pared to their siblings and healthy control subjects, suggests a progressive loss of WM microstructure in patients with schizophrenia in older age.
ID: 977332

FRONTO-TEMPORAL PATHOLOGY IN FIRST-EPISODE PSYCHOSIS PATIENTS WITH POOR INSIGHT AS REVEALED BY CONVERGENT FINDINGS FROM MULTIMODAL STRUCTURAL NEUROIMAGING

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Background: A substantial proportion of patients with psychotic disorders have poor insight. Insight comprises awareness and attribution dimensions, with awareness referring to the recognition of symptoms, and attribution to one's explanations about the cause of their symptoms. In a previous work, we observed cortical thinning in prefrontal and temporal cortices in association with misattribution for two symptoms, hallucinations and delusions, in people with a first-episode psychosis. The current investigation applied multimodal imaging (cortical thickness, diffusion tensor imaging tractography) to a larger sample and aimed to (1) replicate our previous cortical thinning findings, and (2) explore whether fronto-temporal dysconnectivity is evident in patients with hallucination and delusion misattribution. Methods: Fifty-one people with a first-episode psychosis were rated on the misattribution of hallucination and delusions items of the Scale for assessment of Unawareness of Mental Disorder. Participants were assessed with magnetic resonance imaging. Scores on the two misattribution items were regressed on cortical thickness at 40 962 vertices across the cortical mantle. Second, misattribution scores were correlated with diffusion tensor imaging tractography-determined fractional anisotropy (FA) in two tracts connecting frontal and temporal regions, the uncinate fasciculus and superior longitudinal fasciculus. Results: Greater misattribution of hallucinations associated with cortical thinness in left dorsolateral prefrontal cortex (DLPFC) (BA9) and left inferior temporal gyrus (BA 20), and to lower FA values in the left uncinate and left superior longitudinal fasciculus. Greater misattribution of delusions associated with cortical thickness in right DLPFC (BA 9) and right inferior, middle and superior temporal gyri (BA 20/19/22), and to lower FA values in bilateral uncinate fasciculus and left superior longitudinal fasciculus. Conclusion: These data suggest that patients who erroneously attribute their hallucinations to causes other than a mental disorder appear to show dysconnectivity in left fronto-temporal brain areas, while those who misattribute delusions appear to show right fronto-temporal dysconnectivity. These regions have also been implicated in awareness of illness deficits, suggesting fronto-temporal pathology may reflect a commonality in the topographic basis for awareness and attribution dimensions in first-episode psychosis.
ID: 976989

SCALE RELATIONSHIP BETWEEN BRAIN VOLUME AND CORTEX AREA: AN ALLOMETRIC STUDY IN SUBJECTS AT RISK MENTAL STATE AND FIRST-EPISODE PSYCHOSIS PATIENTS

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Background: Compelling evidences suggest that schizophrenia results from aberrations in neurodevelopmental processes, including early prenatal and adolescent brain maturation deviations (Weinberger 1987; Rapoport 2005). Recent studies have shown that during ontogenesis cortical surface area and cerebral volume are related by a scaling law whose exponent, or allometric scaling factor, gives a quantitative measure of cortical development (Kapellou 2009). As cortical growth is impaired during the transition to psychosis (Wood 2008), we tested the hypothesis that the normal allometric scaling factor should be disrupted after the transition to psychosis, namely in first episode psychosis (FEP) patients, but not in individual At Risk Mental State (ARMS) (Yung 1998). To discard possible cortical growth deviations early before the transition to psychosis, only ARMS who did not convert to psychosis 24 month after the scanning were investigated. Methods: MRI data were acquired from healthy controls (HC) ($N = 34$), FEP patients ($N = 15$), and ARMS ($n = 24$) at the Institute of Psychiatry (London). The cerebral volume and the cortex area were estimated from T1 MRI (Toro 2008; Im 2008) automatically segmented with Brainvisa software (http://brainvisa.info). To estimate the scaling exponents between cerebral volume and cerebral area, multiple regression analyses were performed on logarithmically transformed measures with age and gender as confounding covariates (Kapellou 2006; Im 2008; Toro 2008). Results: A significant slope difference was detected between HC (.853 ± .148) and FEP (−.207 ± .266) ($P = .0001$). There was no slope difference between HC and ARMS (.920 ± .209) ($P = .75$). Conclusion: In this first allometric study in psychosis, we found that the normal scaling allometric factor (.85) (Changizi 2001, for review) holds in ARMS but not in FEP, supporting the impaired cortical growth during the transition to psychosis (Wood 2008). Deviant allometric scaling factor could be associated to connectivity disruption in schizophrenia (Stephan 2009) as theoretical works show that the typical allometric factor of .85 enables optimizing the axon length and the time processing within cortical networks (Cherniak 1999, 2004; Chklovskii 2002).
ID: 986666

ALTERED WHITE MATTER INTEGRITY PREDICTS LANGUAGE IMPAIRMENT IN CHILDHOOD-ONSET SCHIZOPHRENIA

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Background: Childhood-onset schizophrenia (COS), defined as having onset of symptoms before age 13, represents a rare and severe form of schizophrenia. Many of the core symptoms of schizophrenia, eg hearing voices and disorganized speech, support the idea that abnormalities in the language system form a potential basis of schizophrenia. Additionally, several studies have reported that adults with schizophrenia had significant speech delays as children. Methods: In this study, diffusion tensor imaging (DTI) was acquired on twenty patients (ages 8.5–17.9 years) with COS and twenty-five normal controls (ages 7.9–18.4 years). Approximately half of the COS patients had significant linguistic impairments, defined as having spoken language quotient (SLQ) less than 1.5 standard deviations below normal. A white matter DTI-derived atlas of eleven major tracts was used to investigate how white matter integrity is impacted in COS. Results: Results showed that patients had lower fractional anisotropy (FA) in the corticospinal tract (CST), inferior fronto-occipital fasciculus (IFO), and the inferior longitudinal fasciculus (ILF). Strikingly, the COS patients had higher mean diffusivity (MD) in every tract investigated. The linguistically impaired patients had lower FA in the IFO and higher MD in the CST, ILF, and the superior longitudinal fasciculus (SLF) compared to the patients without linguistic impairments. Conclusion: These results suggest that alterations in white matter integrity in the IFO, CST, ILF, and SLF can

account for the presence of linguistic deficits in COS; however, alterations in the white matter integrity of the anterior thalamic radiations, the cingulum bundle, and the corpus callosum are not specific to linguistic impairments but appear characteristic of the disorder itself.
ID: 979851

PATTERN CLASSIFICATION USING PRINCIPAL COMPONENTS ANALYSIS OF CORTICAL THICKNESS IN NEUROPSYCHOLOGICALLY DEFINED SCHIZOPHRENIA SUBTYPES

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Background: Neuropsychological deficits are particularly marked in schizophrenia; however, some groups have observed a subset of patients who function at or near cognitively normal levels. Recent work has suggested that differences in the level of cognitive impairment are related to differential patterns of structural change in the cortex. Differences of cortical thickness in schizophrenia can be viewed as neuroanatomic signatures of the disease. Underlying dimensions of these variables have proven useful for classification purposes. The aim of this research was to utilize variations in cortical thickness across the entire surface to identify unique patterns of change in schizophrenia subtypes Methods: Schizophrenia (SCHIZ; $n = 82$) and healthy participants (CON; $n = 70$) were included in this study, and did not differ with regard to demographics. Neuropsychologically Impaired (NPI) and Near-Normal (NPNN) schizophrenia subtypes were derived using k-means clustering on cognitive variables. MR scanning included T1 weighted MPRAGE images processed using the FreeSurfer toolkit. Cortical thickness values for each vertex along the surface for every subject were used in a principal components analysis for dimensionality reduction. Subsequently derived eigenvectors for each hemisphere were evaluated for mean group differences using MANOVA. Separate logistic regression models using subtype as the dichotomous outcome variable (eg, CON vs. NPI; CON vs NPNN) and eigenvectors as predictor variables, examined patterns of cortical thickness variation for the two subtypes. Results: PCA analysis resulted in 33 eigenvectors per hemisphere that explained ~80% of the variance in cortical thickness estimates. MANOVA on these eigenvectors revealed a significant main effect for group in both hemispheres. Logistic regression revealed significant non-overlapping sets of eigenvectors that discriminated NPI from CON (RH-74.3%, LH-68.6%), and NPNN from CON (RH-59.6%, LH-63.8%). A greater distribution of cortical thinning occurred in bilateral temporal and parietal regions for the NPI group, compared to NPNN subjects. Conclusion: Results from this study indicate differential effects on cortical thickness mapping for NPI vs NPNN schizophrenia subjects. Using this technique, both subtypes were distinguished with moderate degrees of accuracy. Discrete discriminating eigenvectors for each group implies separate neurobiological processes underlying the phenotype for each group, and informs theory on disease heterogeneity.
ID: 978155

HIPPOCAMPAL VOLUMES PREDICTING EMOTIONAL AND BIOLOGICAL STRESS-REACTIVITY IN PSYCHOSIS

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Background: Reduced hippocampal volume (HV)has been reported in schizophrenia patients. Moreover, patients and their first-degree relatives show higher stress-reactivity, reflected in larger increases in negative emotions in the face of everyday stress. Siblings show increased cortisol secretion as a response to daily hassles. Since the hippocampus is an important regulator of the Hypothalamic-Pituitary-Adrenal axis, it may play a role in the underlying biological mechanisms determining this increased stress-reactivity in individuals at risk for psychosis. The current study investigated in healthy controls, first degree relatives, and schizophrenia patients whether HV is associated with increased emotional and biological stress-reactivity, indexed by levels of negative affect (NA) and cortisol. Methods: T1-weighted MRI scans were acquired from 20 schizophrenia patients, 38 of their healthy siblings, and 33 controls. Emotional stress-reactivity (ie increases in NA associated with everyday stress) was assessed with Experience Sampling (a structured diary technique). Cortisol levels, assessed in siblings and healthy controls, were used as a measure of biological stress-reactivity. Results: Multilevel linear regression analyses revealed a significant three-way interaction between group, HV, and stress in the model of NA ($\chi^2(4) = 17.9$, $P < .01$) and in the model of cortisol ($\chi^2(2) = 6.72$, $P < .05$). While there was no significant difference in stress-reactivity between individuals with small, medium and large HV in the control group, HV influenced the association between stress and NA in individuals at risk for psychosis. Patients with larger HVs were significantly less stress-reactive than patients with smaller HVs. In addition, patients with small HVs were more stress-reactive than controls with small HVs. Patients with large HVs were less stress-reactive than controls with large HVs. The effect of HV on stress-reactivity in first-degree relatives was intermediary to that of patients and controls. With regard to biological stress-reactivity, larger HVs were associated with less cortisol reactivity to stress in siblings. No such effect was found in controls. Conclusion: Findings support the notion that, in individuals with an increased psychosis-risk, HV is a potential underlying mechanism explaining increased emotional and biological stress-reactivity in daily life. A larger HV may be a protective factor against increased stress-reactivity in these individuals.
ID: 979422

DUPLICATION IN THE 16P11.2 REGION IS ASSOCIATED WITH ALTERED HIPPOCAMPAL MORPHOLOGY IN SCHIZOPHRENIA

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Background: Schizophrenia is highly heritable, although the genetic basis is complicated and not yet clear. Recent genome-wise association studies (GWAS) have begun to reveal associations between copy number variations (CNVs) and schizophrenia. One area of interest is a large ~600 kb region at 16p11.2. This region spans 29 genes, including several that are expressed in the brain and implicated in cognition, neural differentiation, and neuroplasticity. Duplications in this region confer an increased risk of schizophrenia and other neuropsychiatric disorders; deletions here are associated with autism and neurodevelopmental disorders. To date, there are no studies examining structural brain correlates of CNVs in schizophrenia in this region. Methods: Genetic data and magnetic resonance (MR) brain images were obtained from a cohort of 117 individuals with schizophrenia and 127 matched comparison subjects. Three quantitative PCR (qPCR) probes were used to identify CNVs in the 16p11.2 region. T1-weighted MR brain images were processed using high-dimensional brain mapping algorithms to obtain information about volume and shape deformation of the hippocampus. Results: All three qPCR probes suggested that one individual with schizophrenia had a duplication in the 16p11.2 region. Compared to other individuals in our dataset with schizophrenia, this in-

dividual had less volume loss in the anterior hippocampus, with more pronounced volume loss in the tail of the hippocampus. Conclusion: The incidence of the 16p11.2 duplication in our sample is consistent with its reported incidence in larger populations of individuals with schizophrenia. This individual showed a reversal of the pattern of shape change seen in schizophrenia, in which volume loss is normally seen in the anterior rather than posterior regions. Duplications in the 16p11.2 region may alter the expression of genes in a way that reverses the typical pattern of hippocampal volume loss in schizophrenia. If replicated, this finding would be among the first to establish a link between a specific genetic abnormality and a specific neuroanatomical deformation.
ID: 980526

THALAMIC MORPHOLOGY IN SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

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Background: Biomarkers are needed that can distinguish between schizophrenia and schizoaffective disorder to inform the ongoing debate over the diagnostic boundary between these two disorders. Neuromorphometric abnormalities of the thalamus have been reported in individuals with schizophrenia and linked to core features of the disorder, but have not been similarly investigated in individuals with schizoaffective disorder. In this study, we examine whether individuals with schizoaffective disorder have a pattern of thalamic deformation that is similar or different to the pattern found in individuals with schizophrenia. Methods: T1-weighted magnetic resonance images were collected from individuals with schizophrenia ($n = 47$), individuals with schizoaffective disorder ($n = 15$), and controls ($n = 42$). Large-deformation, high-dimensional brain mapping was used to obtain three-dimensional surfaces of the thalamus. Principal component (PC) analysis on the surface was used to represent shape variation. Multiple analyses of variance were used to test for group differences in volume and measures of surface shape. Results: Individuals with schizophrenia or schizoaffective disorder have similar thalamic volumes. Thalamic surface shape deformation associated with schizophrenia suggests selective involvement of the anterior and posterior thalamus (specific PCs), while deformations in mediodorsal and ventrolateral regions were observed in both groups. Schizoaffective disorder had distinct deformations in medial and lateral thalamic regions. Conclusion: Abnormalities distinct to schizoaffective disorder suggest involvement of the central and ventroposterior medial thalamus which may be involved in mood circuitry, dorsolateral nucleus which is involved in recall processing, and the lateral geniculate nucleus which is involved in visual processing.
Between-group comparisons of shape measures and significant principle components for thalamus

F(df1, df2) = P-Value	3-Group MANOVA	2-Group MANOVA		
		SCZ vs. CON	SA vs. CON	SA vs. SCZ
Thalamus	$F(2, 104) = 7.0$; $P < .001$	$F(1, 87) = 2.7$; $P = .006$	$F(1, 55) = 11.2$; $P < .001$	$F(1, 60) = 13.2$; $P < .001$
PC Scores		1, 3, 4, 6, 10	1, 3, 5, 9	1, 3, 5, 9, 10

ID: 979565

INDIVIDUALIZED PREDICTION OF ILLNESS COURSE AT THE FIRST PSYCHOTIC EPISODE: A SUPPORT VECTOR MACHINE MRI STUDY

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Background: In the last decades, brain structure has been investigated using Magnetic Resonance Imaging (MRI) as a potential predictor of outcome in psychosis. However, neuroanatomical changes in psychosis appear subtle and spatially distributed, although possibly more marked in the advanced illness stages. As a result, the use of imaging has made little impact on the diagnosis and monitoring of psychoses in individual patients. The aim of this study was to determine if a Support Vector Machine (SVM) whole-brain classification approach could predict future illness course at individual level from MRI data obtained at the first psychotic episode. Methods: In this study, patients at their first psychotic episode, and healthy controls had an MRI scan. Patients were re-evaluated 7 years later, classified as having either an Episodic or Continuous illness course, and matched to healthy controls. Results: At baseline, patients with a Continuous course were already distinguishable from both patients with an Episodic course (71% correctly classified; $P = .005$), and from healthy individuals (68% correctly classified; $P = .001$). Patients with an Episodic course could not be distinguished from healthy individuals. Conclusion: This study provides preliminary evidence of MRI application in the individualized prediction of future illness course. A simple and automated SVM pipeline such as the one used in this study can enable quick early clinical targeted decisions based on imaging data, with benefit to patient care and reduction of health care costs. In fact, the clinical application of these methods could help direct to more vulnerable individuals the early implementation of targeted interventions which have been shown to reduce relapse rates, such as optimized pharmacological treatment, assertive case-management or family interventions, resulting in better clinical and functional outcomes.
ID: 978807

THE BRAIN PREDICTORS OF LONG-TERM OUTCOME FOLLOWING THE FIRST EPISODE OF PSYCHOSIS: APPLICATION OF IMAGING AT THE INDIVIDUAL LEVEL

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Background: This study investigated what are the brain neurodevelopmental and volume abnormalities associated with the onset of psychosis, and with its long-term clinical outcome. Furthermore, it sought to establish if any brain abnormality present at illness onset could already predict future clinical outcome. Methods: We evaluated a sample of 100 patients who had an MRI scan at the time of their first psychotic episode, and were re-assessed with MRI and clinical measures approximately 7 years later. We used a variety of imaging approaches, including region of interest, shape analysis, and Support Vector Machine (SVM) techniques. We

assessed the presence of neurodevelopmental and progressive brain changes, and their relationship to 7-year clinical outcome. This was evaluated through subject interview, case-note review, and informant interview, and recorded using the WHO Life Chart. Results: Over time, there was a reduction in graygray matter volume ($P < .001$), and a significant increase in ventricular volume ($P = .02$). Contrary to what originally expected, there was also a change in neurodevelopmental measures, such as reduction in brain asymmetry and a change in hippocampal shape over time. These changes were particularly marked in individuals with a poorer outcome (indicated by a higher number of hospitalization and a continuous illness course). However, SVM analyses showed that in fact the MRI obtained at illness onset could already predict future clinical outcome with a significant degree of accuracy ($P < .001$). Conclusion: These data suggest that there are progressive brain changes following psychosis onset, even in brain structures that are thought to be developmental in origin such as brain asymmetry, and that these are more marked in individuals with poorer clinical outcome. However, brain structure at illness onset is already predictive of future outcome and can potentially be used to inform clinical decisions.
ID: 978762

EFFECT OF FAMILIAL SINISTRALITY ON PLANUM TEMPORALE ASYMMETRY IN PATIENTS WITH SCHIZOPHRENIA

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Background: Several studies have reported a reduced leftward asymmetry of the planum temporale (PT) in patients with schizophrenia but results are still controversial. Recently, Tzourio et al (Cerebral Cortex. 2010) showed that healthy subjects with familial sinistrality (FS+), defined by having left-handed relatives, had a reduced PT asymmetry. Therefore, we investigated the impact of FS on the leftward asymmetry of PT in patients with schizophrenia. We hypothesized that only patients with no FS (FS-) should exhibit a lower leftward asymmetry than FS- controls. Methods: 43 patients (33 right-handed (RH)) with schizophrenia (DSMIV) and 274 healthy subjects (195 RH) were scanned (MRI, 1.5 T). FS+ was defined as the presence of at least one left-hander among the parents and siblings of a subject. PT surfaces were delineated on a single brain slice according to Kulynych et al(1993). The size of PT was analysed with a mixed-model covariance analysis (ANCOVA) with repeated measures (left and right values) including a within-subject ''hemisphere'' factor, a subject random effect and 4 between-subjects fixed factors (illness, gender, handedness and FS). Age, cultural level and total intracranial volume (TIV) were included as confounding covariates. Results: A significant effect of hemisphere side ($P < .001$) was found on the size of PT, together with illness x hemisphere (.03) and illness × FS (.04) interactions. In FS- subjects, left PT was larger in controls ($N = 170$; 677.8 ± 193.2) than in patients ($N = 22$; 596.7 ± 255.9) whereas right PT was larger in patients (559.8 ± 200.9) than in controls (476.5 ± 180.9). No such differences were observed between FS+ patients ($N = 21$; left: 634.2 ± 224.9; right: 498.6 ± 218.8) and FS+ controls ($N = 104$; left: 624.9 ± 167.5; right: 477.7 ± 189.5). Conclusion: This is the first study evaluating the impact of FS on PT asymmetry in patients with schizophrenia. The results confirm the reduced leftward asymmetry of PT in patients as compared to controls, but only in subjects with no familial sinistrality. This finding supports the idea that reduced brain lateralization in schizophrenia is related to illness rather than to family left-handedness. The presence of left-handed relatives (FS+) reduced left PT lateralization in patients but no more than it did in controls. These results must lead to consider familial sinistrality in future research on cerebral asymmetry in schizophrenia.
ID: 978503

ALTERED FRACTIONAL ANISOTROPY IN LIMBIC TRACTS IN FIRST-EPISODE ANTIPSYCHOTIC-NAÏVE SCHIZOPHRENIA AND ASSOCIATIONS WITH THE SCHIZOPHRENIA SUSCEPTIBILITY GENE ZNF804A

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Background: ZNF804A is the first gene to have achieved genome-wide significance for schizophrenia and it has recently been implicated in the functional connectivity between limbic and frontal brain regions. Here we investigated if antipsychotic-naïve first-episode schizophrenia patients had reduced fractional anisotropy (FA) in the cingulum and uncinate fasciculus, the major fiber tracks connecting the limbic and frontal brain regions. Moreover, we investigated if FA alterations were most pronounced in risk allele carriers. Methods: Whole brain diffusion-weighted magnetic resonance images were acquired in 37 antipsychotic-naïve first-episode schizophrenia patients (26 males, mean age: 26.4, SD = 5.3 years) and 41 matched healthy controls (28 males, mean age: 27.1, SD = 5.7 years) on a 3 Tesla scanner. TBSS (Tract-Based Spatial Statistics, part of FSL) was used to spatial normalize calculated fractional anisotropy (FA) images. Using a region of interest (ROI) approach, the cingulum and uncinate fasciculus were drawn on the mean TBSS skeleton and mean ROI FA values were extracted. A subset of the cohort (21 patients and 31 controls) was genotyped using Illumina HumanHap610 and the rs1344706 genotype of ZNF804A was imputed based on the HapMap CEU sample using rs12477914 and rs1366840. Results: Global FA tended to be reduced in patients ($P = .068$) compared to controls. ANCOVA (covaried for age, sex and global FA) showed that patients had reduced cingulum FA ($P = .051$) but not uncinate fasciculus FA ($P = .44$). Six patients and 6 controls were homozygote for the ZNF804A risk allele (TT) and 15 patients and 25 controls were not (GT/GG). In the genotyped sub-sample we observed a significant Hemisphere x Diagnosis interaction ($P = .027$) for the cingulum. Patients had lower left cingulum FA than controls, while they did not differ in right cingulum FA. For the uncinate fasciculus we observed a significant effect of Hemisphere ($P = .042$; Right > Left) and a significant Hemisphere × Genotype interaction ($P = .013$), with TT carriers having higher left FA compared to GT/GG carriers. Conclusion: Our preliminary analyses indicate subtle reductions in cingulum FA in first-episode schizophrenia patients before exposure to antipsychotic medication. Although the genotyped subset of our sample is small our findings suggest that the risk allele of the ZNF804A gene may influence structural limbic connectivity.
ID: 978279

CORTICAL CORRELATES OF COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

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Background: Patients with schizophrenia and individuals at risk for schizophrenia are characterized by cognitive impairments and subtle graygray matter reductions in multiple brain regions. Previous studies have found varying relationships between cognitive functioning and reduced brain volumes in patients with schizophrenia. However, cortical thickness may more closely reflect cytoarchitectural characteristics than gray matter density or volume estimates. Here we aimed to compare associations between regional variation in cortical thickness and neuropsychological testing measures of working memory, episodic memory as well as verbal and spatial processing in a large group of patients with schizophrenia and healthy controls. Methods: We obtained MRI and neuropsychological data for 131 patients and 138 matched controls. Automated cortical pattern matching methods (FreeSurfer) allowed testing for associations with cortical thickness estimated as the shortest distance between the gray/white matter border and the pial surface at thousands of points across the entire cortical surface. Monte-Carlo simulations were used to control the alpha error probability. Results: Compared to healthy controls, patients with schizophrenia were found to have reductions in cortical thickness in frontal, temporal and parietal regions. In addition, two independent measures of working memory showed robust associations with cortical thickness in lateral prefrontal cortex in healthy controls whereas patients exhibited associations between working memory and cortical thickness in the right middle and superior temporal lobe. Conclusion: The present findings suggest widespread reduction of cortical thickness in patients with schizophrenia. Furthermore, this study provides evidence for a disrupted structure-function relationship in schizophrenia. In line with the prefrontal inefficiency hypothesis, schizophrenia patients may engage a larger compensatory network of brain regions other than frontal cortex to recall and manipulate verbal material in working memory.
ID: 948170

ASSOCIATION BETWEEN BRAIN STRUCTURE AND PSYCHOMETRIC SCHIZOTYPY

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Background: Schizophrenia is associated with replicable graygray matter volume reductions in fronto-temporo-limbic and subcortical regions. Psychometric schizotypy refers to a set of behavioral traits and cognitions thought to represent the subclinical manifestation of schizophrenia in the general population. While there is evidence of overlap between schizophrenia and schizotypy at phenotypic, genetic and cognitive levels, no previous study has observed graygray matter volume reductions associated with increased psychometric schizotypy levels in healthy individuals. Such evidence would provide further support for a relationship between non-clinical schizophrenia-like traits in the general population and the full-blown clinical condition of schizophrenia. Methods: Therefore, we used magnetic resonance imaging to investigate the relationship between psychometric schizotypy and brain structure in 55 clinically unaffected and unmedicated volunteers. We performed a voxel-based morphometry analysis of graygray matter volume data obtained at 1.5 Tesla. Results: Covarying for age and gender, higher scores of self-report positive schizotypy were found to significantly correlate with reduced graygray matter volume in medial prefrontal, orbitofrontal, and temporal cortical regions. Conclusion: These findings show that psychometric schizotypy in healthy individuals is associated with volume reductions in cortical areas known to be altered in schizophrenia, thereby providing neurobiological evidence of an overlap between schizotypy and schizophrenia.
ID: 977797

CORTICAL GYRIFICATION AND NEUROLOGICAL SOFT SIGNS IN FIRST EPISODE PSYCHOSIS

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Background: Schizophrenia is a complex and severe brain disorder with poorly defined etiology. Compelling evidence suggest that schizophrenia results from aberrations in neurodevelopmental processes, including early prenatal and adolescent brain maturation deviations (Weinberger 1987; Rapoport 2005). The presence of neurological soft signs (NSS) in schizophrenia is considered a marker of these early brain insults (Bombin 2005). Brain imaging studies in schizophrenia have reported both functional and anatomical deviations associated with NSS. However, it is still unclear whether these deviations relate to neurodevelopmental impairments. Methods: We investigated the cortex gyrification in schizophrenia patients with NSS as gyrification is considered an indirect marker of brain developmental processes (Mangin 2010). Magnetic Resonance Images of 45 schizophrenia patients - 19 patients with NSS (NSS+) and 26 patients without NSS (NSS−) - were acquired. Gyrification was assessed using both global (g-SI) and local (l-SI) 3D gyrification indices (Cachia 2008) based on an automatically approach to extract, label and measure the sulcus anatomy in the whole cortex. Between-group comparisons and correlations analyses of the main NSS dimensions (motor coordination, motor integration, sensory integration) were then assessed. Effects of age, gender and years of education were controlled using confounding covariates. All analyses were performed using a threshold at $P < .05$. Results: Compared to NSS- patients, NSS+ patients showed a bilateral decrease of g-SI and a l-SI decrease in left dorso-lateral prefrontal cortex and right lateral occipital cortex. NSS dimensions were negatively correlated to l-SI in specific regions: left dorso-lateral prefrontal cortex and right lateral occipital cortex for motor coordination, left medial parieto-occipital cortex for motor integration, left medial frontal cortex and right lateral superior parietal cortex for sensory integration. Conclusion: The detected decreased gyrification in patients with NSS supports the view that this subgroup has particularly high neurodevelopmental loading (Krebs 2007). NSS and gyrification measures could then provide valid intermediate features for genetic research and should help to narrow the phenotypic variability (Meyer-Lindenberg 2006).
ID: 980788

ANOSOGNOSIA OR LACK OF ILLNESS AWARENESS IN SCHIZOPHRENIA: A VBM ANALYSIS

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Background: Anosognosia or lack of illness awareness is common to both schizophrenia and right hemisphere lesions due to stroke, dementia, and traumatic brain injury. It is thought to arise from right hemisphere dysfunction or interhemispheric disequilibrium, which provides an anatomical model for exploring anosognosia in other neuropsychiatric disorders. Methods: A voxel-based morphometric (VBM) analysis was performed on 55 treated schizophrenia subjects, exploring the relationship between insight, as measured by the PANSS lack of insight and judgment item (G12), and gray and white matter volume. Analyses were performed with SPM8, including total intracranial volume as a covariate. Results: Significant correlations were found between lack of insight scores and reduced right hemisphere graygray matter volume in the medial orbitofrontal, insula and premotor cortex, inferior parietal lobule and precuneus, areas hypothesized to be involved in the neurocircuitry of anosognosia in schizophrenia. Significant associations within the right precuneus and right medial orbitofrontal remained after controlling for illness severity, and also in a subsequent analysis that included nine untreated schizophrenia subjects ($n = 64$) and controlled for illness severity and antipsychotic treatment. Significant correlations were also identified between lack of insight and reduced white matter volume in the bilateral anterior corona radiata, right corpus callosum, and bilateral internal capsule. Conclusion: This is the first VBM study of anosognosia in schizophrenia that demonstrates a relationship between insight and white matter volume, and which supports previous volume-based MRI studies showing a relationship between insight and right hemisphere gray matter volume. Functional imaging studies are required to examine the neural mechanisms contributing to these structural observations.
ID: 979664

PRENATAL ISOLATED MILD VENTRICULOMEGALY IS ASSOCIATED WITH PERSISTENT VENTRICLE ENLARGEMENT AT AGES 1 AND 2

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Background: Mild enlargement of the lateral ventricles is observed in many neuropsychiatric disorders, including schizophrenia, and is thought to be the result of abnormalities in early brain development. Isolated mild ventriculomegaly (MVM) is the prenatal enlargement of the atrium of the lateral ventricles in the absence of other CNS abnormalities. Little is known about the effects of prenatal enlarged ventricles on later brain development, though isolated MVM has been associated with developmental delays and neurodevelopmental disorders. We previously found that MVM is associated with persistent enlargement of the lateral ventricles on MRI in the neonatal period, suggesting the potential for prenatal MVM to be a structural marker of risk for neurodevelopmental disorders. Methods: Using 3T magnetic resonance imaging, we investigated the postnatal progression of MVM at ages 1 and 2 years in 29 children with MVM and 58 age and gender matched control subjects with normal prenatal ventricle size. Lateral ventricle volumes, as well as whole-brain gray and white matter volumes, were analyzed. Subjects also underwent developmental testing with the Mullen Scales of Early Learning. Results: At age 1 year, subjects with MVM had lateral ventricle volumes that were 57% larger than controls, though this did not reach statistical significance. At 2 years of age, subjects with MVM had 40% larger total ventricle volume when compared to healthy controls ($P = .0226$). Subjects with MVM had increased intracranial volumes (ICV) at both 1 and 2 years of age (2.5% and 12.5%, respectively). White matter and gray matter volumes were also significantly greater at age 2 (WM, $P = .0084$; GM $P = .0039$). There were no significant differences between MVM subjects and healthy controls on the Mullen Scales of Early Learning at either age. Conclusion: Our results indicate that prenatal enlargement of the lateral ventricle observed on ultrasound persists at least until 2 years of age and is associated with differences in gray and white matter development. In our cohort, MVM was not associated with abnormalities in early motor and cognitive development. Longer follow-up is needed to determine if MVM is a prenatal marker of later childhood brain structure and associated cognitive development abnormalities and increased risk for neuropsychiatric disorders.
ID: 977981

STRUCTURAL PATHOLOGY UNDERLYING NEUROENDOCRINE DYSFUNCTION IN SCHIZOPHRENIA

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Background: Polydipsic hyponatremic schizophrenic (PHS) patients exhibit altered neuroendocrine activity that has been linked to their life-threatening water imbalance, as well as to impaired function and reduced volume of the anterior hippocampus. Polydipsic patients without hyponatremia (polydipsic normonatremic schizophrenics: PNS) exhibit similar, albeit less marked, changes in neuroendocrine activity and anterior hippocampal function, but not reduced anterior hippocampal volume. Indeed, reduced anterior hippocampal volume is seen in patients with normal water balance (nonpolydipsic normonatremic schizophrenics: NNS) whose neuroendocrine activity and anterior hippocampal function differ markedly from those with polydipsia. Methods: In an effort to reconcile these findings we measured hippocampal, amygdala and 3rd ventricle shapes in 26 schizophrenic patients (10 PNS, 7 PHS, 9 NNS) and 12 healthy controls matched for age and gender. Results: Bilateral inward deformations were localized to the anterior lateral hippocampal surface (part of a neurocircuit which modulates neuroendocrine responses to psychological stimuli) in PHS and to a lesser extent in PNS, while deformations in NNS were restricted to the medial surface. Proportional deformations of the right medial amygdala, a key segment of this neurocircuit, were seen in both polydipsic groups, and correlated with the volume of the 3rd ventricle, which lies adjacent to the neuroendocrine nuclei. Finally, these structural findings were most marked in those with impaired hippocampal-mediated stress responses. Conclusion: These results reconcile previously conflicting data, and support the view that anterior lateral hippocampal pathology disrupts neuroendocrine function in polydipsic patients with and without hyponatremia. The relationship of these findings to the underlying mental illness remains to be established.
ID: 985584

DTI MEASURES OF DIFFUSIVITY IN SCHIZOPHRENIA ARE RELATED TO NEUROCOGNITIVE DEFICITS AND SYMPTOM SEVERITY

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Background: DTI studies in schizophrenia (SCZ) have shown abnormalities in some white matter (WM) tracks. Most studies have examined specific tracts and data on the whole brain is lacking. These studies also varied in scanner field strength and the quality of sequences applied. Small sample sizes have precluded examination of age effects and relating anatomic findings to performance on neurocognitive measures and symptom severity. Methods: DTI was examined in 64 patients with SCZ and 83 controls (CNT). Diffusion-weighted images were acquired on a 3T scanner with the 64-direction diffusion scheme, with 70 repetitions (TR/TE = 6300/81 ms, FOV = 240 mm, matrix = 128 × 128, slice thickness/gap = 2.0/0 mm, 48 slices, parallel acceleration, resulting in a 1.9 × 1.9 × 1.9 mm voxel resolution. Images were processed using high-dimensional morphometric methods yielding fractional anisotropy (FA) and diffusivity (TR) measures for standard ROIs. We limited analysis of FA to regions with values >.2. The Penn Computerized Neurocognitive Battery (CNB) was administered and yielded measures of accuracy and speed for executive, memory, reasoning, emotion processing and sensorimotor domains. Positive and negative symptoms were evaluated. Results: FA across samples correlated negatively with age while TR showed positive correlations. For frontal regions the correlations were significantly higher for SCZ (range −.30–−.58) than for CNT (range −.11–−.32), $P = .015$ by CORANOVA. Reduced FA was evident in SCZ in cortico-cortical, cortico-striatal and efferent fiber tracts but not in afferent tracts, except for the sagittal stratum. FA was reduced in SCZ throughout the corpus callosum. For cortical WM regions FA was reduced in SCZ in all frontal and parietal regions examined. For temporal regions, FA was substantially reduced in mid-temporal and superior temporal but not in inferior temporal or fusiform gyrus. Of occipital regions, FA was reduced in mid and superior occipital and cuneus but not in lingual gyrus. Regression analysis identified specific associations of FA and TR values that were predictive of cognitive performance in CNT and SCZ. Regression analysis in SCZ showed that FA and TR were predictive of symptoms severity with some regional specificity for positive and negative symptoms. Conclusion: WM integrity is compromised in SCZ and the effect of age is greater in patients. These abnormalities are diffuse and relate to severity of cognitive deficits and symptoms.
ID: 978947

PITUITARY VOLUME, STRESS REACTIVITY AND GENETIC RISK FOR PSYCHOSIS

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Background: Altered pituitary volumes have been associated with HPA-axis hyperactivity and with increased vulnerability for developing psychosis. As a result of HPA-axis hyperactivity, patients may become more sensitive to stressors, a phenomenon called stress-sensitization. Research has shown that patients with psychosis are more sensitive to daily life stressors resulting in heightened negative emotions. The aim of this study was to examine the association between pituitary volume, stress reactivity and genetic risk for psychosis. Methods: Pituitary volumes were derived from MRI scans of 20 patients with schizophrenia, 37 non-psychotic siblings of these patients, and 32 controls. The Experience Sampling Method was used to measure stress reactivity (changes in negative affect (NA) associated with daily life stress). The effect of group status on pituitary volume was investigated, as well as interactions between group, stress and pituitary volume on NA. Analyses were adjusted for age, sex, estrogen dosage and intracranial volume. Results: Mean pituitary volume did not significantly differ between groups ($\beta = -7.70$ $P = .69$). There was a significant group x stress interaction ($\chi^2 = 10.05$, $P = .00$) on NA, in that patients showed significantly higher stress-reactivity than siblings and controls. In addition, there was a significant group x stress x pituitary volume interaction ($\chi^2 = 20.27$, $P = .00$) on NA, indicating that the effect of pituitary volume on stress reactivity varied with group. Stratified analyses showed that patients with higher pituitary volumes showed significantly higher stress-reactivity ($\beta = .19$, $P = .00$) than controls ($\beta = .10$, $P = .00$) and siblings ($\beta = .08$, $P = .00$) with higher pituitary volumes, whereas there was no difference between the latter two groups. Conclusion: Higher pituitary volume was associated with increased stress-reactivity in patients with psychosis, siblings and controls. The stress-reactivity in patients with higher pituitary volumes was significantly stronger than in the groups with lower genetic risk, suggesting that this phenomenon may be associated with the clinical syndrome of psychosis. HPA-axis dysregulation may underlie this increased stress-reactivity, which will be further examined using cortisol measures.
ID: 979541

STRUCTURAL BRAIN CORRELATES OF SENSORIMOTOR GATING IN SCHIZOPHRENIA PATIENTS AND HEALTHY CONTROLS: A 6 YEAR FOLLOW-UP STUDY OF INITIALLY ANTIPSYCHOTIC NAÏVE, FIRST-EPISODE SCHIZOPHRENIA PATIENTS

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Background: Prepulse inhibition (PPI) of the startle reflex, a cross-species measure of early information processing, is modulated by a complex neural network extending from the brainstem to higher order cortical areas. PPI has consistently been found to be impaired at all stages of schizophrenia. Previous studies investigating the relationship between PPI and structural or functional MRI found brain correlates of PPI to differ between schizophrenia patients and healthy controls. However, these studies were cross-sectional and only included chronically ill and medicated patients and thus cannot control for possible confounding effects of medication and other disease related factors. The current study aimed to examine structural brain correlates of PPI in initially antipsychotic-naïve schizophrenia patients and matched healthy controls in a naturalistic longitudinal design Methods: Twenty-one antipsychotic-naive first-episode schizophrenia patients (16 males; mean age 26.6 years) and 20 matched healthy controls (13 males; mean age 27.0 years) were included in the study. Acoustic PPI assessment and magnetic resonance imaging (1.5T) were performed in separate sessions at baseline and were repeated after 6 years on average. We plan to use a region-of-interest approach and voxel-based morphometry to investigate the relationship between PPI and regional graygray matter volumes at baseline. Tensor-based morphometry will be employed to investigate the relationship between PPI changes and regional graygray matter volume changes from baseline to follow-up Results: Patients had significantly lower PPI than

controls at baseline (P = .01). At 6 years follow-up no significant group differences were found. However, we observed a significant interaction effect of "time x group" (P = .03). At 6 years PPI had significantly increased in patients while it had significantly decreased in controls, resulting in the disappearance of the initially found group difference. The MRI data are currently being analyzed and the results will be presented at the ICOSR 2011 Conclusion: The present results show that PPI in drug-naïve first-episode schizophrenia patients improved significantly over time. That PPI increased in patients over the same period where it decreased in controls, suggests that the increase was caused by disease related factors such as clinical state, or medication. Structural brain correlates of PPI in antipsychotic-naïve schizophrenia patients and how these correlates change over time will be presented at the ICOSR 2011
ID: 975224

WHITE AND GRAY MATTER INTEGRITY IN INDIVIDUALS WITH SCHIZOPHRENIA AND THEIR SIBLINGS

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Background: Alterations in white matter integrity (decreased fractional anisotropy) and gray matter microstructure (increased mean diffusivity) have been demonstrated in individuals with schizophrenia using diffusion tensor imaging (DTI). Only a handful of studies have investigated whether similar alterations are present in the siblings of individuals with schizophrenia. Such studies are important for establishing whether DTI-based measures are potential biological markers (endophenotypes) related to genetic risk for schizophrenia. Methods: DTI was performed on 89 adolescent to young-adults, consisting of 25 individuals with schizophrenia, 29 siblings of individuals with schizophrenia, and 35 healthy controls (mean age = 23 years). DTI consisted of two scans of a b = 800 s/mm^2, 30 gradient direction protocol on a Siemen's 3T TimTrio magnet. Fractional anisotropy (FA) was used to assess white matter integrity of the anterior limb of the internal capsule, cingulum, fornix, uncinate fasciculus, and the superior longitudinal fasciculus - tracts that have been implicated in other schizophrenia studies. Mean diffusivity (MD) was used to assess microstructure in the thalamus, and middle and inferior frontal gyri, since increases in MD in these regions have also been observed in individuals with schizophrenia in other studies, and our own previous work has identified gross structural abnormalities in those regions. Regions were obtained by registering a predefined atlas to each subject's scan using highly elastic Large Deformation Diffeomorphic Metric Mapping. Results: Siblings of the individuals with schizophrenia were not distinguishable from controls in either FA or MD in any of the assessed regions (all P >.15). In the individuals with schizophrenia, FA was reduced compared to controls in the hippocampal (crus) portion of the fornix (−4.7%, P = .01), and MD was increased compared to controls in the thalamus (4.8%, P = .002) and middle frontal gyrus (4.5%, P = .03). Voxel-based maps of MD suggested that the increased MD in the putative thalamic region may actually be reflective of ventricular enlargement (ie, incomplete spatial normalization across subjects), rather than increased MD in the gray matter of the thalamus per se. Conclusion: In this sample of subjects, FA and MD do not appear to be candidate endophenotypes associated with genetic risk for schizophrenia. Further, the results show only limited evidence for FA or MD abnormalities in young individuals with schizophrenia. Support: P50-MH071616
ID: 979672

BRAIN VOLUME CHANGES IN HEALTHY INDIVIDUALS

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Background: There is consistent evidence that brain volume changes in early and late life. Most longitudinal studies usually only span a few years and include a limited number of participants. Here we review and integrate the findings of longitudinal MRI studies in healthy subjects that investigated the volume of the whole brain, gray and white matter and have been published until January 1st 2010. Methods: A systematic search was conducted at PUBMED for relevant studies followed by a search in cross-references. A total of 56 longitudinal MRI studies were included on change over time in whole brain volume. Of these, 10 studies presented data on GM changes and 9 studies presented data on WM changes. Results: Our findings show that whole brain volume change is an ongoing process throughout the full lifespan with pronounced increase in childhood followed by rapid decreases in volume change by the age of approximately 15 years. Thereafter, in adolescent and young adulthood whole brain volume shows possible another increase or at least a period of stabilizing change. After the age of 35 the decrease sets in, first mildly, then more pronounced after the age of 55 years. GM increases in childhood and adolescence and start to decrease after that. WM increases to the age of approximately 45 and thereafter starts to decrease. Conclusion: Brain development with ongoing changes in the whole brain volume is a life long process. Our findings may help understanding the underlying mechanisms of normal brain changes, and may contribute in distinguishing psychiatric and neurodegenerative diseases from healthy aging processes.
ID: 979243

MORPHOLOGICAL CORRELATES OF AUTOBIOGRAPHICAL MEMORY IN CHRONIC SCHIZOPHRENIA: A VOXEL-BASED MORPHOMETRY STUDY

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Background: Schizophrenia is associated with a range of cognitive deficits and cerebral volume alterations, but little attention has been directed to the deficits and structural correlates of autobiographical remembering within this patients group. The aim of this study was to identify whether the patterns of structure-function relationships differ between chronic schizophrenic patients and healthy controls. Methods: So far we have examined the cerebral correlates of autobiographical memory in 35 chronic schizophrenic patients and 19 age and education matched healthy volunteers. MRI data were obtained at the German Cancer Research Centre with a 3-T Siemens Magnetom scanner and were analysed via voxel-

based-morphometry (VBM). Personal episodic memory and personal semantic memory were investigated using a semi-structured interview. Results: Schizophrenic patients had significantly smaller gray and white matter volume in the (medial) frontal, parietal and medial temporal lobe. Compared with control participants, patients had significantly lower memory scores for episodic and semantic autobiographical memory. The proportion of episodic details correlated in the patients group significantly with predominantly left lateralized gray and white matter volumes in medial temporal lobe (parahippocampal gyrus), occipital and parietal lobe and with white matter volume of inferior frontal gyrus. In control subjects greater left medial frontal and left temporal white matter volumes were positively correlated with remembering episodic details. Conclusion: Correlations between brain regions and autobiographical memory performance revealed different sets of significant associations for the two groups. The structure-function relationship in the schizophrenic patients might possibly reflect a functional compensation. Further analyses may dissociate the cerebral correlates of episodic and semantic autobiographical remembering and compare the cerebral correlates of autobiographical memories of varying remoteness.
ID: 975816

PROGRESSIVE BRAIN TISSUE LOSS IN SCHIZOPHRENIA: IS THE IMMUNE SYSTEM IMPLICATED?

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Background: Brain structure in adulthood has often been considered to be static, with only marginal changes occurring over time. However, a static brain seems to be at odds with our continued intellectual and social development as adults. Is progressive brain tissue loss in schizophrenia due to aberrant adult plasticity and if so does this implicate the immune system? Methods: Of 242 participants from 106 twin families who had a MRI brain scan, 183 from 87 families completed the 5-year follow-up (Brans et al, J Neurosci 2010). In addition, 92 participants among whom 9 MZ and 10 DZ twin pairs discordant for schizophrenia and 14 MZ and 15 DZ healthy twin pairs completed the 5-year longitudinal MRI follow-up (Brans et al, Arch Gen Psychiatry, 2008). Structural equation modeling was applied to estimate contributions of additive genetic and common and unique environmental factors to changes in cortical thickness over time. Moreover, a meta-analysis was done of MRS studies in schizophrenia. Results: A considerable thinning of the frontal cortex and a thickening of the medial temporal cortex was found with increasing age in adult twins and was heritable. More pronounced cortical thinning over time in frontal and temporal cortices were found in patients with schizophrenia and their unaffected cotwins as compared with control twins. A significant group-by-age interaction was found for glutamate levels in the frontal cortex, due to a more pronounced decrease in glutamate levels in older patients with schizophrenia. Conclusion: Progressive brain tissue loss in schizophrenia is associated with the liability to develop the disease, and this process may be associated with a progressive loss of glutamate mediated synaptic activity. Our research group also found that activated microglia was present in schizophrenia patients within the first 5 years of disease onset, as measured using PET, indicating that neuronal injury may be present and neuronal damage may be involved in the loss of gray matter (Van Berckel et al, Biol Psychiatry 2008). Microglia could be important for control over glutamate levels under pathologic conditions (Hanish and Kettenmann, Nat Neurosci 2007). Possibly, through changing glutamate levels, the immune system may be implicated in the progressive loss of normal adult brain plasticity in patients with schizophrenia.
ID: 978852

TRACT-BASED ANALYSIS OF DTI AND MTR OF CORTICO-CORTICAL CONNECTIONS IN SCHIZOPHRENIA

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Background: Several Diffusion tensor imaging (DTI) and a few magnetic transfer ratio (MTR) studies have reported changes in white matter (WM) integrity in schizophrenia but findings are inconclusive. Moreover, it has long been suggested that schizophrenia is related to a reduced capacity to integrate information between different regions of the brain. However, it remains unknown whether the overall brain network infrastructure is affected. Methods: 145 schizophrenia patients and in 119 healthy comparisons were scanned (Boos et al, Schizophrenia Bulletin, in press). FA and MTR were measured along 16 fibers (Mandl et al, Schizophrenia Bulletin 2010). Using graph theoretical analysis, complex structural brain networks were examined (Van den Heuvel et al, in revision) in 80 scans (40 patients). Results: No differences between groups in FA were found. A higher mean MTR of 1% was found in the right uncinate fasciculus in patients (findings for complete cohort will be presented). Patients had preserved overall small-world network organization, but reduced interregional efficiency, especially frontally. Conclusion: Schizophrenia impacts connectivity with the frontal cortex. Although in schizophrenia the specific connections within frontal networks show increased frontotemporal connectivity (ie increased MTR), the level of global connectivity of these frontal regions towards other regions is reduced.
ID: 978815

GYRAL VOLUME, SURFACE, THICKNESS, SULCAL DEPTH, SULCAL SPAN…WHAT TYPE OF CORTICAL MEASURE MATTERS MORE FOR IDENTIFICATION OF MALE ADOLESCENTS WITH EARLY-ONSET PSYCHOSIS?

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Background: Recent studies suggest that MRI-derived neuroanatomic measures may be used to diagnostically classify patients with psychosis, however it's unclear what type of neuroanatomic measure matters more for classification. Methods: MRI scans were acquired from 42 male adolescents with early-onset psychosis (EOP) and 27 healthy male adolescents. Subjects' age range was 12–18 years, and patients had the first psychotic symptoms before the age of 18 years. All patients had less than 6 months of psychotic symptoms at study enrollment. Four gyral (volume, surface area, thickness, degree of gyrification) and five sulcal (volume, surface area, depth, span, length) measures were obtained. These cortical measures were assessed for 3 gyri and adjacent sulci: the superior frontal gyrus and sulcus, postcentral gyrus and central sulcus, and superior temporal gyrus and sulcus, totaling 27 measures per hemisphere. In order to classify sub-

jects in patients and controls and to determine what measures were more important for classification, all 54 (54 = 2 × 27) measures were entered in a stepwise discriminant analysis with jackknife procedures for cross-validation. Results: The model selected 14 measures (see Table) correctly classifying 21 controls (78%) and 36 patients (86%). Left superior frontal gyral volume had the highest weight. Conclusion: For classification of male adolescents with EOP gyral volume and thickness seem more important than gyral surface and sulcal measures. Superior frontal and temporal measures seem more important than postcentral features.

Table: Model consisting of 14 cortical measures resulting from a Discriminant Analysis of 54 measures.

Cortical Measure (sorted by Weight)	Weight[A]
left superior frontal gyral volume	.53
left superior temporal gyral degree of gyrification	.47
right post central gyral volume	.41
right superior temporal gyral thickness	.33
right superior frontal gyral thickness	.28
right superior frontal sulcal depth	.28
left central sulcal span	−.23
right superior temporal gyral degree of gyrification	.21
left superior frontal sulcal volume	.21
right superior temporal gyral volume	.18
left superior frontal gyral thickness	.17
left superior temporal sulcal volume	−.12
right central sulcal span	−.09
left superior temporal sulcal surface	−.02

[A]: Weight is the correlation coefficient of each measure with the Canonical Discriminant Function.

ID: 976450

VOLUME & SHAPE ABNORMALITIES OF HIPPOCAMPUS & IMMUNE ABERRATIONS IN ANTIPSYCHOTIC NAÏVE SCHIZOPHRENIA

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Background: Evidence from independent studies suggests schizophrenia might be associated with hippocampal deficits as well as aberrant immune activation. Cytokines have been demonstrated to influence hippocampal volume in healthy individuals. This study examined the hippocampal shape abnormalities and immunological correlates of hippocampal volume in antipsychotic-naïve schizophrenia patients. Methods: Using 3 Tesla - MRI (Philips Achieva), we examined antipsychotic-naïve schizophrenia patients (N = 25;M:F-15:10] in comparison with healthy controls [N = 26;M:F-17:9] group matched on age, sex, handedness & education. Hippocampus with Anterior & Posterior subdivisions were manually segmented by blinded raters with good inter-rater reliability using a valid method. Spherical harmonic shape analysis was used to assess local shape changes. Psychopathology was assessed using Scales for Assessment of Negative Symptoms and Positive Symptoms. Cytokines including IL-2, TNF, IFN-g, IL-4, IL-6, IL-10 & IL-17A were measured in blood plasma using cytometric bead array technique (BD Biosciences, CA). Results: Patients had significant volume deficit in bilateral anterior hippocampus (AHc) after controlling for the potential confounding effects of age, sex and intracranial volume (P <.001). Shape analysis revealed significant deformities in both anterior as well as posterior hippocampal (PHc) subdivision (P <.05). Plasma IL-4 & IL-6 were significantly elevated in patients (P <.05). Left AHc volume had a significant negative correlation with hallucinations score (P <.001). Right PHc volume had a significant positive correlation with avolition-apathy score (P = .008). In predominantly negative syndrome patients, there was a significant positive correlation between plasma TNF and left PHc volume (P = .005). Conclusion: Study observations support the role for hippocampal abnormalities and immune aberrations to underlie the pathogenesis of schizophrenia. The influence of peripheral cytokines on hippocampus especially in the context of psychopathology appears complex; this merits further systematic evaluation.

ID: 975804

NEUROANATOMICAL ALTERATIONS IN SCHIZOPHRENIA AND PSYCHOTIC BIPOLAR DISORDERS: INTERIM DATA FROM THE B-SNIP STUDY

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Background: Brain structural alterations are emerging as promising endophenotypes for studies of major psychiatric disorders such as schizophrenia (SZ). It is unclear however whether schizophrenia and psychotic bipolar disorder (BP) are similar or different in regard to neuroanatomical alterations. We present interim analyses from the ongoing Bipolar- Schizophrenia network for Intermediate Phenotypes (B-SNIP) study that address this question. Methods: Five groups of participants (Controls = 172, SZ probands = 156, first degree relative of BP probands = 111, relatives of SZ patients = 172, and BP probands = 112) underwent MRI scans using a 3T scanner. Lobar regional structural measures were compared using MANCOVAs with group as the independent variable and gender, site, age and intracranial volume as covariates, and followed by ANCOVAs of component brain regions. Results: Significant group main effects were seen with volume and/or cortical thickness reductions in bilateral frontal, temporal, parietal, and left limbic (amygdale and hippocampi) regions, with the most prominent reductions being seen in SZ (in general, Controls> BP probands> SZ relatives > BP relatives> SZ probands). Basal ganglia volumes were increased in both proband groups, more so in SZ. Occipital lobar structural measures did not differ across groups. Conclusion: Our data support the view that SZ and BP show structural alterations that lie on a continuum with the most prominent alterations in schizophrenia. The basal ganglia changes may reflect previously known medication effects, notably those due to antipsychotics.

ID: 978756

PREFRONTAL CONTRIBUTIONS TO OUTCOME IN EARLY PSYCHOSES

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Background: Observations of prefrontal structural, functional and neurochemical deficits in the early course of psychotic disorders are well known. The clinical significance of these deficits depend on the nature and neuroanatomical localization of these abnormalities. Methods: We will summarize data pertaining to these questions from MRI structural and spectroscopic (using proton MRS) data in two separate longitudinal studies

of antipsychotic naïve and treated early course schizophrenia patients at the University of Pittsburgh. Results: Structural, functional and spectroscopic alterations are seen in dorsolateral (DLPFC), orbital and medial PFC as well as the cingulate in the early course of schizophrenia. *N*-acetyl aspartate reductions in DLPFC were related to earlier illness onset, and PFC structural alterations were related to impaired insight and foresight. Volumetric deficits in DLPFC and related structures predicted poorer outcome in naturalistically treated patients as well as in those treated with cognitive remediation. Conclusion: Prefrontal alterations may constrain functional outcome in schizophrenia both by their effects on cognition as well as their effects on insight and foresight.
ID: 979343

A DTI INVESTIGATION OF WHITE MATTER ABNORMALITIES IN EARLY PSYCHOSIS PATIENTS

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Background: Fibers connecting fronto-temporal and fronto-medial structures pass through the anterior limb of the internal capsule (ALIC) subserve executive and psychomotor functioning, both of which are adversely affected in schizophrenia, and may be present at onset of illness. In a study of early psychosis patients, we used diffusion tensor imaging (DTI) to examine potential deficits in the ALIC. Methods: Subjects: 15 early psychosis patients (EPP) (age range 16–38 years) and 30 healthy volunteers (age range 15–38 years) were included in this investigation. Patients had a received a mean of 8.37 weeks of atypical antipsychotic treatments at baseline. Imaging: All structural and diffusion scans were acquired on a GE Signa 1.5T scanner. A T1-weighted 3D FSPGR IR series was performed for manual seeding in structural space. Diffusion imaging (16 directions) was performed, and all DTI images were co-registered to structural space. Seeds were manually drawn bilaterally on the coronal plane at a specified location. Diffusion images were post-processed for subsequent TBSS (Tract-based Spatial Statistics) analysis. Clinical Assessments: Symptoms were assessed with the PANSS. Attention and processing speed were assessed with Trails A & B and the Stroop Color test. Imaging Assessments: Images were processed with FSL freeware to extract total brain volumes. The FSL diffusion toolbox was used to extract seed-based tracts. A 3D fractional anisotropy (FA) skeleton was generated from the diffusion images to perform whole-brain voxelwise statistical analysis. Results: EPP had significantly smaller fronto-medial and fronto-temporal ALIC tracts compared to healthy volunteers on the left (P = .0006), but not on the right (P >.10). No differences in mean FA were seen within either left or right tracts (P-values >.10), nor did TBSS reveal any other differences in FA values between groups across the whole brain. EPP had a mean PANSS of 73.3 at time of scan. Significant positive relationships between patients' Stroop adjusted word score and left tract volume (r = .714, P = .0028), and Stroop adjusted color score and left tract volume (r = .640, P = .01) were observed in patients, but not in healthy volunteers. Conclusion: Volumetric deficits in fronto-medial and fronto-temporal white matter tracts are observable in the early phases of illness. These deficits appear to affect attention and processing speed in early psychosis.
ID: 979632

REDUCED PREFRONTAL CORTICAL THICKNESS IN RECENT ONSET SCHIZOPHRENIA

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Background: Structural neuroimaging research has focused on identifying specific neuroanatomical features associated with schizophrenia (SZ) and meta-analyses of voxel-based morphometry (VBM) studies have revealed reduced gray matter density relative to control subjects (HC) in frontal and subcortical structures. However, cortical thickness measurements have the advantage of being derived from surface-based registration methods where homologous regions are matched as opposed to relying upon spatial smoothing of VBM analyses—potentially offering increased sensitivity to subtle cytoarchitectural changes. Reduced cortical thickness may also be interpreted in the context of reduced neuropil in post mortem brain analyses of schizophrenia. We examined cortical thickness in SZ individuals within 1 year of illness onset and hypothesized that they would show decreased cortical thickness compared to HC primarily in frontal regions. Methods: Recent onset SZ (n = 32), and HC (n = 34) participants were identified from referrals to the UC Davis Early Detection and Preventative Treatment clinic using the Structured Clinical Interview for DSM-IV. Images were obtained on a 1.5-Tesla General Electric scanner and processed using Freesurfer. An exploratory analysis using a vertex-wide threshold of P <.01 was followed by a correction for multiple comparisons (5000 Monte Carlo simulations, P <.05). Results: Exploratory analyses revealed reduced cortical thickness in SZs relative to HCs in a distributed network of frontal (eg, middle and superior frontal gyri, lateral and medial orbitofrontal cortex, and frontal pole), temporal (eg, temporal pole and superior temporal gyrus), and parietal (eg, BA39/40) regions. After correction for multiple comparisons, right frontal pole, right rostral middle frontal gyrus, and left medial orbitofrontal cortex remained significant. Conclusion: These results are consistent with existing literature and suggest that morphological changes in the prefrontal cortex are present within the first year of illness onset. Ongoing analyses will investigate the change in brain structure over one year of follow-up, examine associations with medication effects, and explore structure-function relationships by correlating cortical thickness with BOLD signal from prefrontally-based fMRI tasks. Results from an expanded sample of approximately 80 HC and 80 SZ will be presented.
ID: 978659

NEUROIMAGING STUDIES OF SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: The nosologic boundaries of schizophrenia and bipolar disorder have increasingly been diminished by findings from studies of disease phenomenology, genetics and brain morphology. These results have raised the question of whether the disorders may exist on a pathophysiologic continuum or derive from common etiologic factors. Methods: We examined the studies of brain morphology using structural MRI and diffusion tensor imaging as well as fMRI in patients with schizophrenia and bipolar disorder. Results: This growing body of data indicates that structural abnormalities are overlapping in both disorders but the extent of the pathology is more extensive in patients with schizophrenia. In bipolar disorder patients there are consistent regional gray matter reductions in paralimbic regions (anterior cingulate and insula) implicated in emotional processing. While in schizophrenia patients gray matter reductions were more extensive and involved limbic and neocortical structures as well as the paralimbic regions

affected in bipolar disorder. Conclusion: These and the results of other studies including with functional MRI will be presented and their implications discussed.
ID: 1002987

THE IMPACTS OF YOGA AND EXERCISE ON NEURO-COGNITIVE FUNCTION AND SYMPTOMS IN EARLY PSYCHOSIS

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Background: Both physical exercise and Yoga have been shown significant benefits in symptoms and cognitions in some mental disorders. The present study compared the effectiveness of a 12-week yoga therapy and physical exercise on neuro-cognitive function in female psychosis patients, aimed to develop a complementary treatment to improve cognitive function in patients with psychosis. Methods: A total of 60 female psychosis patients were recruited, and randomized into three groups: a) 1 12-week yoga therapy group (n = 20), b) a 12-week physical exercise group (n = 20), and c) a waitlisted group which acted as the control group (n = 20) for 12 weeks. All participants were assessed in structural and functional brain (sMRI and fMRI), clinical symptom, neurocognition, physical fitness and quality of life both at baseline and after 12 weeks intervention. Results: Out preliminary data showed significant improvements in the general health (P = .001), physical functioning (P = .001), energy (P = .034) and emotional well-being (P = .036) with the measure of SF-36 in normal female subjects after a basic level of Hatha Yoga course, each session lasted for 60 minutes, twice weekly for 6 weeks. The preliminary finding indicated that yoga therapy have a positive effect both physically and psychologically. Conclusion: The study results would not only facilitate our understanding of the relative effectiveness of yoga and physical exercise, but may also shed light on the future development of adjunct non-pharmacological therapy in improving neurocognitive functions in patients with psychosis.
ID: 978238

GENOME-WIDE ASSOCIATION STUDY OF STRUCTURAL MRI PHENOTYPES IN A SWEDISH TWIN COHORT

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Background: This study aims to discover genetic determinants of brain structure variation and susceptibility to bipolar disorder and schizophrenia. Methods: We used a genome-wide association study (GWAS) design to associate one million single nucleotide polymorphisms (SNPs) with neural phenotypes measured by structural magnetic resonance imaging. These phenotypes included whole brain volume and gray and white matter volume normalized to intracranial volume. Though data collection is on-going, the sample used in this analysis was composed of over one hundred twin pairs ascertained from the Swedish Twin Registry, including healthy pairs and pairs discordant for schizophrenia or bipolar disorder. Genotyping was done on the Illumina Human Omni1 array. The genome-wide association analysis was done within the PLINK software package (PLINK v1.07, Shaun Purcell, http://pngu.mgh.harvard.edu/purcell/plink/). The analysis used linear and logistic regression models that allowed for age and sex covariates when testing quantitative trait, disease trait, and SNP associations as well as permutation procedures to account for genetic similarity among cotwins. In addition, several methods of multiple testing correction were applied to determine valid genome-wide significance. Results: Intracranial and brain volume were both associated with several SNPs on chromosome 8, 12, and 17 at a genome-wide significance level across diagnosis groups. Preliminary analyses did not reveal any SNPs associated with psychiatric diagnoses. These results suggest several novel genetic loci associated with brain structure. Future analyses will use voxel-wise methods to refine the localization of the genetic signal to specific brain regions and, with expanded sample sizes, will examine the potential relevance of the brain-associated SNPs to susceptibility to schizophrenia and bipolar disorder. Conclusion: Preliminary study results suggest several novel genetic determinants of brain structure variation in a sample of twin pairs including healthy pairs and pairs discordant for schizophrenia or bipolar disorder. Support provided by NIH grant R01 MH052857 (to TDC) and a gift to the UCLA Foundation from the International Mental Health Research Organization (IMHRO).
ID: 978786

CAN WE USE NEUROIMAGING DATA TO PREDICT TRANSITION TO PSYCHOSIS?

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Background: It is difficult to predict which individuals at ultra high risk (UHR) will later develop psychosis on the basis of their presenting clinical features. We examined whether neuroimaging can be used to distinguish between UHR subjects who will subsequently develop psychosis and those who will not. Methods: In a series of studies, UHR subjects meeting PACE criteria for an At Risk Mental State were assessed using volumetric MRI, Diffusion Tensor Imaging, functional MRI (during a verbal fluency task), MR spectroscopy for glutamate, and F-dopa PET. Subjects were then followed clinically to determine which individuals later developed psychosis, and were re-scanned using the same techniques. Baseline and longitudinal data from UHR subjects who had developed psychosis were compared with data from those who had not. Results: At baseline, UHR subjects who had subsequently developed psychosis had smaller medial temporal volumes, greater prefrontal, medial temporal, and midbrain activation, and greater dopamine function than UHR subjects who had not. The longitudinal imaging data revealed that transition to psychosis was associated with progressive within-subject reductions in medial temporal volume, thalamic glutamate levels and white matter integrity, and an increase in striatal dopamine function. Application of machine learning methods indicated that neuroimaging data could be used to classify individual UHR subjects according to their risk of subsequent illness. Conclusion: Certain structural,

functional and neurochemical imaging abnormalities in UHR subjects at clinical presentation are specifically associated with the later onset of psychosis. There is also evidence that transition to psychosis involves longitudinal changes in the structure and chemistry of the brain. Machine learning methods may provide a means to use these neuroimaging findings to estimate the risk of psychosis in an individual subject.
ID: 983821

GENETIC CONTRIBUTIONS TO WHITE MATTER INTEGRITY IN SCHIZOPHRENIA

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Background: While the functional disconnectivity hypothesis of schizophrenia has been the subject of much study, very little is known about the contribution of individual genotypes to white matter integrity in either schizophrenia patients or in healthy controls. Methods: In this study, diffusion tensor imaging maps and genome-wide SNP data were obtained from 74 cases and 86 age-matched controls. Correlations were performed between functional anisotropy (FA) values in networks of regions representing 20 maximally independent components and 140 SNPs in genes that have been found to be important in myelination and/or schizophrenia. By using independent component analysis (ICA) to analyze the FA data we move beyond single voxels (voxel based morphometry) to a source based morphometry, and we can study the relationship of SNPs with networks of FA values, each of which covaries in a similar way among subject. Results: We found several SNPs that are significantly associated with white matter integrity both in schizophrenia patients as well as in controls. In addition, we report several SNPs that show significantly different correlations with white matter integrity in case subjects vs controls. In particular, the minor allele of rs7412, which defines the apoE3 subtype, was associated with lower FA values in schizophrenia patients ($P < .001$) in a component containing a significant proportion of white matter in the forceps minor, a tract thought to be important in schizophrenia. Likewise, the minor allele of rs8177191, located in an intronic region of the transferrin gene, was associated with lower FA values ($P < .001$) in a component containing a significant fraction of white matter in the superior longitudinal fasciculus in the schizophrenia group alone. Both of these genes have been associated with myelin and schizophrenia; however, the frequencies of these two minor alleles were not different in cases and controls. Conclusion: Our results suggest that variants in myelin-associated genes differentially contribute to white matter integrity in schizophrenia patients and controls. Supported by NIH grants 1RC1MH089257and 5P20RR021938.
ID: 979700

MULTIMODAL IMAGING WITH EEG AND MRI FOR THE INVESTIGATION OF AUDITORY VERBAL HALLUCINATIONS

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Background: Auditory verbal hallucinations (AVH) are among the most common symptoms in schizophrenia. Earlier studies suggest changes in the structural connectivity of auditory areas involved in the pathophysiology of auditory hallucinations (Hubl et al, 2004; Whitford et al, 2010). Combining Diffusion Tensor Imaging (DTI) and fiber tractography provides a unique opportunity to visualize and to quantify entire fiber bundles. In addition, advanced EEG analysis based on both source localization and phase coherence analysis can be used to investigate functional relationships between brain regions. Methods: Here, we used the combination of DTI and fiber tracking for different samples including patients with first episode of schizophrenia and patients with chronic schizophrenia in comparison to healthy controls. We also investigated phase synchrony of gamma oscillations between auditory areas. Results: In patients with first episode schizophrenia, the subgroup of patients hearing conversing voices showed increased FA relative to patients without these symptoms ($P = .028$) and relative to healthy controls ($P = .038$). Gamma phase synchrony between auditory areas was reduced in schizophrenic patients and there was a positive correlation between auditory hallucination scales and interhemispheric phase coupling. Conclusion: Our findings suggest that in addition to local deficits in the left auditory cortex and disturbed fronto-temporal connectivity, hyperfunction of the interhemispheric auditory pathway might be an important factor in the pathogenesis of AVH.
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ID: 978314

VIOLENCE IN SCHIZOPHRENIA: IMAGING STUDIES

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Background: There is firm evidence to support an independent association between schizophrenia and violence, though little indicating the illness-specific factors that drive the association. There are an increasing number of structural and functional imaging studies that attempt to identify the biological substrate for violent behavior in schizophrenia. Methods: We conducted a database literature search using combinations of the terms schizophrenia, psychosis, imaging, MRI, antisocial, aggression and violence. We included all MRI studies identified, nine structural, five functional and one diffusion tensor imaging. Results: There are considerable methodological inconsistencies in the definitions of violence employed across studies and the inclusion of patients with co-morbid antisocial personality disorder and substance misuse. Despite this, there is limited but consistent evidence of reduced graygray matter volume in the hippocampus and medial temporal lobe in patients with schizophrenia who are violent. There is further evidence of probable gray matter volume loss and cortical thinning in the medial frontal lobe. The few functional studies show reductions in frontal activity in response to working memory and an emotional face paradigm, but increases in a response inhibition task. There is limited but consistent evidence of impaired structural and functional connectivity between frontal and medial temporal lobes. Conclusion: Despite the methodological challenges, there is emerging evidence that violent patients with schizophrenia are characterized by medial temporal and probable frontal lobe deficits. These findings appear to overlap in part with the neurobiological underpinnings of violent behavior in antisocial personality disorder and psychopathy. More detailed investigation of violence in patients with schizophrenia, with appropriate consideration of the relevant co-morbidities, is required to elucidate which deficits, if any, are specific to violence in schizophrenia.
ID: 976971

MRI-BASED APPROACHES TO DISSECTING WHITE MATTER ABNORMALITIES IN SCHIZOPHRENIA

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Background: Many diffusion tensor imaging (DTI) studies have documented abnormalities in white matter integrity in schizophrenia. The exact nature of these findings is not clear, however, since DTI abnormalities could be caused by alterations in myelination, axonal diameter/packing density, inflammation, and other factors. MR-based techniques such as magnetization transfer ratio (MTR) and diffusion tensor spectroscopy (DTS) provide additional information in myelination and axonal diameter/packing density, respectively. Therefore, these techniques can be valuable in providing additional insights into white matter abnormalities in schizophrenia. Methods: On a 4 Tesla Varian MRI scanner, we have implemented a sequence which collects data from a 9cc pure white matter voxel in the right prefrontal cortex. The sequence acquires data on MTR, DTS-based diffusion parameters for water and *N*-acetylaspartate (NAA), and T2 (transverse) relaxation times for water and NAA. Using this sequence we are scanning age- and gender-matched groups of participants with schizophrenia and healthy controls. All participants are younger than 45, right handed, have no history of substance dependence or current substance abuse, and no major medical/neurological conditions. Results: Results provide evidence for both myelin- and axon-related abnormalities in the white matter in schizophrenia. Total myelin content as estimated by MTR is reduced (Flynn et al 2003). Mean diffusivity for water and NAA are both increased in schizophrenia, consistent with larger axonal diameters and reduced axon packing density. Finally, T2 relaxation times are prolonged for water but shortened for NAA in schizophrenia, suggesting that the local microenvironment for NAA provides increased interactions with macromolecules while that for water is impoverished in this regard. Conclusion: Our results provide evidence for abnormalities in both total myelin content and axonal diameter/packing density in the white matter in schizophrenia. NAA is localized to the intracellular space in neurons and NAA diffusion abnormalities in schizophrenia must reflect axonal abnormalities, not myelination. The divergence of T2 relaxation time changes in water vs. NAA is intriguing, suggesting that their spin-spin interactions with surrounding lipids and proteins are affected differently. A model of microstructural white matter changes that can explain these findings will be presented.
ID: 978965

COMPROMISED WHITE MATTER INTEGRITY IN DEFICIT SCHIZOPHRENIA

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Background: Diffusion tensor imaging studies have shown altered frontal-parietal network in patients with deficit schizophrenia when compared to non-deficit patients. We used a fully-automated tractography method to compare white matter integrity in deficit and non-deficit matched patients with schizophrenia. Methods: 26 adults (20 males; mean age 30; 19–51 years) with a DSM-IV diagnosis of schizophrenia, matched on age, sex, handedness, and years of education, were scanned on a Siemens 3 Tesla MRI scanner. The Schedule for the Deficit Syndrome was used to determine deficit status ($n = 13$). MRI data acquisition included T1MPRAGE, diffusion tensor imaging and a fieldmap. FreeSurfer was used to obtain white matter parcellations from the T1MPRAGE. Seed and target masks for tractography were selected by examining mask overlap with distal ends of tracts from the JHU Tractography Atlas. Connectivity distributions were generated with FSL BEDPOST/PROBTRACKX for five tracts: Cortico-spinal Tract (CST), Inferior Fronto-Occipital Fasciculus (IFOF), Inferior Longitudinal Fasciculus (ILF), Superior Longitudinal Fasciculus (SLF), and Uncinate Fasciculus (UNC). Mean fractional anisotropy was determined for each tract. Results: Fractional anisotropy (FA) was significantly lower ($p < .05$) in deficit patients compared with non-deficit patients bilaterally in the ILOF (Cohen effect size $d = .90$/left, .67/right), in the right SLF ($d = .71$), and in the left ILF ($d = .985$). FA was lower, bilaterally, in all five white matter tracts (Signs test $P = .002$). Findings in SLF replicate a previous finding (Rowland et al, 2009). Conclusion: Fiber tractography detected lower FA in deficit vs non-deficit schizophrenia subjects. The neurobiological pathophysiology of deficit schizophrenia is believed to be distinct. These data provide further support for differences in the underlying white matter integrity in this subtype of schizophrenia. This work was supported by R01MH060662 (K.O.Lim); R03MH076025.
ID: 979786

ABNORMAL TRAJECTORIES OF NEURODEVELOPMENT AND BEHAVIOR FOLLOWING IN-UTERO INSULT IN RATS: MODELING PSYCHOSIS EMERGENCE IN AN ANIMAL MODEL

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Background: Schizophrenia is a neuropsychiatric disorder of a neurodevelopmental origin manifested symptomatically after puberty. Structural neuroimaging studies show that neuroanatomical aberrations occur prior to onset of symptoms, but their onset and time course remains unknown, and their relationship to symptoms is debatable. We used a neurodevelopmental animal model of schizophrenia to delineate the developmental trajectories of schizophrenia-like brain structural and behavioral changes between adolescence and adulthood. Methods: Pregnant rats were injected on gestational day 15 with the viral mimic polyriboinosinic-polyribocytidylic acid (poly-I:C) or saline. Lateral ventricular and hippocampal volume in male and female offspring were assessed repeatedly at postnatal days 35, 46, 56, 70 and 90 using in-vivo MRI (longitudinal assessment). At parallel time windows, groups of offspring from the same litters underwent behavioral testing (latent inhibition; LI and amphetamine-induced hyperactivity (AIA) and imaging (cross-sectional assessment). Results: Hippocampal and ventricular volume increased with age in both poly-I:C and saline offspring but HIP volume expansion was smaller and LV volume expansion was larger in poly-I:C offspring. There were conspicuous sex differences in the developmental trajectories of both lateral-ventricular and behavioral abnormalities, with delayed onset in females. Hippocampal volume loss begins in late adolescence and predicted the appearance of behavioral abnormalities in both sexes. Conclusion: Our results suggest that prenatal insults influence postnatal brain maturation, which in turn results in the manifestation of behavioral abnormalities. Hippocampal volume loss during a critical period of adolescence may serve as a risk marker for later behavioral pathology and a neural target for assessing preventive treatments.
ID: 946034

BRAIN DEVELOPMENT IN HEALTHY SIBLINGS OF CHILDHOOD ONSET SCHIZOPHRENIA PATIENTS

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Background: Since 1990 children and adolescents with childhood onset schizophrenia, (COS) and their first degree relatives have been followed prospectively at the National Institute of Mental Health (NIMH) with clinical and brain imaging measures. Striking brain developmental abnormal-

ities were seen similar to that seen in adult onset disorder. As part of this study, the largest sample of healthy full COS siblings has been assembled and followed prospectively. We were interested in familial/genetic abnormalities in developmental pattern. Methods: Healthy full siblings were followed with anatomic brain MRI scans at approximately two year intervals. 95 of these siblings have at least one scan between the ages of 5 and 28 (total 281 scans). Scans were examined using several measuring packages including CIVET (Montreal Neurological Institute) for cortical gray matter (GM) thickness, FreeSurfer for deeper GM structures such as hippocampus and a manual method for cerebellar measures. Results: In two separate non overlapping samples, measures of cortical thickness showed that early cortical regional thinning in frontal and temporal regions "normalized" by late adolescence ie the controls "caught up" with respect to regional thinning of cortex. Total cerebellar volume showed an overlapping developmental trajectory between the siblings and COS probands. Finally hippocampal volume was virtually identical for the healthy siblings compared to controls while COS probands showed significantly smaller hippocampal volume which remained fixed. Conclusion: The slowing of regional cortical thinning for healthy siblings may represent a protective "healthy intermediate phenotype". Finally the abnormal total cerebellar decline may also reflect an intermediate phenotype while disease specific effects are seen at sub-regional levels. The fixed reduced hippocampal volume in schizophrenia may be a non genetic, critical disease related phenotype as postulated in prior animal models.
ID: 975821

AUDITORY HALLUCINATIONS IN FIRST EPISODE PSYCHOSIS: A DTI STUDY OF THE ARCUATE FASCICULUS

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Background: One of the most frequent and key aspect of psychosis is the presence of auditory hallucinations, which occurs with a lifetime prevalence of 60%. The arcuate fasciculus has been implicated in the generation of auditory hallucinations (AH). DTI studies of this tract have led to contradictory findings, with some but not all studies showing an altered white matter integrity in subjects with AH. As the arcuate fasciculus is constituted by different segments, it is possible that each one is differentially affected, and this may not be apparent when the arcuate is studied as a whole. Secondly, FA, an index of white matter integrity, has traditionally been the single measure evaluated, but this is informative of the white matter microstructural abnormalities that may be involved. This study evaluated the different segments constituting the arcuate fasciculus in patients with AH, to elucidate the microstructural underpinnings of such symptom. Methods: 22 first episode psychosis patients with auditory hallucinations, 28 without auditory hallucinations and 45 healthy controls were enrolled in this study. All subjects underwent MRI within 3 months of their contact with the services. Arcuate DTI tractography dissection was performed using a three Region Of Interest approach procedure, and bilaterally divided on three segments: direct, indirect posterior and indirect anterior segments. 5 diffusivity metrics, sensitive to myelin abnormalities and axon integrity were then obtained for each of the segments: Fractional Anisotropy (FA), Mean Diffusivity (MD), MODE and axial and radial diffusivity. Psychotic symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) on the day of MRI. Results: Patients with auditory hallucinations showed an increased axial diffusivity in comparison to patients without auditory hallucinations (P = .038). In comparison to healthy controls, they showed an overall increase in MODE in the right direct segment (P = .027). Finally, there was a significant positive correlation between severity scores of auditory hallucinations and mean axial diffusivity in the right posterior indirect segment in patients with auditory hallucinations (P = .020). Conclusion: The increase in axial diffusivity in patients with auditory hallucination, an index of axonal damage, which is also correlated to its severity, may shed light on the microstructural abnormalities underpinning auditory hallucinations and support the hyperconnectivity hypothesis of auditory hallucinations.
ID: 980002

STRUCTURAL MRI IN THE 1986 NORTHERN FINLAND BIRTH COHORT (1986-NFBC): FINDINGS AMONG DIFFERENT PSYCHOSIS RISK PROFILES IN A CROSS SECTIONAL STUDY

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Background: We assessed brain structure in psychosis high-risk groups, in a population based, cross sectional comparison between groups at Clinical Risk (CR), Family Risk (FR) or both Family Risk plus Clinical Risk (FRCR). We wished to test the hypothesis that risk for psychosis would be associated with structural brain abnormalities, with increased deficits in those at both FR and CR. Methods: To define the population at risk we applied a stepped approach. First we used a population-based methodology on the 1986-Northern Finland Birth Cohort (n = 9479), screening for sub-threshold symptoms using questionnaires (PROD-Screen). We identified cohort members at FR for psychosis by including those with a parent with psychosis. We invited cohort members with FR or deemed at risk from the PROD-Screen, along with a control group (CON), and interviewed them using the SIPS. After this procedure, 172 subjects were included in the study. Subjects were classified in three different risk groups: FR excluding CR according to the SIPS (FR, n = 60), CR without FR (CR, n = 26), and individuals at both FR and CR (FRCR, n = 13). A control group was selected from the Cohort (CON, n = 73). T1-weighted brain scans were acquired at 1.5 Tesla. Data was processed using a FSL-VBM analysis. Modulated gray matter images were analyzed using CamBA permutation statistics, using gender, handedness and total intra-cranial volume as covariates in an ANCOVA model. Results: In the comparison between the FRCR vs CON, we found lower gray matter volume (GMV) in a cluster (1689 voxels at −4.00, −72.00,−18.00 mm) covering both cerebellar hemispheres and the vermis. This cluster was subsequently used as a mask to extract mean cerebellar GMV in all four groups. The Family Risk group had a volume (9191 mm^3) intermediate between the CON group (9528 mm^3) and the FRCR group (8037 mm^3): FR vs CON (P = .014); FRCR vs FR (P = .002). Within the FRCR group there was an association between cerebellar cluster brain volume and motor function as assessed by the grooved pegboard test (P = .049, R^2 = .422). Conclusion: The FRCR group had lower cerebellar GMV compared to CON. This deficit was correlated

with performance on the grooved pegboard test suggesting a detrimental effect of this structural difference on motor function. The FR group had a cerebellar GMV intermediate between the FRCR group and CON. These findings are consistent with an evolving pattern of cerebellar deficits in psychosis risk with the most pronounced deficits in those at highest risk of psychosis.
ID: 975610

CINGULUM BUNDLE DIFFUSION AND DELUSIONS OF REFERENCE IN FIRST EPISODE SCHIZOPHRENIA

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Background: The cingulum bundle is the major white matter tract connecting the cortex and limbic system, and is involved in memory, reasoning and emotion. It has been observed to be abnormal in patients with chronic schizophrenia (Kubicki, McCarley et al 2007), but it has been less studied in first episode (FE). Using Diffusion Tensor MRI, a method that examines the tissue structure and connectivity of different brain regions by measuring the diffusion of water, this study explores the changes between first episode and chronic schizophrenia in the cingulum bundle. Methods: 18 patients with FE schizophrenia, 20 patients with chronic schizophrenia (CSZ) and 20 controls were matched to each patient group (FENC and CSZNC), and received diffusion imaging on a 3T GE Echospeed system. Two regions of interest, anterior and posterior portions of the cingulum bundle, were manually placed for each subject to initiate streamlined tractography. After successful fiber tracking mean trace (TR), fractional anisotropy (FA), axial and radial diffusivity (AD and RD) were calculated for each subject. Results: No significant differences in FA were found between groups, though the FENC group showed a trend towards increased FA in the right hemisphere in comparison to FE ($t(36) = -1.438$, $P = .159$) and in comparison to CSZNC ($t(38) = 1.961$, $P = .057$). FE exhibited higher TR in comparison to FENC in both hemispheres (left: $t(36) = 3.113$, $P = .004$; right: $t(36) = 3.324$, $P = .002$) and on the left in comparison to CSZ ($t(36) = .2.454$, $P = .019$). AD was increased in the FE bilaterally in comparison to FENC (left: $t(36) = 4.358$, $P < .001$; right: $t(36) = 4.201$, $P < .001$) and CSZ (left: $t(36) = 3.257$, $P = .002$; right: $t(36) = 2.511$, $P = .017$). RD was higher in FE compared to FENC bilaterally (left: $t(36) = 2.105$, $P = .042$); right: (36) = 2.610, $P = .013$). In addition, RD was correlated with Delusions of Reference (Pearson's $r(36) = -.413$, $P = .023$) in patients with schizophrenia. Conclusion: Our results suggest that both axial and radial diffusivity contribute to the change in overall white matter health and organization measured by FA and trace between first episode and chronic schizophrenia. Results further suggest that the underlying pathology in FE schizophrenia in the cingulum bundle involves abnormalities in both axon integrity and myelination. In particular the myelin integrity may be related to the severity of Delusions of Reference. This is consistent with abnormal myelin development that results in partial degeneration of the underlying axons.
ID: 962052

A COMBINED DIFFUSION TENSOR AND MAGNETIZATION TRANSFER IMAGING INVESTIGATION IN FIRST EPISODE SCHIZOPHRENIA

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Background: Neuropathology and neuroimaging studies have consistently identified white matter abnormalities in schizophrenia, however, the nature and development of this neuropathology remains unclear. One potentially informative approach is to acquire complementary multimodal imaging data in individuals at the onset of the disorder. Methods: In the same scan session, Diffusion tensor Imaging (DTI) and Magnetization Transfer Imaging (MTI) data were acquired from 16 people with first episode schizophrenia or schizophreniform disorder and 16 age and gender matched controls. Intensity values were sampled from the major fronto-temporal tracts in native space and compared between groups. Results: In the absence of whole brain differences, the first episode group demonstrated lower FA, higher Radial Diffusivity and lower MTR values in the left uncinate fasciculus. Conclusion: This study concurrently acquired DTI and MTI data in first episode schizophrenia and we have found independent and converging evidence of abnormalities of axonal structure, most likely due to reduced myelination, at the onset of the schizophrenia.
ID: 977497

MEDIAL PREFRONTAL CORTEX STRUCTURE AND FUNCTION IN YOUTH AT FAMILIAL RISK FOR SCHIZOPHRENIA FROM THE HARVARD ADOLESCENT HIGH RISK STUDY

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Background: Regional prefrontal cortex (PFC) gray matter reductions and altered PFC function have been identified in schizophrenia, likely reflecting a combination of genetic vulnerability and disease effects. Few morphometric studies to date have examined regional PFC abnormalities in non-psychotic biological relatives who have not passed through the age range of peak risk for onset of psychosis and fewer have evaluated PFC function

in the same subjects using functional(f) MRI. We conducted a study of PFC subregions and default mode functioning in adolescent and young adult relatives of schizophrenia patients. Methods: Twenty-seven familial high-risk (FHR) first-degree relatives of schizophrenia patients and forty-eight control subjects without a family history of psychosis (ages 13–28) underwent high-resolution MRI at 1.5 Tesla, and 17 relatives and 20 controls performed the 2-back working memory test in fMRI. The prefrontal cortex was parcellated into polar, dorsolateral, ventrolateral, ventromedial and orbital subregions. The Chapman scales and Hopkins Symptom Checklist measured subpsychotic symptoms. Associations of PFC subregion volumes and medial PFC BOLD activity with familial risk and subpsychotic symptoms were evaluated. Results: FHR subjects had significantly reduced bilateral ventromedial prefrontal and frontal pole gray matter volumes compared with controls, and had significantly less suppression of default activity in the medial PFC. Ventromedial volume was significantly negatively correlated with magical ideation and anhedonia scores in FHR subjects, and failure to suppress medial PFC default activity was associated with subpsychotic symptoms (Whitfield-Gabrieli et al, 2009). We therefore have converging anatomical and functional imaging evidence in the same sample that medial PFC abnormalities are associated with familial risk for schizophrenia in young adulthood. Because it is known that subpsychotic symptoms predict the emergence of full-blown psychosis in certain high-risk samples we postulate that ventromedial PFC deficits may partly mediate the transition to psychosis by becoming more pronounced among FHR adolescents who convert. Conclusion: Selective, regional prefrontal gray matter reductions and altered medial PFC default mode activity may differentially mark genetic vulnerability and predispose to early symptom processes among non-psychotic young adults at familial risk for schizophrenia.
ID: 979344

CHANGES IN WHITE MATTER IN THE EARLY STAGES OF SCHIZOPHRENIA

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Background: Recent magnetic resonance imaging studies demonstrate gray matter reduction in both temporal and frontal cortices at the schizophrenia onset, as well as progressive changes in those regions following illness onset. In contrast, far less is known about the existence, evolution and progression of white matter abnormalities at this stage of the disease. Methods: We used Diffusion Tensor MRI and Streamline Fiber Tractography to analyze the integrity of major white matter tracts in 18 First Episode Schizophrenics and 20 group-matched Healthy Controls. Average values for Fractional Anisotropy, a measure of tract coherence and integrity, and Trace, a measure of overall diffusion, were calculated and compared between groups for the Cingulum Bundle, Uncinate Fasciculus, Superior Longitudinal Fasciculus, Inferior Occipito-Frontal Fasciculus, Inferior Longitudinal Fasciculus and Corpus Callosum. Results: Our results demonstrate extensive abnormalities in overall diffusion (Trace) that affect all frontal and interhemispheric white matter connections. In addition we also observed Fractional Anisotropy group differences, which were much more restricted, ie, within the anterior Corpus Callosum, and the left Uncinate Fasciculus. Conclusion: Our findings suggest that in addition to abnormalities in white matter at FE, including measures of tract coherence and integrity, which may be neurodevelopmental and/or progressive in nature, an additional acute process is taking place, as indicated by increased trace. As there is little evidence of neuronal death in schizophrenia, we interpret this finding of increased trace in FE patients, which we have not seen in chronic patients, as suggesting increased extracellular water content, which in turn, suggests possible edema associated with neuroinflamation, neurodegenerative loss of dendrites/synapses (neuropil), stress, etc., that affects both soma/dendrites and axons, and is present at disease onset thus providing a possible putative marker of brain pathology at first episode of illness.
ID: 978409

PRENATAL INFLUENZA INFECTION ALTERS OFFSPRING BRAIN DEVELOPMENT: DIFFUSION TENSOR IMAGING (DTI) TRACTOGRAPHY OF WHITE MATTER PATHWAYS IN THE RHESUS MONKEY

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Background: Maternal flu infection during pregnancy may be a risk factor for altered fetal brain development. An association between influenza and neurodevelopmental disorders, such as schizophrenia, is hypothesized from both rodent and retrospective human studies. Our research with primates has recently identified structural alterations in the brains of offspring following maternal influenza infection: reduced total gray matter and increased cingulate white matter (WM) volumes. Brain development in these offspring is further characterized in the current study using Diffusion Tensor Imaging (DTI) to examine the structural integrity of several WM tracts. Methods: Ten pregnant rhesus monkeys were infected with a human-derived influenza virus, A/Sydney/5/97(H3N2), at week 17 post-conception (late 2nd trimester) and compared to 5 control pregnancies. Structural MR imaging and DTI (3T) were preformed on offspring at 13mos. (equivalent to late childhood). Automatic atlas-based methods determined regions and fiber tracts for analyses of WM organization and myelination. DTI parameters included fractional anisotropy (FA), mean (MD), axial (AD) and radial (RD) diffusivities. Results: Tract based analyses revealed multiple regions of significant focal differences in all diffusion parameters. Significant differences ($P < .05$) were seen bilaterally for all fiber tracts studied: Uncinate, Anterior Cingulate, and Corpus Callosum (Genu, Prefrontal, Primary and Supplemental Motor, Parietal and Temporal sections). Compared to Control offspring, differences in diffusion parameters suggest that Flu-exposed monkeys have less organization and greater myelination in several WM tracts. Conclusion: These findings demonstrate that a moderate viral infection during pregnancy can impact offspring neural development, influencing the structural integrity of WM tracts throughout the brain. DTI parameters indicate reduced fiber organization with increased myelination in specific regions and along particular tracts in Flu-exposed offspring. Overgrowth of WM is a possible explanation for these findings. This research was supported by funding from the NIAID (AI067518) and from a NICHD grant (HD383386). S. Short had an NRSA fellowship from the NIMH (F31 MH076606). Additional funding came from the UNC Conte Center for Schizophrenia Research [MH 064065] and the UNC Neurodevelopmental Disorders Research Center (HD 03110).
ID: 979624

LANGUAGE AND BRAIN VOLUMES IN CHILDREN WITH SCHIZOPHRENIA

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Background: Children and adolescents with schizophrenia are known to have disorganized speech and thought disorder, which suggests that they have language deficits. Prior volumetric studies have also demonstrated involvement of frontal and temporal regions in children with schizophrenia. However, very few studies have examined the association of regional volumetric measures and language skill in children with schizophrenia. Therefore, this study compared the relationship between language scores and fronto-temporal volumes in language-related regions in children and adolescents with schizophrenia to those of normal children of comparable age and gender distribution. Methods: Age-appropriate versions of the Test of Language Development (TOLD)-2 (Newcomer & Hammil, 1988) administered to 29 children with schizophrenia and 16 normal children, aged 8.5–17.6 years, generated Spoken Language Scores (SLQ). Study subjects underwent brain magnetic resonance imaging scans at 1.5 Tesla. Tissue was segmented and total brain, frontal lobe, frontal parcellations and temporal lobe volumes were computed. Non-parametric analyses were used for group comparisons and language-volume associations. Results: Sixty-two percent of the children with schizophrenia had significant linguistic impairments, defined as having SLQ scores less than 1 standard deviation below normal. Orbital frontal gray matter volumes in children with schizophrenia with linguistic deficits were significantly smaller compared to those without deficits ($P < .04$) and to normal children ($P < .007$). Further, linguistically impaired children with schizophrenia did not show any significant associations of volumes with SLQ scores; however in children with schizophrenia but no linguistic impairments, higher SLQ scores were associated with greater orbital frontal gray matter volumes ($P < .02$) and in normal children, higher SLQ scores were associated with greater superior frontal and temporal gray and white matter volumes ($P < .002$–$.03$). Conclusion: This first study of language skill and fronto-temporal volumes in childhood schizophrenia highlights discrepancies in brain regions involved in the linguistic skills of children with schizophrenia compared to typically developing children. Although cross-sectional, these findings support those of Sporn et al (2003) showing a relationship between progressive gray matter volume reduction and premorbid dysfunction of language, motor, and/or social skills in children with schizophrenia.
ID: 986776

PREFRONTAL PROTECTIVE FACTORS IN SCHIZOTYPAL PERSONALITY DISORDER

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Background: Patients with schizophrenia demonstrate both reduced cortical gray volumes in frontal and temporal cortex on magnetic resonance imaging (MRI) and impaired performance on associated neurocognitive tasks. Although schizotypal personality disorder (SPD) patients share many features of schizophrenia (SCZ), they are protected from the severe psychosis and cognitive impairment of SCZ, perhaps due to a relatively preserved prefrontal cortex. Methods: In order to test this model, a new analysis of 79 SPD patients and 148 healthy controls using MRI volume of key Brodmann areas (BAs) previously shown to be reduced in schizophrenia-spectrum samples (BA 10, 21 and 22) and tasks of cognitive functions (CVLT, DOT Test, and PASAT) known to be impaired in schizophrenia-spectrum patients was performed. D1 binding was imaged with [11C]NNC by PET in 19 SPD patients. Results: Using multiple regression analysis, we could predict the SPD diagnosis, $F(6, 102) = 9.99$, $P < .001$. Although volume of BA 21 (middle temporal gyrus; $P = .03$) and BA 22 (superior temporal gyrus; $P < .001$) predicted diagnosis, the DLPFC region BA 10 did not ($P > .05$). Indeed, BA10 volume is increased in SPD compared to SCZ and HCs ($P < .05$). However, both verbal (PASAT; $P < .01$) and visual (DOT Test 30 second delay; $P < .001$) working memory tasks associated with DLPFC functioning predicted group membership; in the current sample verbal learning (CVLT Long Delay; $P > .05$), associated with both temporal and frontal functioning, did not. Reduced D1 binding, consistent with increased frontal dopaminergic presynaptic activity, was associated with better cognitive performance ($P < .05$). Conclusion: Temporal region indices do not distinguish between schizophrenia and SPD patients, suggesting a spectrum-wide vulnerability, while SPD patients have a relative sparing of frontal (particularly dorsolateral) regions suggesting it may be a protective factor against psychosis. In addition, although SPD patients' performance on our neurocognitive measures of DLPFC differentiated them from HCs, their performance on these tasks was less impaired than seen in chronic schizophrenia suggesting that DLPFC integrity and dopaminergic activity modulate severity of cognitive impairment along the spectrum.
ID: 979902

DIFFUSION TRACTOGRAPHY STUDY IN COMMUNITY BASED SCHIZOTYPES

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Background: Dysconnectivity of white matter has been implicated in schizophrenia. Diffusion tensor studies (DTI) enables the visualization and quantification of white matter in vivo. Via measures of diffusion anisotropy such as fractional anisotropy (FA), differences in white matter tract coherence have been observed in chronic and first-episode patients, as well as high risk groups. There is theoretical importance in examining whether changes in white matter occur prior to development of psychosis. Schizotypal samples represent a group on the psychosis continuum that could share etiological risk factors to clinical disorders, but do not possess the confounds of illness. In the current study, it was hypothesized that a schizotypal sample would demonstrate altered levels of tract coherence in comparison to a control group. Methods: DTI was performed at 3T on 12 high schizotypes and 12 controls matched for age, sex and IQ. We examined bilaterally the uncinate and arcuate fasciculi with a probabi-

listic tractography algorithm (PICo). FA values were extracted from the tractography derived tracts and compared between schizotypes and controls. Partial correlations were also examined between measures of subclinical hallucinatory/delusional features and FA values. Results: High schizotypes were found to have significantly higher FA values in the uncinate fasciculi ($F(1, 23) = 5.25$, $P < .05$). There was no significant difference in FA values in the arcuate fasciculi. In the whole sample there was a positive correlation between increasing FA values and "vivid daydreams" in the right arcuate fasciculus ($r(20) = .64$, $P < .001$). Conclusion: Increased FA values in bilateral uncinate fasciculi in high schizotypes could represent either: (1) increased connectivity which is either a compensatory mechanism and/or an artifact of increased dopaminergic tone; or (2) increased FA values due to reduction in crossing fibers, suggesting a decrease in diffuse connectivity in fronto-temporal connections. Correlations between mild hallucinatory experience and increasing FA values could indicate increasing connectivity, or "hyperconnectivity", is associated with symptom formation.
ID: 977230

BRAIN DERIVED NEUROTROPHIC FACTOR AND HIPPOCAMPAL SIZE IN FIRST-EPISODE PSYCHOSIS

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Background: Hippocampal neuronal plasticity may be affected by a common polymorphism of the brain-derived neurotrophic factor (BDNF) gene (val66met). Studies of healthy individuals suggest the met allele is associated with smaller hippocampal volume although findings from psychiatric patients have been inconsistent. The goal of the present study was to assess the association between hippocampal volume and BDNF genotype in first-episode psychosis. Methods: Participants included 59 patients with first-episode psychosis (schizophrenia = 36, schizoaffective = 11, mood disorder = 12) and 46 healthy volunteers. MRI scans and blood samples were obtained at recruitment. Automated measures of hippocampal and brain volume were acquired. Analysis of covariance was used to assess differences in hippocampal volume between diagnosis (patient vs. control) and genotype (val-val vs. val-met/met-met) with brain volume and gender as covariates. Results: Results indicated a statistically significant difference in hippocampal volume (3.4%) related to diagnosis but not genotype. In addition, a significant diagnosis-by-genotype interaction was seen. Similar results were obtained for the left and right hippocampi and for the subset of patients with a diagnosis of schizophrenia. In agreement with previous research, healthy subjects with a met allele had smaller hippocampi (4.7%) than val-val homozygotes. Hippocampal volume in patients was very similar to that of controls for those with a met allele. However, hippocampal volume in val-val patients was smaller than that of patients with a met allele (3.5%) and substantially smaller than val-val controls (7.4%). Post hoc analyses suggested associations between hippocampal volume and birth hypoxia, poor academic achievement and low family income in patients with the val-val but not val-met/met-met genotype. Conclusion: Finding suggest the associations between hippocampal volume and BDNF genotype are atypical in patients with psychosis.
ID: 937982

CANNABIS AND ALCOHOL INFLUENCE THALAMIC AND STRIATAL SHAPE IN SCHIZOPHRENIA

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Background: Cannabis and alcohol have been reported to exacerbate the clinical course of schizophrenia. However, the neurobiological bases of these comorbid interactions are unknown. This study examined whether a history of cannabis or alcohol use disorder (CUD, AUD) influenced thalamic and striatal shape abnormalities in schizophrenia. We hypothesized that AUD-related abnormalities would be present across the entire structures while CUD abnormalities would be most evident in subregions dense with cannabinoid receptors. Methods: T1-weighted magnetic resonance images were collected from schizophrenia patients with no history of substance use (SCZ_0, $n = 47$), schizophrenia patients and a history of CUD (SCZ_CUD, $n = 15$) or AUD (SCZ_AUD, $n = 16$), control subjects without a history of substance use (CON_0, $n = 62$), and control subjects with a history of CUD (CON_CUD, $n = 10$) or AUD (CON_AUD, $n = 15$). Large-deformation, high-dimensional diffeomorphic brain mapping was used to obtain three-dimensional surfaces of the thalamus and striatum. Principal component (PC) analysis on the surfaces was used to represent shape variation. Multivariate analysis of variance (MANOVA) was used to test between-group shape differences. Results: The main effects of group membership were significant when examining the shape of the thalamus($P < .001$ and $P < .001$, respectively) and striatum ($P < .001$ and $P = .001$, respectively). SCZ_0 were characterized by inward deformations of the anterior and posterior thalamus, and anterior striatum. A comorbid CUD in schizophrenia was associated with inward shape deformity in the lateral and mediodorsal regions of the thalamus (specific PCs), and dorsal and ventral regions of the striatum. A comorbid AUD in schizophrenia was associated with exaggerated inward shape deformity across the anterior and posterior thalamus, and anterior, dorsal and ventral striatum. Conclusion: Shape analysis suggests that comorbid AUD exaggerates structural defects in the thalamus and striatum as compared with schizophrenia patients without substance abuse. In contrast, CUD contributed more uniquely to the deformity of the thalamus and striatum in a substance- and region-specific manner with the effects of cannabis being at least partially consistent with regions that densely express cannabinoid receptors. Further research is needed to determine the mechanistic basis of these structural changes and whether there are specific substance-disease interactions.
ID: 977686

MICRO STRUCTURAL ALTERATIONS OF THE ARCUATE FASCICULUS IN SCHIZOPHRENIA PATIENTS WITH FREQUENT AUDITORY VERBAL HALLUCINATIONS

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Background: Auditory verbal hallucinations (AVH) are a characteristic symptom of schizophrenia, occurring in some 70% of the patients. A failure in self-attribution may explain why patients with AVH do not recognize these language fragments as self produced. A disturbed connectivity between frontal and temporo-parietal language areas might underlie this de-

ficiency in self-attribution. This hypothesized disturbed connectivity could be reflected in the microstructure of the arcuate fasciculus (AF), the major tract connecting language production to language perception areas. Methods: In this study we compared various microstructural properties of the AF and three unrelated control tracts using diffusion tensor imaging (DTI) and magnetic transfer imaging (MTI) as indices for fiber integrity (FA) and macromolecular content (including myelin). DTI and MTR are complementary techniques, as the combination of these two quantifications can differentiate between fiber integrity and defiant myelinisation of a tract. DTI and MTI scan were acquired from 42 schizophrenia patients with chronic AVH and 42 healthy controls matched for gender, age and handedness pwith a 3T MRI scanner. The DTI scans were used to reconstruct the various fiber bundles and to compute FA, while the MTI scans were used to compute MTR values. For left and right AF and three control bundles FA and MTR values were sampled along the reconstructed tracts. Results: The patient group showed a significant higher mean MTR for the left AF as compared to the healthy control group. No significant differences in mean MTR were found in any other bundles. A significant association was found between mean MTR values in both AF and severity of the positive symptoms. FA showed a general decrease in all bundles and correlated negatively with age. Conclusion: The combination of increased MTR in the presence of decreased FA of the left arcuate fasciculus, indicates microstructural alterations in the connection between the language production and the language perception areas in schizophrenia patients with severe auditory verbal hallucinations.
ID: 976118

ALTERED STRUCTURAL BRAIN DEVELOPMENTAL TRAJECTORY IN YOUTH AT CLINICAL RISK FOR PSYCHOSIS

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Background: Schizophrenia may be associated with abnormal brain development during adolescence and early adulthood. This view has gained support from longitudinal neuroimaging investigations that show faster thinning of the cerebral cortex in patients with schizophrenia and psychotic disorders. Following individuals at clinical risk for psychosis and tracking longitudinal brain changes can provide stronger evidence for neurodevelopmental deviation predating psychosis, as factors secondary to the disease that affect brain volumetric measures could be ruled out. However, there have been only a few small-sized studies of such kind and the results need confirmation in larger cohorts. If abnormal cortical changes occur in psychotic disorders over time, altered age-related gray matter variations can be expected during the at-risk stage in cross-sectional settings. Methods: In this multi-site structural MRI study, we compared age-related variation of cortical gray matter density (GMD) in individuals at clinical risk for psychosis with that in healthy controls. 170 at-risk individuals and 105 age-matched control subjects were included in the analysis. Cortical gray matter density was measured using cortical pattern matching, in which accurate cortical surface registration was applied. Group differences and age-GMD correlations were mapped onto a probabilistic cortical atlas, and the interaction between group and age on GMD was examined. Results: At-risk individuals showed significant gray matter deficits in cortical areas including the medial parietal and occipital regions and lateral temporal and parietal regions, and both at-risk and control groups showed significant negative correlations between GMD and age across the dorsal cortical areas. Intriguingly, right prefrontal and anterior cingulate gray matter showed different age-related tendencies in the two groups, with that of at-risk individual demonstrating a significantly steeper decrease across the age range. Conclusion: We show exaggerated age-related gray matter decreases in a large young cohort at clinical risk for psychosis. The cortical regions that show the different developmental trajectory are known to undergo prolonged maturational processes including continuous synaptic pruning and myelination in youth. Although it needs to be confirmed in future large-scaled longitudinal studies, our finding provides further support to the view that disrupted neurodevelopment plays a critical role in the neurophysiopathology of schizophrenia and psychosis.
ID: 979699

INVESTIGATION OF GRAY AND WHITE MATTER IN SCHIZOPHRENIA AND BIPOLAR I DISORDER: A DIFFUSION TENSOR IMAGING STUDY

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Background: A dichotomy between schizophrenia (SCZ) and bipolar disorder (BPD) was originally described by Kraepelin and continues to exist today. Few studies, however, have directly assessed similarities and differences in the gray or white matter in patients with SCZ compared to patients with BPD. The goal of this study was to investigate the relationship among measures of gray and white matter integrity using diffusion tensor imaging (DTI) in 35 patients with SCZ, 20 patients with bipolar I disorder (18 with psychotic features) and 56 healthy controls (HC). Methods: Fractional anisotropy (FA) was used as a measure of white matter integrity. We examined MD within the gray matter as a surrogate marker for greater water diffusion in cerebrospinal fluid and concomitant gray matter loss. The dependent measures included average FA and MD within 44 prescribed regions-of-interest within the frontal, temporal, parietal, occipital and limbic lobes identified using the LPBA40 Atlas. Pearson product moment correlations were used to examine the relationship among brain regions separately in groups. Results: Patients with SCZ had significantly lower FA compared to patients with BPD and HC in the superior temporal, parahippocampal, superior occipital and middle occipital white matter. Patients with BPD did not differ significantly in FA from HC in any of these white matter regions. Both patient groups had higher MD within the superior temporal and parahippocampal gray matter compared to HC. Patients with SCZ had significantly higher MD within the hippocampus compared to HC and significantly higher MD compared to HC and patients with BPD in the inferior temporal gyrus gray matter. Furthermore, lower FA within the parahippocampal gyrus white matter correlated significantly with higher MD within the inferior temporal gyrus gray matter among patients with SCZ, but not among patients with BPD or HC. Conclusion: Our data implicate overlapping gray matter temporal lobe structural alterations in the neurobiology of SCZ and BPD, but suggest that temporal lobe white matter pathology may be an additional risk factor for SCZ. These findings further implicate a defect involving parahippocampal and inferior temporal circuitry in the neurobiology of SCZ compared to BPD. These findings may have relevance for diagnostic classification systems and future research focusing on the identification of susceptibility genes for these disorders.
ID: 976002

HERITABILITY AND GENETICS OF SOURCE BASED MORPHOMETRY IN SCHIZOPHRENIA

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Background: Source Based Morphometry (SBM) is an independent components analysis used to identify common covariation in grey or white matter among subjects. Gray matter patterns significantly associated with schizophrenia have been identified using SBM[1]; we combine structural and genetic data from three multi-site neuroimaging studies of schizophrenia (SZ) (FBIRN and MCIC[2]; NWdata[3]) including sibling-pair data to assess genetic influences on gray matter covariation. Methods: 754 datasets were used in the SBM analysis (323 from SZ subjects). Structural images and genetic data were collected for FBIRN and MCIC. The NWdata included 281 structural datasets, including 29 pairs of SZ and unaffected siblings, and 41 pairs of controls matched to the SZ group, and their siblings. All SZ subjects were stable on their medications; duration of illness varied from .25 to 44 years. Age ranged from 19 to 61 years for the SZ subjects, 14–67 for the controls and siblings. Smoothed, unmodulated gray matter images were created for voxel-based morphometry analysis (VBM) on each dataset[2]. The spatially independent components from the SBM analysis of the smoothed images were analyzed to determine the effect of diagnosis, covarying for age, gender, and dataset. The loading coefficients on the components were phenotypes for the heritability and genetic analysis. Genotyping used the Illumina HumanOmni-Quad BeadChip on the MCIC samples, and the HumanHap 300 Bead Chip on the FBIRN samples. Results: All three VBM analyses were consistent in the pattern of gray matter loss in SZ. The SBM analysis on the combined dataset resulted in five components that were significantly different by diagnosis. Two of these identified the same networks as were published in an independent sample[1]. The loading coefficients on the 5 components showed significant heritability. The coefficients from 160 MCIC subjects were analyzed as 5 quantitative traits in a massively univariate GWAS analysis with diagnosis, age and gender. The smallest p-value was 4×10^{-7}, for rs11537993 in BRMS1on chr. 11; future analyses will combine the genetic datasets for power. Conclusion: The analysis of multiple independent structural imaging datasets shows repeatable univariate VBM and multivariate SBM patterns of gray matter loss in SZ. The multivariate components are heritable, and suitable for testing for genetic effects in GWAS.
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1U24RR021992, 1RC1MH089257-01, 1R01MH084803
ID: 978506

ABERRANT COMPLEX BRAIN NETWORK ORGANIZATION IN SCHIZOPHRENIA

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Background: Our brain is a network. All regions are interlinked by white matter tracts, forming one integrative complex structural network. Interestingly, recent studies have shown that the efficiency of this structural network plays a crucial role in the capacity of the brain to integrate information. Schizophrenia, a severe psychiatric disorder characterized by hallucinations, loss of initiative and cognitive impairments, has long been hypothesized to be related to a reduced capacity to integrate information between regions of the brain. Here, using graph theoretical analysis, we demonstrate that schizophrenia affects the organization of the structural brain network. Methods: Brain networks of 40 patients and 40 matched healthy controls were explored using Diffusion tensor imaging, an MRI technique that enables the reconstruction of white matter tracts, with the strength of the white matter connections defined as their level of myelination (MagnetizationTransfer Ratio MRI). Using graph theory, the organization of the brain networks was examined by measuring the connectivity strength S, indicating how tightly regions are interconnected, their level of local clustering, and their level of global accessibility, indicating how efficient regions can connect to all other regions of the network (ie path length L). Results: Although patients displayed a normal overall ''small-world'' organization, focusing on specific brain regions and their capacity to communicate with other regions of the brain, revealed significantly reduced connectivity strength and longer node specific path lengths L of inferior/superior frontal cortex and temporal pole regions in patients. Furthermore, superior frontal (P = .0373) and anterior cingulate regions (P = .0130), regions marked by a hub-analysis as important connectivity hubs in the brain, showed a less central position in the overall network. Conclusion: Our findings show that schizophrenia involves a decreased hub-role of especially frontal brain regions to structurally connect to the rest of the brain network. These findings suggest an underlying structural cause of a limited capacity to integrate information across brain regions in schizophrenia.
ID: 979092

PROGRESSIVE BRAIN VOLUME LOSS IN SCHIZOPHRENIA IS NOT LIMITED TO THE EARLY STAGES OF THE DISEASE: COMPARISON BETWEEN FIRST-EPISODE AND CHRONIC PATIENTS

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Background: It has been suggested that excessive loss is not limited to the early stages of the disease but also occurs in patients that have been ill for many years. However, so far, there are only a limited number of studies that directly compare effects in first episode (FE) and chronically ill patients (CHR) relative to their age-matched control groups. Methods: Two Magnetic Resonance Imaging brain scans were obtained with a 5-year interval of 96 schizophrenia patients and 113 healthy subjects. Based on hospital records and a diagnostic interview patients were divided in two groups,

ie nFE = 46 and nCHR = 50. The control group was divided in a younger (n = 57) and older group (n = 56) based on a median split. Volumes of the cerebrum, gray (GM) and white matter cerebrum, lateral and third ventricles, and hippocampus were performed. In addition, change in cortical thickness was measured across the cortical mantle (CortT) using the CLASP algorithm. Linear regression analyses were performed adding volume or CortT change as dependent variable. The interaction between these group (schizophrenia vs. control) and age (FE/younger vs. CHR/older) was added into the analysis, as well as both main effects and gender. Results: Percentage volume decrease over time of cerebrum and GM in FE patients was .9% and 3.8% respectively, while in CHR patients this was 2.0% and 5.1%. Both in younger and older control subjects volume decreases were significantly smaller, ie, in younger subjects respectively .3% and 1.6% and in older subjects 1.2% and 3.4%. No significant interactions were found on change in volume or CortT, indicating that the volume and CortT loss in FE relative to their age-matched controls is similar to the loss in CHR relative to controls of comparable age. An exception was the hippocampus. Older controls showed a more pronounced loss as compared to younger controls, where for patients the loss was similar between first episode and chronically ill patients. The areas of cortical thinning in first-episode and chronic patients are similar to those that were found when comparing all patients to all controls. Conclusion: FE and CHR show similar decreases of cerebral (GM) volume and CortT over time relative to control groups of similar age. This indicates that excessive tissue loss in patients with schizophrenia is not limited to the early stages of the disease, except maybe for the hippocampus.
ID: 979392

GENETIC MECHANISMS OF DISRUPTED WHITE MATTER CONNECTIVITY IN SCHIZOPHRENIA

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Background: Oligodendrocyte and myelin related (OMR) genes have been implicated in schizophrenia. At the same time, diffusion tensor imaging (DTI) studies have implicated white matter tract disruption in schizophrenia. No study has yet related these molecular genetic and neuroimaging findings. The objective was to determine whether (i) white matter tract integrity is related to cognitive performance, (ii) OMR gene variants are related to white matter tract integrity and (iii) whether OMR gene variants are related to cognitive performance. Methods: 48 schizophrenia patients were matched to 48 controls on measures of age, gender, handedness, and ethnicity. All participants completed DTI, genetics, and cognitive protocols. Participants were recruited at the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada, via referrals, study registries, and advertisements. Using the multivariate partial least squares (PLS) approach, singular value (SV) decomposition was performed to discover latent variables that might relate DTI measures to cognitive performance, OMR gene variants to DTI measures, and OMR gene variants to cognitive performance. Results: Significant latent variables (LVs) were found across several comparisons using PLS: (i) white matter tract integrity predicted cognitive performance – schizophrenia patients (SV= 2.0, cross-block covariance (CC) = 63.4% P <.001) and controls (SV = 1.5, CC = 45.6% P = .01); a particularly robust pattern was noted in schizophrenia patients (ii) OMR gene variants influenced DTI white matter measures - schizophrenia patients (SV = 1.8, CC = 74.1 P <.001) and controls (SV = 1.5, CC = 67.7, P <.01), and, finally (iii) OMR gene variants influenced cognitive performance – schizophrenia patients (SV = 1.2, CC = 33.8 P = .03), and controls (SV = 1.1, CC = 37.4 P = .09). Conclusion: Taken together, our findings provide further evidence for the oligodendrocyte/myelin/white matter hypothesis in schizophrenia by bridging findings from genetics and neuroimaging, and lend insight into this pathway as a potential neurobiologic substrate of impaired cognitive performance in schizophrenia. Consistent with the imaging-genetics paradigm, gene effects demonstrated greater penetrance on brain (ie white matter tract integrity) rather than behavioral (cognitive) phenotypes.
ID: 978190

NEURAL CORRELATES OF A GENOME-WIDE SIGNIFICANT RISK VARIANT FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Schizophrenia and bipolar disorder share considerable genetic risk. Recent genome-wide association studies suggesting that the ZNF804A risk variant, rs1344706, may confer susceptibility for both disorders, with a putative function in myelination. In the brain, cortico-cortical white matter tracts may be disrupted in schizophrenia and in bipolar disorder. However, postmortem data demonstrating downregulated oligodendrocyte genes in these disorders emerge from cortical gray matter tissue. Therefore, the ZNF804A variant may exert its effects in cortical gray matter, white matter tracts or both, to confer risk for schizophrenia and bipolar disorder. Methods: In 72 healthy adults, we used high resolution MRI imaging to examine cortical thickness and diffusion tensor tractography approaches to segment and measure major fronto-temporal and interhemispheric white matter tracts. Cognitive performance at those domains with shared deficits in these disorders was measured: attention control, working memory, and verbal episodic memory. False discovery rate correction (5%) was used for cortical thickness, and repeated measures ANCOVAs were used for microstructural integrity of white matter tracts, and cognitive measures respectively. Results: T allele homozygotes (ie those homozygous for the risk variant) demonstrated reduced cortical gray matter volumes in both superior temporal gyrus and cingulate cortex compared to C allele carriers. No tract by genotype interaction was found, nor was any main effect of the risk variant found at microstructural integrity of white matter tracts. For cognitive performance a genotype by task interaction was found on the Stroop Color Word Score (a test of attention control), and a trend-level main effect of genotype was found on cognitive performance overall, where T allele homozygotes had reduced attention control compared to C allele carriers. Conclusion: We localized effects of the ZNF804A risk variant to thickness of cingulate cortex and superior temporal gyrus, structures disrupted in both schizophrenia and bipolar disorder, but not at white matter tracts. Furthermore, a relationship of the ZNF804A variant with attentional control, a cognitive domain mediated primarily by cingulate cortex was found. Therefore, we have shown genetic susceptibility conferred by this variant on at-risk cortical gray matter structures and cognitive function susceptible in both schizophrenia and bipolar disorder.
ID: 978176

SCHIZOPHRENIA DATA AND TOOL SHARING USING BIRN INFRASTRUCTURE

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Background: We propose to federate imaging data along with demographic, clinical neurocognitive and genotyping data from 139 subjects with schizophrenia and 136 control subjects group matched for age and gender, using Extensible Neuroimaging Archive Toolkit (XNAT) infrastructure provided by the bioinformatics research network (BIRN). XNAT is a software platform designed to facilitate common management and productivity tasks for neuroimaging and associated data. The XNAT framework relies on XML which provides a powerful tool for building extensible data models, and XML schema documents (XSDs) for its data representation, security system, and generation of user interface content. Methods: XNAT includes a base XSD that provides a framework for capturing specific experimental protocols. For schemas that are not direct derivations from the base XSD, extensions are developed so that the schemas can be integrated into the data model to be related to types already defined in the XNAT schema. Results: The demographicData type was extended to include sibling information as well as education level, years of schooling and Edinburgh Inventory handedness information. The abstract subjectAssessorData type was extended to create encounterLog type that included study registration information. The abstract subjectAssessorData type was also extended to create symptomsSAPSSANS type that included positive and negative symptom domain scores. Of these extensions, demographics already existed and have been extended to reflect the added new features. Subject registration and symptom domains are new XNAT schema extensions. All three extensions have been made ready to be used by other XNAT users. The data was converted to XML format and XNAT's REST API was used with a PHP program to upload related XML data for all subjects into XNAT Central (http://central.xnat.org/). Magnetic resonance imaging data for all subjects are also being uploaded into XNAT Central. Conclusion: When made accessible, these high resolution scans and the associated data will be very valuable to the neuroscience community. These data can be used to generate or test new hypotheses related to the maldevelopment of brain structures and neural networks in schizophrenia. They can also be used to rapidly replicate findings and to test and validate new brain mapping tools. Further, brain mapping pipelines designed for the analysis of these datasets can be used to study MR datasets collected from other studies.
ID: 971076

THE IMPACT OF SUBSTANCE USE ON BRAIN STRUCTURE IN PEOPLE AT GENETICALLY HIGH RISK OF SCHIZOPHRENIA

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Background: A variety of structural brain abnormalities are consistently found in schizophrenia. Substance misuse is associated with similar abnormalities and is often established at first presentation. Clarification of the relationship between substance use and imaging abnormalities in people who are well but at high risk of schizophrenia is important. It may yield insights in to the role of substance use in the development of the structural abnormalities seen in schizophrenia. Furthermore it may suggest how substance use influences transition to illness. Methods: We employed a prospective cohort study with nested case-controlled comparison design to examine the relationship between substance misuse, brain imaging abnormalities and the subsequent development of schizophrenia. Both volumetric and voxel-based morphometric (VBM) image analysis techniques were used to examine structural imaging associations with cannabis, alcohol and tobacco use in 147 high risk subjects and 36 controls at point of study entry. Regions exhibiting a significant relationship between level of drug use and structure volume were identified. In addition to the baseline scan, the first 57 high risk subjects also had a follow-up scan approximately 18 months later. This enabled longitudinal comparison of brain structural changes in high risk subjects who did and did not use drugs of abuse between scans. Results: In the baseline analysis, increased ventricular volume was associated with alcohol and cannabis use in a dose-dependent manner. Alcohol consumption was associated with reduced frontal lobe volume. Multiple regression found both alcohol and cannabis were significant predictors of these abnormalities when simultaneously entered into the statistical model. Complementing volumetric findings, VBM identified baseline cannabis-associated left thalamic abnormalities. Longitudinal volumetric analysis demonstrated cannabis use between scan points was associated with bilateral thalamic volume loss. Alcohol and cannabis misuse by point of entry in to the study were associated with increased risk of schizophrenia. Conclusion: We provide prospective evidence that use of cannabis or alcohol by people at high genetic risk of schizophrenia is associated with brain abnormalities and later risk of psychosis. A family history of schizophrenia may render the brain particularly sensitive to the risk-modifying effects of these substances.
ID: 978716

16. Neuropathology, Histology

PREFRONTAL CORTICAL DENDRITIC SPINE LOSS INDUCED BY DOPAMINE DEPLETION OCCURS IN DISTINCT POPULATIONS OF PYRAMIDAL CELLS DEFINED BY PROJECTION TARGET

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Background: Dystrophic changes in the dendrites of pyramidal cells in the prefrontal cortex (PFC) are among the most replicated of postmortem findings in schizophrenia. We have previously found that dopamine denervation of the PFC in the rat results in a sharp decrease in dendritic spine density of PFC pyramidal cells (PCs); this effect is seen in layer V but not II/III of the prelimbic cortex within the medial PFC. However, it is clear that not all neurons are affected, with some layer V cells having normal dendritic morphology. Methods: We examined layer V PCs in the PFC that project to the nucleus accumbens (NAS) or the ventral tegmental area (VTA), both in vivo and in studies of organotypic slice co-cultures. For in vivo studies animals were injected with 6-OHDA into the VTA and examined three weeks later; PFC dopamine loss averaged 70%. Intracellular biocytin injections of retrogradely-labeled cells from the NAS or VTA was used to determine dendritic morphology of PFC PCs in vivo. We also examined organotypic slice co-cultures of the PFC and VTA and cultures comprised of the PFC, NAS, and VTA, with ballistic labeling of cortical PCs using diI. Dopamine denervation of the PFC was accomplished by MPP+ treatment after three weeks in culture, with cultures harvested two weeks later. Results: Dendritic spine density of PFC neurons was greater in cells projecting to the NAS than those cells innervating the VTA; this was observed both in vivo and in vitro. Dopamine denervation of the PFC in vivo resulted in a significant decrease in dendritic spine density of cortico-accumbens neurons but not of PCs that project to the VTA. The organotypic slice cultures showed appropriate target-specific development of projections over five weeks, with projections from the PFC to the NAS and VTA as well as the presence of a dopaminergic innervation of the forebrain sites from the VTA. Dopamine denervation of the cultures resulted in a decrease in dendritic spine density only in PFC-NAS-VTA cultures, but not in PFC-VTA cultures. Conclusion: We observed that PFC neurons projecting to the nucleus accumbens but not VTA showed loss of dendritic spines in response to dopamine denervation, using both in vivo and in vitro preparations. These data suggest the presence of defined corticofugal circuits that undergo dendritic remodeling in schizophrenia, with the functions of these different corticofugal circuits being differentially impacted in schizophrenia.
ID: 979437

CONTRIBUTIONS OF POST MORTEM STUDIES TO THE UNDERSTANDING OF DISC1 AND ITS ROLE IN PSYCHOSIS

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Background: While animal and in vitro studies are important in elucidating what Disrupted-in-schizophrenia 1 (DISC1) does and how its disease-associated variants may impinge upon its function, the pathology of schizophrenia is often subtle. As such, model systems may not always be the most relevant to understanding the disease process and its genetic underpinnings. Here we demonstrate the utility of combining post mortem with in vitro studies in revealing convergent findings as to how DISC1 genetic variants may exert their pathogenic influence(s). Methods: DISC1 has been shown to regulate the recruitment of its partner, pericentriolar material 1 (PCM1), to the centrosome. Using SH-SY5Y cells, we first found that one DISC1 coding variant, Leu607Phe, influenced the extent of centrosomal localization of PCM1. To examine if DISC1 variants exerted a similar influence in human brain, we extended our study to post mortem tissue, and included another DISC1 coding variant, Ser704Cys. We also asked whether altered centrosomal localization of PCM1 occurs in schizophrenia. Using immunohistochemistry we characterized the distribution of PCM1 in human superior temporal gyrus (STG), and found that PCM1 was localized to the centrosome in glia, but not in neurons, which showed a widespread immunoreactivity. Therefore, we quantified centrosomal PCM1 immunoreactivity in STG glia of 81 controls and 67 subjects with schizophrenia, genotyped for the two polymorphisms. Results: Centrosomal PCM1 immunoreactive area was smaller in Cys704 carriers than in Ser704 homozygotes ($P = .015$), with a similar trend in Phe607 homozygotes compared to Leu607 carriers ($P = .061$), replicating the finding in SH-SY5Y cells. For both SNPs, no interactions between genotype and diagnosis were detected. No difference in PCM1 centrosomal immunoreactive area was seen between subjects with schizophrenia (.638 ± .155 μm^2, mean ± SD) and controls (.657 ± .150 μm2; F1, 142 <.50, $P > .50$). Conclusion: Our findings confirm in human brain that DISC1 coding variants modulate centrosomal PCM1 localization, highlight a role for DISC1 in glial function, and provide a possible cellular mechanism contributing to the disease-association of the SNPs examined. Ongoing post mortem studies are exploring whether interstitial white matter neuron alterations, thought to be indicative of aberrant neuronal migration, are associated with DISC1 coding variants as suggested by recent findings in rodent models.
ID: 979352

$GABA_A$ α1 SUBUNIT MRNA EXPRESSION IN PYRAMIDAL CELLS AND INTERNEURONS IN THE DORSOLATERAL PREFRONTAL CORTEX OF SCHIZOPHRENIA SUBJECTS

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Background: Cortical gamma oscillations (30–80 Hz) are associated with cognitive processing, are impaired in schizophrenia and depend upon parvalbumin (PV) basket cell activity. PV basket cells robustly innervate the perisomatic region of pyramidal cells via $GABA_A$ receptors containing α1 subunits. Lower levels of $GABA_A$ α1 subunit mRNA have been found in the DLPFC of subjects with schizophrenia using microarray and qPCR, and studies using *in situ* hybridization have demonstrated this deficit is prominent in layer 3. Decreased layer 3 α1 subunit mRNA may not be specific to pyramidal cells, as interneurons also express $GABA_A$ receptors containing α1 subunits. Methods: Dual-label *in situ* hybridization was used to determine $GABA_A$ α1 subunit mRNA expression levels within pyramidal cells and interneurons in DLPFC area 9 from a cohort of 16 matched pairs of schizophrenia and normal comparison subjects. The schizophrenia subjects in these 16 pairs had previously been shown to have a mean 28% reduction in α1 subunit mRNA levels in DLPFC layer deep 3 relative to their comparison subjects. Each subject pair was matched for sex and as closely as possible for age; subject groups did not differ in these measures, or in RNA integrity number (RIN) or brain pH, which reflect mRNA quality. For each subject, RIN was ≥7 which is associated with excellent RNA quality. Specific ^{35}S -labeled riboprobes for $GABA_A$ α1, and digoxigenin (DIG)-labeled riboprobes for calcium/calmodulin-dependent kinase IIα (CaMKIIα) to identify pyramidal cells and GAD65 to identify interneurons were designed. The number of α1 subunit grains per DIG-labeled neuron was determined in layer deep 3 of area 9 using systematic sampling. Results: The mean number of α1 subunit grains per pyramidal cell was significantly 40% lower in the schizophrenia subjects. The mean number of α1 subunit grains per interneuron was significantly 14% lower in the schizophrenia subjects. The decrease in $GABA_A$ α1 subunit mRNA in layer deep 3 pyramidal cell bodies in schizophrenia subjects is nearly three times the deficit

identified in interneurons. Conclusion: The predominant deficit in pyramidal cell α1 mRNA suggests that PV basket cell inputs to pyramidal cell bodies are more affected in schizophrenia than inhibitory inputs onto other interneurons. This postsynaptic α1 subunit deficit may reflect fewer PV basket cell synapses onto pyramidal cell bodies in schizophrenia.
ID: 978647

GSK3α INACTIVATION NORMALIZES DENDRITIC SPINE DENSITY IN DISC1 MUTANT MICE

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Background: Disrupted-in-Schizophrenia 1 (DISC1), a strong candidate gene for schizophrenia and other mental disorders, regulates neurodevelopmental processes including neurogenesis, neuronal migration, neurite outgrowth, and neurotransmitter signaling. Glycogen synthase kinase-3 (GSK3) directly interacts with DISC1 and also plays a role in neurodevelopment. Recently, our group showed that the Disc1 L100P mutant protein has reduced interaction with both GSK3α and β. Genetic and pharmacological inhibition of GSK3 activity rescued behavioral abnormalities in Disc1 L100P mutant mice. However, the cellular mechanisms mediating these effects of GSK3 inhibition in Disc1 mutant mice remain unclear. Methods: We sought to investigate the effects of genetic inactivation of GSK3α on frontal cortical neuron morphology in Disc1 L100P mutant mice. We compared dendritic length, arborization and spine density of Disc1 L100P mutant mice, GSK3α knockout mice (KO), Disc1 L100P/GSK3α double mutants, and wildtype control mice, using Golgi-Cox staining. Results: Consistent with our previous results, we found a significant decrease in dendritic length, surface area and spine density in Disc1 L100P mutants when compared to wildtype littermates. Overall, both GSK3α KO and Disc1 L100P/GSK3α double mutants showed similar histological deficits. There was no difference in dendritic arborization for all mice. No significant rescue in dendritic length and surface area was observed with Disc1 L100P/GSK3α mutants vs Disc1 L100P mice, but spine density of Disc1 L100P/GSK3α mice was comparable to wildtype. Conclusion: Neurite outgrowth and spine development abnormalities induced by Disc1 mutation may be partially corrected through GSK3α inactivation, which also normalizes behavior. However, many of the other dendritic abnormalities in the Disc1 L100P mutant mice were not corrected by GSK3α inactivation, suggesting that only some of the anatomical defects have observable behavioral effects. These findings suggest novel treatment approaches for schizophrenia, and identify a histological read-out for testing other therapeutic interventions.
ID: 977170

CANNABINOID SIGNALING IN THE PREFRONTAL CORTEX OF SUBJECTS WITH SCHIZOPHRENIA

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Background: The cannabinoid 1 receptor (CB1R) mediates the effects of cannabinoids and alterations in CB1R signaling may contribute to the pathophysiology of schizophrenia. For example, altered inhibition (due to lower levels of the GABA synthesizing enzyme glutamic acid decarboxylase, GAD67) from the subpopulation of GABA neurons that express CB1Rs may contribute to dorsolateral prefrontal cortex (DLPFC) dysfunction in schizophrenia, and we found that reduced GAD67 mRNA was associated with lower levels of CB1R mRNA and protein in DLPFC area 9 in schizophrenia subjects. However, other studies have reported unaltered or higher levels of CB1Rs in schizophrenia. Methods: To clarify these findings and to explore the relationship between altered expression of CB1R and GAD67 mRNAs, we conducted three sets of studies in postmortem human brain and rodent models. Results: First, using immunocytochemical techniques, we found that CB1R immunoreactivity levels in DLPFC area 46 were 19% lower in schizophrenia subjects than in matched normal comparison subjects, a deficit similar to that observed in area 9 in the same cohort. In a new cohort, CB1R immunoreactivity levels were 20% and 23% lower in schizophrenia subjects relative to matched comparison and major depression subjects, respectively. Lower levels of CB1R immunoreactivity in schizophrenia subjects were not explained by other factors such as cannabis use. In addition, CB1R immunoreactivity was not altered in monkeys chronically exposed to oral olanzapine or haloperidol or to haloperidol decanoate. Thus, lower levels of CB1R immunoreactivity may be common in schizophrenia, conserved across DLPFC regions, not present in MDD, and not attributable to other factors, and thus due to the underlying disease process. Second, the mRNA expression of enzymes involved in cannabinoid synthesis and degradation were not altered in schizophrenia, suggesting that lower CB1R levels are not secondary to altered cannabinoid metabolism. Third, in the PFC of GAD67+/- mice, GAD67 and CB1R mRNA levels were significantly reduced by 37% and 16%, respectively. In contrast, GAD67 mRNA levels were unaltered in CB1R+/- and CB1R-/- mice. Conclusion: In concert, these findings suggest that lower CB1R levels in the DLPFC of subjects with schizophrenia reflect a homeostatic response to deficient GAD67-mediated GABA synthesis, and partially compensate for this deficit by reducing cannabinoid suppression of GABA release.
ID: 978342

MOLECULAR AND CELLULAR ABNORMALITIES IN CORTICAL CIRCUITS IN SCHIZOPHRENIA: WHAT DO WE KNOW AND WHERE SHOULD WE GO?

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Background: Defining the neuropathology of schizophrenia is central to understanding the disease process and to identifying novel targets for rational treatment development. Postmortem studies remain the only research strategy that permits investigations of neuropathology at the level of molecules and cells in the context of neural circuits that subserve thought and behavior. However, interpreting the pathophysiological significance of a given postmortem finding requires answers to at least the following three questions: (1) How robust are the methods that were employed and how widely replicated is the finding? (2) To what extent is the finding related to measures of disease severity? (3) Is the finding best understood as a causal upstream factor, a detrimental downstream consequence, or a homeostatic compensation? Methods: A review of the literature and results of ongoing investigations will be used to present examples that address each of these questions. Results: The following answers to the questions raised above will be discussed: (1) Stereological sampling provides a means to obtain accurate and precise quantitative estimates of components of neural circuits, and thus offers promise of an enhanced capacity to detect subtle alterations in brain structure associated with schizophrenia. Current stereological studies support a slightly reduced cortical volume in schizophrenia, without global deficits in cortical cell number. Cellular level analyses have revealed smaller somal volumes and reduced dendritic spine densities on layer 3 pyramidal neurons in several cortical regions, but the existing studies did not

fully employ unbiased stereological methods. (2) Perhaps the most widely replicated molecular abnormality in postmortem studies of schizophrenia is lower cortical levels of the mRNA for the 67 kD form of glutamic acid decarboxylase (GAD67), the enzyme responsible for most GABA synthesis. However, the magnitude of the deficit in GAD67 mRNA differs substantially among subjects with schizophrenia. The relationship between GAD67 mRNA levels and predictors and measures of disease severity in a large cohort will be presented. 3) The current findings regarding excitatory pyramidal neurons and inhibitory GABA neurons in a local cortical circuit will be considered from the perspective of cause, consequence and compensation. Conclusion: Examples of questions that need to be addressed in order to further advance our understanding of the cortical neuropathology of schizophrenia will be discussed.
ID: 988701

PERINEURONAL NET ABNORMALITIES IN THE PREFRONTAL CORTEX IN SCHIZOPHRENIA

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Background: Chrondroitin sulfate proteoglycans (CSPGs) are predominant components of the extracellular matrix (ECM). They regulate neural circuitry formation, structural plasticity, synaptic maturation and stabilization, all of which are thought to be disrupted in schizophrenia (SZ). Extracellular aggregates of CSPGs, together with other ECM components, form perineuronal nets (PNNs), which envelop parvalbumin-containing (PV) inhibitory neurons, which are known to be functionally disturbed in SZ. PNNs are thought to regulate synaptic plasticity in development and adulthood as well as provide a buffer for cations, thus facilitating the fast-spiking firing of PV neurons. The goal of this study is to address the hypothesis that PNN abnormalities may occur in the prefrontal cortex (PFC) in SZ. Methods: In a pilot experiment, we used biotin-labeled lectin from Wisteria floribunda agglutinin (WFA) to visualize CSPG-containing PNNs, which exhibited characteristic hollow mesh-like appearance, encompassing the cell body and proximal processes, in Brodmann's area 9 of the PFC from 5 SZ and 5 matched normal control subjects. Results: The majority of the PNN-associated neurons were of non-pyramidal morphology. We also saw a significant number of cells that were WFA-labeled but were not associated with PNNs; virtually none of which appeared to be astrocytes. We quantified the densities of PNNs and WFA-labeled cells within a 500 μm-wide traverse in the PFC in a blind method. We found that the mean density (±SD) of PNNs in layers 2–3 was decreased by as much as 93% in the SZ (.47 ± .28 cells/mm^2) compared to the normal control (7.2 ± 4.9 cells/mm^2) subjects, but was unchanged in the deep layers. Conversely, the mean density (±SD) of WFA-labeled cells, which were most likely neurons, was increased by 33% in layers 2–3 in subjects with SZ (36.6 ± 16.6 cells/mm^2) compared to normal control subjects (27.5 ± 9.6 cells/mm^2), but was unaltered in the deep layers. Conclusion: Our data points to disturbances in regulatory CSPG functions in the PFC in SZ. These disturbances may contribute to or may be a consequence of PV neuronal dysfunction. In addition, it appears that in the human PFC, CSPGs may be produced by neurons and that CSPG secretion deficits may explain, at least in part, the finding of decreased PNNs. Taken together, identifying the neurobiological mechanisms that underlie CSPG abnormalities would further our understanding of the aberrations in the structural and functional architecture of SZ in the human brain.
ID: 979764

SCHIZOPHRENIA AND MAJOR DEPRESSION HAVE DISTINCT PROFILES OF ALTERED OF GABA NEURON DENSITY IN THE AUDITORY CEREBRAL CORTEX

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Background: GABAergic interneurons of the cerebral cortex are thought to have disrupted function in psychiatric diseases, and there are some reports that they are reduced in number. In postmortem brains, antibodies to the calcium binding proteins can be used to divide these neurons into three large subgroups that represent separate components of the cortical circuitry. Parvalbumin neurons are more involved in feed-forward inhibition, whereas calbindin and calretinin neurons are more involved in feedback or modulatory inhibition. Calretinin neurons form strong synaptic connections with other GABA cells. In schizophrenia, previous quantifications of these neurons have provided somewhat inconsistent results, with reports of decreased calbindin and parvalumin cells, but other reports of unchanged densities, or even increased calbindin cell density (Daviss and Lewis, 1995; Psych. Res. 59:81). In major depressive disorder (MDD), there are reports of decreased calbindin cell density in several brain areas. Methods: In the present study, we compared the densities of these three subtypes of GABAergic interneurons in the auditory cerebral cortex of schizophrenia (n = 14), MDD (n = 15), and nonpsychiatric (n = 20) brains. The tissue preparation was optimal for immunolabeling, because formalin fixation was limited to 5 days before storage in cold buffer, and immunolabeling was done on frozen sections. Stereological counting methods were used, and separate estimates of neuron density were made in the primary auditory cortex and in the caudal superior temporal gyrus (von Economo's area TA). The density of each cell type was expressed as a percent of total neurons by comparison with total neuron density from adjacent Nissl stained sections. Results: In MDD, all three neuron types, expressed as a percentage of total neurons, were significantly reduced, and similar results were obtained in both primary auditory cortex and area TA. The schizophrenia sample showed a distinct pattern: the calbindin cells were significantly increased, whereas parvalbumin and calretinin cells were unchanged compared to the nonpsychiatric brains. Conclusion: The findings in MDD confirm published findings of reduced calbindin cell density, and indicate that this finding extends to other GABA cells. The schizophrenia sample, in contrast, had an increase of relative neuron density that was selective for the calbindin neurons.
ID: 979903

MRNA AND MICRORNA EXPRESSION PROFILING OF PYRAMIDAL NEURONS IN LAYER 3 OF THE SUPERIOR TEMPORAL GYRUS IN SCHIZOPHRENIA

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Background: The dendritic architecture of pyramidal neurons in the cerebral cortex, including the superior temporal gyrus (STG), appears to be disturbed in schizophrenia (SZ). These disturbances may contribute to information processing deficits that underlie some of the symptoms and cognitive impairment seen in patients with this illness. Methods: To explore the molecular underpinnings of these disturbances, we used the Arcturus Laser Capture

Microdissection (LCM) system to isolate homogeneous populations of Nissl-stained pyramidal neurons from layer 3 of Brodmann's area 42 of the STG from 9 SZ and 9 demographically matched normal control subjects. After verifying RNA quality, high throughput TaqMan®-based multiplex quantitative real-time polymerase chain reaction (qRT-PCR) and the Affymetrix platform-based microarray approaches were used to interrogate the profiles of microRNA and mRNA expression, respectively. Results: We found evidence of dysregulated growth factor genes and their signaling pathways pertaining to the transforming growth factor beta superfamily, specifically the bone morphogenetic protein, and epidermal growth factor, in subjects with SZ. In addition, various genes that regulate extracellular matrix components and cytoskeletal plasticity, and a number of synaptic plasticity-related genes such as HLA-A also appear to be differentially expressed. Conclusion: Together these findings provide insight into the possible pathophysiological mechanisms, including dysregulation of miRNA expression, that underlie pyramidal cell dysfunction in SZ and have the potential of leading to the identification of rational drug targets for the treatment of SZ.
ID: 978803

THE ROLE OF MICROGLIAL CELLS IN SCHIZOPHRENIA - CURRENT KNOWLEDGE AND FUTURE THERAPEUTIC APPROACHES

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Background: Inflammatory process have been discussed to play a role in the pathophysiology of schizophrenia. One of our recent postmortem studies revealed increased microglial densities in two schizophrenic patients who had committed suicide. Therefore, the hypothesis of microglial activation during acute psychosis was proposed. Alternatively, microgliosis might be a factor which is present during acute episodes of major psychiatric disorder in general (both in schizophrenia and affective disorders). Methods: To clarify this question, microglial HLA-DR expression was analyzed by immunohistochemistry in the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), mediodorsal thalamus (MD) and hippocampus of 16 schizophrenics, 14 depressed patients with affective disorder and 10 matched controls. A subgroup of six schizophrenics and seven patients with affective disorder who committed suicide was included. Results: ANOVA revealed no effect of diagnosis on microglial density (DLPFC: $P = .469$; ACC: $P = .349$; MD: $P = .569$; hippocampus: $P = .497$). However, significant microgliosis was observed in the DLPFC ($P = .004$), ACC ($P = .012$) and MD ($P = .004$) of suicide patients. A similar trend was seen in the hippocampus ($P = .057$). Conclusion: Immunological factors may play a role particularly during acute disease stages of schizophrenia and depression. These findings are in line with two recent in-vivo PET studies on an increased binding of the radioligand PK11195 in the gray matter of cases with schizophrenia, (particularly during acute disease phases). Moreover, there are promising data on a beneficial effect of microglial immunomodulators in schizophrenia, eg minocycline and cyclooxygenase-2 inhibitors.
ID: 980392

17. Neuropathology, Biochemistry

RPTPZ/PHOSPHACAN ABNORMALITIES IN THE AMYGDALA OF SUBJECTS DIAGNOSED WITH SCHIZOPHRENIA

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Background: Recent findings implicate the extracellular matrix (ECM) in the pathophysiology of schizophrenia (SZ). Substantial abnormalities affecting ECM molecules chondroitin sulfate proteoglycans (CSPGs) were detected in the medial temporal lobe of subjects with SZ. Marked increases of CSPG-positive glial cells were accompanied by decreases of CSPG-positive pericellular ECM condensations, ie perineuronal nets (PNNs), pointing to anomalous CSPG expression intracellularly in glial cells as well as in ECM. Receptor-type protein-tyrosine phosphatase zeta/beta (RPTPz), and its secreted form phosphacan, are key CSPGs in the brain. The membrane-bound receptor form, RPTPz, is known to interact with other ECM components, linking them to the cell membrane. As a step toward investigating the interactions between glial-ECM pathology and neuronal abnormalities in SZ, we tested the hypothesis that numbers of RPTPz-positive cells may be altered in the amygdala of subjects with SZ. Methods: Serial sections from normal control ($n = 15$) and schizophrenic subject ($n = 15$) were immunostained using an antibody raised against RPTPz. Numbers of cells immunolabeled for RPTPz were counted in the lateral, basal, accessory basal and cortical nuclei of the amygdala and in the white matter lateral to the amygdala using computer-assisted light microscopy. Results: Intracellular labeling in cells identified morphologically as neurons, indicates prevalent expression of the receptor-type form of RPTPz. In subjects with SZ, numbers and numerical densities of RPTPz-positive neurons were significantly decreased in the lateral, accessory basal and cortical nuclei, adjusted for life time exposure to antipsychotics ($P < .05$). Consistently, positive significant correlations with lifetime exposure suggests that these drugs tend to bring numbers of RPTPz-positive cells toward normality. In the lateral nucleus, where significant PNNs decreases were detected in SZ, PNNs densities showed a significant effect on RPTPz densities ($P < .05$) and greater significant positive correlations in controls. The basal nucleus and white matter showed no changes. Conclusion: These findings provide direct evidence for neuronal involvement in CSPG pathology in SZ. RPTPz role in neuronal migration, neuritogenesis, dendritogenesis during development and plasticity, including PNN formation, in adulthood are highly relevant to the pathophysiology of SZ and suggest that these functions may be disrupted in the amygdala of subjects with this disease.
ID: 980033

ANALYSIS OF PROMOTER-SPECIFIC BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) AND TRKB SPLICE VARIANT MRNA TRANSCRIPTS IN POST MORTEM SAMPLES OF PREFRONTAL CORTEX AND HIPPOCAMPUS FROM SCHIZOPHRENIA, BIPOLAR DISORDER AND MAJOR DEPRESSION

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Background: BDNF signaling plays an important role in synaptic plasticity, LTP, cell survival and protection. Regulation of BDNF at the transcriptional level occurs by splicing of specific 5' exons, each containing alternative tissue-specific promoters, to a single 3' protein-coding exon. Signaling of BDNF is controlled by binding to full length TrkB (TrkB_FL) receptor which activates intracellular signaling pathways (PLCγ, PI3K, MEK); however truncated forms of TrkB (TrkB_T1), missing the intracellular kinase signaling domain, can act as dominant negative inhibitors of TrkB_FL. Methods: We examined mRNA expression by quantitative real-time PCR (qRT-PCR) in area 46 of the dorsolateral prefrontal cortex (DLPFC) and hippocampus from 19 tetrads of schizophrenia (SCZ), bipolar (BPD), major depressive disorder (MDD) and normal comparison subjects matched for sex, and as closely as possible for age. To identify the most stably expressed reference gene(s) for relative quantification, qPCR was performed for 19 potential reference genes on 8 tetrads for each brain region. The 6 most stable genes, as determined by NormFinder, were evaluated in all samples and the combination of 2 genes with the lowest stability value (Psmb2 and Rpn1 for HPC; Rpl13a and Rpn1 for DLPFC) were used for relative quantification of selected genes of interest. Transcripts for BDNF I, BDNF IV, and BDNF IX (total BDNF), TrkB_FL and TrkB_T1 were evaluated by TaqMan qRT-PCR. Results: None of these genes differed in the MDD subjects. No change in total BDNF expression was observed in either brain region for BPD or SCZ subjects; however, both BDNF transcripts I and IV were significantly decreased in the hippocampus of SCZ subjects (−2.2-fold and −1.7-fold change, respectively). In the DLPFC of SCZ subjects only BDNF IV was significantly decreased (−1.4-fold) and no BDNF transcripts were altered in BPD. TrkB_FL was not changed in either brain region, but TrkB_T1 was significantly increased in DLPFC of both SCZ and BPD subjects (1.5-fold and 1.2-fold, respectively). Conclusion: The combination of decreased levels of activity-dependent BDNF transcripts and increased TrkB_T1 dominant negative receptor in SCZ and BPD subjects lends strong support to the hypothesis that BDNF signaling is disrupted in these diseases. Further work to identify and validate other genes and pathways that are dysregulated in these samples is ongoing.
ID: 979682

INCREASED EXPRESSION OF APRIL (TNFSF13) IN DORSOLATERAL PREFRONTAL CORTEX FROM PATIENTS WITH SCHIZOPHRENIA MAY CONTRIBUTE TO ABERRANT NEUROPLASTICITY

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Background: The observed neuropathology of schizophrenia includes a reduction in dendritic spines in the absence of large scale neuronal cell death. Since activation of cell-death pathways can lead to loss of dendritic spines without ensuing cell death, the changes observed in schizophrenia are consistent with apoptotic pathways having a role in disease development. Evidence supporting the over activity of apoptotic pathways in schizophrenia is limited and the ligands and receptors that may trigger these events have not been identified. We hypothesized that certain cell-death related pathways would be increased in people with schizophrenia and that this increase would negatively correlate with markers on dendritic spines and/or NMDA receptors in people with schizophrenia. Methods: Data mining on the microarray findings of the Stanley Medical Research Institute was followed by quantitative PCR with cDNA from total RNA isolated from postmortem dorsolateral prefrontal cortex (37 schizophrenia patients and 37 controls) supplied with ethics approval by the NSW Tissue Resource Centre. Gene expression of APRIL, FASR, NMDA receptor subunits, spinophilin and PSD95 was measured. Results: The microarray analysis revealed increased expression of FAS receptor (FASR) and FASR ligand, APRIL (TNFSF13) in schizophrenia. We confirmed the change in APRIL by qPCR where 25% significant increase in expression in patients with schizophrenia relative to controls was found ($U = 500.0$, $P = .046$, $r = -.23$). Ex-

pression of APRIL correlated positively with FASR, and with two of the NMDA receptor subunits (R1 and 2C) and a structural spine marker, spinophilin (r values = .6–.7 in schizophrenia). Interestingly, we found that NMDAR1 ($t(69) = 2.43$, $P = .02$) and NMDAR2C ($t(55) = 2.46$, $P = .02$) mRNA were significantly reduced in people with schizophrenia compared to controls. Conclusion: We have identified and confirmed an increase in mRNA for cell-death stimulating ligand APRIL and found that increased levels of APRIL mRNA are linked to increased mRNAs encoding spine-enriched proteins. This provides evidence that apoptotic proteins are implicated in spinal neuroplasticity in human cortex and suggests that the aberrant neuroplasticity reported in schizophrenia may be contributed to by a dysregulation of apoptotic pathway genes.
ID: 986957

GABAB RECEPTOR SUBUNITS AND FRAGILE X MENTAL RETARDATION PROTEIN ARE REDUCED IN CEREBELLA OF SUBJECTS WITH SCHIZOPHRENIA AND MOOD DISORDERS

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Background: There is evidence that GABAergic signaling system is impaired in subjects with schizophrenia through postmortem studies which demonstrate reduction of glutamic acid decarboxylase 65 and 67 kDa proteins (GAD65/67), and linkage studies showing positive associations between SNPs for GABAA receptor subunits and schizophrenia. Gene silencing of the fragile X mental retardation-1 gene (FMR1) and loss of its protein product fragile X mental retardation protein (FMRP) have been shown in animal studies to result in loss of expression of various GABAA receptor subunits. Methods: In the current study we sought to examine whether there changes in protein levels of GABAB receptor subunits R1 (GABBR1) and R2 (GABBR2) and FMRP in cerebella of subjects with schizophrenia, bipolar disorder, major depression vs. matched controls via SDS-PAGE and western blotting. Postmortem samples were derived from cerebella from subjects with schizophrenia ($N = 14$), bipolar disorder ($N = 13$), major depression ($N = 12$), and controls ($N = 12$) from the Stanley Neuropathology Consortium. All results were normalized against beta actin and expressed as ratios to beta actin. Results: We observed that there were significant reductions in GABBR1 in cerebella of subjects with schizophrenia ($P < .0007$), bipolar disorder ($P < .040$) and major depression ($P < .023$) when compared with controls. Similarly, GABBR2 was also significantly reduced in subjects with schizophrenia ($P < .0001$), bipolar disorder ($P < .0063$), and major depression ($P < .002$) when compared to controls. Finally, FMRP expression was also reduced in patients with schizophrenia ($P < .002$), bipolar disorder ($P < .008$), and major depression ($P < .005$). In contrast there was no reduction in beta actin which suggests that the observed differences were not the result of changes in cell number between the four groups. Conclusion: These results provide further evidence of GABAergic dysfunction in brains of subjects with schizophrenia and mood disorders. The generous support by the National Institute of Mental Health (1R01MH086000-01A2) to S.H.F. is greatly appreciated.
ID: 945803

DECREASED PERIPHERAL BRAIN-DERIVED NEUROTROPHIC FACTOR LEVELS ARE NOT SPECIFIC FOR SCHIZOPHRENIA OR MOOD DISORDERS

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Background: In the last years has been suggested that the brain-derived neurotrophic factor (BDNF) is involved in the pathophysiology of schizophrenia (SZ) and mood disorders (MD). Recent studies show that BDNF levels are consistently decreased in both SZ and MD, namely major depressive disorder (MDD) and bipolar disorder (BD). To validate the specificity of serum and plasma BDNF levels we synthesize and compare here the results from a systematic and meta-analysis for SZ and MD. Methods: We conducted a systematic review using electronic databases. Inclusion criteria were studies that measured BDNF in plasma or serum in vivo in adult patients with SZ or schizoaffective disorder, MDD or BD. The resulting studies were compiled to measure the effect sizes (ESs) of the differences in BDNF levels between patients in the different conditions and controls. To adjust for systematic measurement effects we calculated the effect size (ES) of each study (d) according to Cohen as the difference of the means of the patient (mp) and control group (mc) divided by the standard deviation of the control group (SDc). This measure represents normalized elevations of BDNF in the patient groups. For comparisons among the groups, unpaired t test or analysis of variance (ANOVA) followed by Tukey post-test were used, as appropriate. All tests were two tailed. We considered statistically significant P values <0.05. Results: The meta-analysis included 17 studies involving 1114 subjects with SZ, 13 involving 548 subjects with BD, 11 involving 366 subjects with MDD, and 1917 controls. Serum and plasma BDNF levels reach high ES in MDD (.97 ± .33), SZ (.46 ± .82), in BD in depressive state (.96 ± .86), and in BD in manic state (.80 ± .42). As there are no significant differences between BD during depression, BD in mania and MDD ($P = .71$), we considered here BD in acute episodes and MDD together. Effect size was higher in MD than in SZ (.92 ± .49 and .46 ± .82, respectively, $P = .03$). Conclusion: Our results support the hypothesis that BDNF is involved in the pathogenesis of both, SZ and MD. In SZ, the decrease in peripheral BDNF levels are less accentuated than in MD. Moreover, there are no differences in serum and plasma BDNF levels between MDD and BD during acute episodes. Though BDNF might not differentiate between MDD and BD, it dissociates SZ and MD.
ID: 985258

A NEW ROLE FOR THE SEPTIN FAMILY OF CYTOSKELETAL PROTEINS IN SCHIZOPHRENIA AND BIPOLAR DISORDER?

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Background: Schizophrenia is one of the most severe psychiatric disorders affecting 1% of the world population.
The identification of underlying molecular alterations could lead to an improved disease understanding and may yield an objective panel of biomarkers to aid in the diagnosis and treatment of this devastating disease. Using a proteome approach, we have recently identified over 200 proteins in the human hippocampus which may be differentially expressed in psychotic disorders. These proteins are implicated in a range of different processes, eg cytoskeletal, synaptic, and metabolic changes and overall the findings provide novel insights into disease pathogenesis. One of these proteins identified to be significantly down-regulated is Septin 11; recent findings indicate that this protein plays important roles in the cytoarchitecture of neurons, including dendritic arborization and dendritic spines, as well as Septin 11 playing a role in GABAergic synaptic connectivity too. Methods: We have undertaken validation of our Septin findings using Western Blot-

ting in order to quantify and visually confirm the localization of these differentially expressed proteins. Results: We confirmed a Septin 11 decrease in schizophrenia human hippocampal samples ($P = .002$). A similar significant decrease was not seen in bipolar disorder samples (although the decrease approached significance). Findings using samples of human DLPFC showed a significant reduction in Septin 11 in schizophrenia, whereas the bipolar disorder results did not reach significance. Chronic haloperidol treatment had no effect on Septin 11 expression in mouse hippocampal and cortex samples. As there is evidence from the literature of Septin 7 and Septin 11 co-localization in cultured hippocampal neurons and a knockdown of Septin 7 diminished levels of Septin 11 and Septin 5, further investigations on the relationship between Septins 5, 7 and 11 are currently undertaken. Conclusion: While the mechanism by which Septins, particularly Septin 11, may be involved in the pathogenesis of schizophrenia is unknown, there is now strong and intriguing evidence which implicates them. Future studies will characterize the developmental expression pattern in man, regional expression patterns in schizophrenia, and protein interaction partners.
ID: 930603

PROTEOMIC ANALYSIS OF HUMAN HIPPOCAMPUS SHOWS DIFFERENTIAL PROTEIN EXPRESSION IN THE DIFFERENT HIPPOCAMPAL SUBFIELDS

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Background: The hippocampus has critical roles in learning and memory and is centrally implicated in many neuropsychiatric disorders. It is divided into sub-regions, and these differ with regards to morphology, connectivity, electrophysiology and susceptibility to insults. These different sub-regions have distinct roles in regulation of hippocampal circuitry and alterations within them are likely to contribute in a primary way to the clinical presentation. Methods: In the current investigation we aimed to characterize the differential protein expression in each of the hippocampal sub-regions in healthy control samples ($n = 20$). We used laser-assisted microdissection, and Difference-in-Gel-Electrophoresis to enrich for these tissues and to compare protein profiles. Image analysis was carried out using Progenesis-SameSpots. Extensive statistical analysis was undertaken to correct for possible confound (age, pH of the brains, and post mortem interval). Samples with a P-value $<.01$ and an expression of at least $+/- 1.2$ were considered significant. Proteins were identified using Mass Spectrometry (Agilent 6520 Accurate Mass Q-TOF with the HPLC-Chip Cube and 1200 series HPLC system). The raw mass spectral data was analysed using Spectrum Mill MS Proteomics software. Data was searched again the Swissprot FASTA database. Results: Samples were grouped according to the different subregions and we found 185 unique spots to be differentially expressed between the different hippocampal sub-regions. Differential expression in the subregions was observed as follows: CA4 vs. dentate gyrus, 59 spots, CA4 vs. CA2/3, 85 spots; CA2/3 vs. dentate gyrus, 74 spots; CA2/3 vs. CA1, 68 spots. Identification of these differentially expressed proteins by mass spectrometry revealed proteins that are implicated in a range of different processes, including cytoskeletal, synaptic, and metabolic functions. Conclusion: This is the first investigation to characterize region-associated protein expression in hippocampus in man. This baseline data will be helpful in helping us to understand the central role of the hippocampus in schizophrenia and the evidence that particular hippocampal subregions are differentially affected in disease.
ID: 979815

EVALUATION OF ACETYLCHOLINESTERASE IN BRAIN AND SERUM OF ANIMALS CHRONICALLY TREATED WITH KETAMINE

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Background: Schizophrenia is a psychiatric disorder that affects approximately 20 million people worldwide, causing serious professional and social damages to patients. Regarding the genesis of the disorder it is seen that memory deficit in schizophrenia seems to be related to changes in the cholinergic system, specifically the action of acetylcholinesterase (AChE). Acetylcholine is a neurotransmission which is fundamental for the nervous system function. The AChE is the enzyme which hydrolyses and inactivates acetylcholine, thereby regulating the concentration transmitter at the synapse. This neurotransmitter is important for motor, cognition and memory function. To study the chronic effects of ketamine on the activity of AChE is objective of this study. Methods: In his work, we used the ketamine, an anesthetic substance, administered chronically for 7 days, once a day, for posterior dosage of levels of AChE in different time intervals of 1, 3, 6 and 24 hours after the last injection. The effects of ketamine in both brain structures and in serum level were verified, in the possible search of any correlation. Results: In the evaluation of AChE in brain structures, we observed an increase in the activity of enzyme in all structures analyzed at the time intervals of 1, 3, and 6 hours, however there was no difference in enzyme action within 24 hours. Regarding the AChE in serum, it has not presented any changes compared to the control group at different time intervals assessed. Conclusion: The administration of ketamine in animal models of schizophrenia is connected to changes in AChE activity in rat brains, a fact also seen in degenerative diseases like Alzheimer's, therefore, new studies are necessary to provide help in the diagnosis and treatment of these disorders.
ID: 979321

PROLACTIN IN FIRST EPISODE OF NON AFFECTIVE PSYCHOSIS: GENDER DIFFERENCES AND IMPLICATIONS

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Background: Prolactin is a polypeptide hormone synthesized and secreted by the pituitary gland, which secretion is controlled primarily by dopamine. In patients with schizophrenia is usually increased due to antipsychotic treatment side-effects and associated with sexual disturbances that increase treatment discontinuation. We attempt to measure prolactin levels in antipsychotic-naïve patients with non-affective psychosis. Methods: Patients with a first episode of non affective psychosis (13 women and 21 men) and matched controls (14 women and 23 men) underwent a blood test after an overnight fast where prolactin, thyrotropin-releasing hormone (TSH), ghrelin, and cortisol levels were measured. All subjects were interviewed using the Spanish translation of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Patients were administered the positive and negative symptom scale (PANSS). Results: Patients showed a significantly higher pro-

lactin blood level mean compared with controls. Female patients showed a difference statistically significant (mean [SD]) 35.1 ng/mL [24.7] compared with matched controls 13.5 ng/mL [7.2] ($P < .001$). Male patients showed the same pattern. Prolactin level was 15.1 ng/mL [8.9] compared with matched controls 7.8 ng/mL [2.7] ($P = .001$). Prolactin levels were correlated in female patients with reality distortion (PANSS items hallucinatory behavior and delusions). Age of onset for female patients was older than male patients Conclusion: Prior to the use of antipsychotic treatment, patients with a first episode of non affective psychosis have an increased level on prolactin compared with controls. These findings could not be attributed to differences in age, cortisol, ghrelin, body mass index and TSH. This situation may increase the subsequent treatment-risk of hyperprolactinemia and its long-term complications. Hyperprolactinemia has been associated with hypoestrogenemia, and might play a role in the estrogen hypothesis related to age of onset and gender differences in schizophrenia.
ID: 977597

ALTERED EXPRESSION OF METABOTROPIC GLUTAMATE RECEPTOR PROTEINS IN FRONTOSTRIATAL REGIONS IN SCHIZOPHRENIA

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Background: The metabotropic glutamate receptors (mGluRs, GRMs) are implicated in schizophrenia. Increased interest in these receptors comes from animal and human studies that demonstrate antipsychotic potential of novel agonists of mGluR2/3 receptors and allosteric modulators of mGluR5. We conducted a comprehensive examination of mGluR protein expression in human post mortem brain tissue to determine the regional specificity of distinct mGluR alterations in schizophrenia. Methods: Human brain tissue was obtained from the Dallas Brain Collection (DBC). The tissue cohort consisted of 12 pairs of matched schizophrenia subjects and normal controls. mGluR- specific antibodies were used in immunoblotting experiments to determine their individual expression levels in the dorsolateral prefrontal cortex (DLPFC), anterior cingulate (ACC), caudate nucleus (CN) and nucleus accumbens (NAc). To determine potential effects of chronic antipsychotic treatment, Sprague-Dawley rats were given a first-generation antipsychotic (haloperidol), second-generation antipsychotic (risperidone) or placebo via drinking water continuously for 6 months following which they were sacrificed and frontal cortex and CN processed for immunoblotting experiments. Results: In the schizophrenia DLPFC, we find an increase expression of mGluR1a and mGluR7 and a reduction of mGluR3 protein. mGluR1a was also increased in the ACC. Significantly increased expression of mGluR2 and mGluR5 were found in the CN in schizophrenia. There were no differences in any of the mGluRs examined in the NAc. Chronic antipsychotic treated animal experiments show that risperidone is associated with a decrease in mGluR1a and mGluR7 expression in the frontal cortex. In the CN, haloperidol treatment led to an increase in mGluR2 and mGluR5 protein expression. Conclusion: We find that a distinct regional pattern of mGluR alterations in schizophrenia with the majority of mGluR alterations localizing to the DLPFC and CN. The changes in mGluR1, mGluR3 and mGluR7 in the DLPFC are not secondary to antipsychotic drug treatment and could be disease-specific. Increases in mGluR2 and mGluR5 in the schizophrenia CN could be due to antipsychotic drug treatment. While this could be a confound, it is also possible that these CN changes are related to the therapeutic effects of antipsychotic drugs. The localization of the mGluR alterations to the DLPFC and CN could suggest a role for mGluRs in cognitive deficits in schizophrenia.
ID: 989989

MOVING BEYOND OBSERVATION TO POTENTIAL FUNCTION, CAUSE AND EFFECT

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Background: During the past decade, multiple in vivo imaging, genetic association and postmortem studies have confirmed the initial observations of myelin and oligodendrocyte related (OMR) abnormalities in schizophrenia. It is now time that we move from mere observation of OMR abnormalities to the analysis of the mechanisms, processes and consequences of abnormal OMR gene and protein expression. Methods: Microarray, qPCR and Western blot analysis of multiple regions of postmortem brain, including the temporal and cingulate cortices, from 16 to 45 persons with SZ and 19–34 comparison controls. Cases and controls were selected for comparable short postmortem interval (average <12 hours), high integrity mRNA (average pH >6.5), antemortem research diagnosed SZ, and absence of comorbid neuro- or psychopathology. Results: Gene and protein expression abnormalities involved processes that implicate aberrant cell-cycling which can impact the remyelination of axons following oligodendrocyte apoptosis, and changes in the expression of genes and proteins associated with maintaining tight junctions between myelin sheaths and the axon. Abnormally expressed cell-cycle associated genes included Quaking, Cyclins D1 and D2, Cyclin dependent kinases and retinoblastoma protein. Tight junction and nodal genes included Neurofascin, NRCAM, Claudin 11, TJP1 & 2, Ankyrin3 and Contactins. Conclusion: These and similar results argue that the mechanistic consequences of oligodendroglial cell-cycle abnormalities may be the failure of oligodendroglial precursor cells to terminally differentiate. The failure to adequately "repopulate" oligodendrocytes following normal or abnormal apoptosis could result in abnormal remyelination of axons, denuding axon segments or decreasing the lengths of internodes. The loss of integrity of tight-junctions between myelin sheaths and the axolemma could compromise the integrity of the nodes of Ranvier, impair saltatory conduction and lead to slower and less efficient propagation of action potentials in affected axons. These potential consequences of abnormal cell-cycle and tight junction gene and protein expression have implications for information processing and disconnectivity in SZ.
ID: 977676

ANALYSES OF FYN-TYROSINE KINASE AND *N*-METHYL-D-ASPARTATE (NMDA) RECEPTOR IN THE POST-MORTEM BRAINS OF SCHIZOPHRENIA

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Background: Fyn-tyrosine-kinase is highly expressed in brain and participates in learning, emotion and sensitivity to antipsychotics, through the phosphorylation of *N*-methyl-D-aspartate (NMDA) receptor subunits. Recently, we found that Fyn protein levels are decreased in the platelets of schizophrenic patients. In the present study, we aimed to investigate if Fyn alteration is also observed in the brains of schizophrenia patients. We also evaluated protein levels of Fyn's substrate including NMDA receptor subunits. Methods: First, we measured the protein levels of Fyn and NMDA receptor subunits in postmortem frontal cortex tissues (BA6) from 15 individuals with schizophrenia, 15 with bipolar disorder, 15 with major depression, and 15 controls (Stanley neuropathology consortium) using newly developed Fyn-ELISA and dot-blot system. Second, we measured

mRNA of fyn, NR2A and NR2B by quantitative polymerase chain reaction. Finally, we evaluated the effect of antipsychotic treatment on above analyses by preparing frontal cortex from acute and chronic antipsychotics treated mice. Results: While Fyn protein levels were similar in the 4 diagnostic groups, Fyn's activities were significantly elevated in schizophrenia, compared to the control group. We also found that the levels of two NMDA receptor subunits, NR2A and NR2B were significantly decreased in schizophrenia, though the level of the obligatory subunit, NR1 was not altered. We then analyzed mRNA expression of fyn, NR2A and NR2B; however, there was no significant difference between diagnostic groups. Acute antipsychotics (haloperidol, clozapine, olanzapine) treatments all enhanced Fyn's activity in the frontal cortex of mice. On the other hand, chronic risperidone treatment did not alter the levels of NR2A or NR2B. Conclusion: The NR2A and NR2B reduction might be the cause of NMDA receptor hypofunction, which has been hypothesized in schizophrenia pathophysiology. On the other hand, increased activity of Fyn might be a result of antipsychotic treatment or a compensatory consequence of reduced NMDA receptor function.
ID: 979069

CHRONIC GLUCOCORTICOID ALTERS VEGF SIGNALING THROUGH AKT-INDEPENDENT PI3K/MTOR PATHWAY

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Background: Stress and glucocorticoid hormones have been shown to contribute significantly to the manifestation of various psychiatric illnesses including schizophrenia. Recent studies indicate that vascular endothelial growth factor (VEGF) signaling through its receptor Flk1 plays a critical role in stress-mediated changes in structural and functional plasticity in prefrontal cortex (PFC)and hippocampus (HIPP). In the present study, we investigated the chronic effects of corticosterone exposure on VEGF signaling in in vivo and in vitro animal models. Methods: In in vivo studies, adult male CD-1 mice were treated with vehicle or corticosterone (5 mg/kg/day) through drinking water for 7 weeks. In in vitro studies, primary cortical neurons were treated with corticosterone (1μM) for 0–96 hours. To understand the signaling pathways involved in the regulation of VEGF signaling following corticosterone exposure, we used specific inhibitors in the in vitro studies. Further, we analyzed the mRNA and protein levels of VEGF and Flk1 in postmortem PFC samples from schizophrenia and control subjects. RT-PCR was used to assess mRNA levels. Western blot analysis was used to detect protein expression. Results: A significant decrease in Flk1, but increase in HIF-1α and VEGF protein levels was found in mouse PFC and HIPP following 7-week corticosterone exposure. Flk1, HIF-1α and VEGF protein levels were found increased upto 48 hours whereas a significant reduction in Flk1 was found at 72 hours following corticosterone treatment in primary cortical neurons. Treatment with LY294002 (PI3Kinase inhibitor) or RAD001 (mTOR inhibitor) could significantly attenuate corticosterone-induced increase in HIF-1α and VEGF levels in neurons. We found a significant decrease in phospho-Akt levels following corticosterone treatment in neurons indicating that changes in HIF-1α and VEGF levels are not associated with change in phospho-Akt levels. Furthermore, we a found a significant decrease in VEGF and Flk1 mRNA and protein levels in postmortem PFC samples from schizophrenia subjects. Conclusion: The increased VEGF levels found in animal studies following corticosterone treatment could be a result of decreased Flk1 expression. Our studies also indicate that corticosterone regulates VEGF signaling through Akt-independent PI3K/mTOR pathway. Further studies to understand the molecular mechanism of glucocorticoid action on VEGF signaling related to neuroplasticity are in progress.
ID: 978639

GABA SIGNALING MOLECULES IN DEVELOPMENT AND SCHIZOPHRENIA

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Background: The most widely replicated postmortem brain findings in schizophrenia are related to GABA signaling. Most studies have focused on postmortem changes in adulthood, although the pathogenesis of schizophrenia is thought to involve neurodevelopmental perturbations. The possibility that the pattern of GABA abnormalities associated with schizophrenia might reflect genetically regulated developmental processes has not been systematically explored. Methods: Postmortem human brains were obtained at autopsy with consent from next of kin. Brain specimens were processed, RNA was extracted, and quantitative RT-PCR (qRT-PCR) was performed using a standardized paradigm (Mathew et al, 2007. The DLPFC gray matter (BA 9 & 46) and hippocampus were micro-dissected. Results: We examined the expression of transcripts derived from GAD1 (GAD67 and GAD25), SLC12A2 (NKCC1), and SLC12A5 (KCC2) in DLPFC and hippocampus in human brains ($n = 240$) across the lifespan (from fetal week 14–80 years), and in patients with schizophrenia ($n = 30–31$). We examined whether a schizophrenia risk-associated promoter SNP in GAD1 (rs3749034) is related to expression. Development of both the PFC and hippocampal formation is characterized by progressive switches in expression from GAD25 to GAD67 and from NKCC1 to KCC2. In hippocampus, GAD25/GAD67 and NKCC1/KCC2 ratios are increased in patients with schizophrenia. These increased GAD25/GAD67 and NKCC1/KCC2 expression ratios in hippocampus are associated with GAD1 rs3749034 genotype, with risk alleles predicting the relatively less mature pattern. Conclusion: The maturation of GABA signaling in PFC and hippocampus of human brain is characterized by progressive switches in expression from GAD25 to GAD67 and from NKCC1 to KCC2. The former leads to the synthesis of GABA; the latter to GABA switching from an excitatory to inhibitory neurotransmitter. Ratios of GAD25/GAD67 and NKCC1/KCC2 reflect the maturational state of GABA function in the human PFC and hippocampus. In the hippocampus of patients with schizophrenia, GAD25/GAD67 and NKCC1/KCC2 ratios are increased, reflecting a potentially immature state of the GABA system. Remarkably, these increased GAD25/GAD67 and NKCC1/KCC2 expression ratios in hippocampus are associated with GAD1 rs3749034 genotype, with risk alleles predicting the relatively less mature pattern. These findings suggest that abnormalities in GABA signaling that are critical for human brain development and maturation contribute to genetic risk for schizophrenia.
ID: 981860

ALTERATIONS IN THE EXPRESSION OF PSA-NCAM AND GAD67 IN THE DORSOLATERAL PREFRONTAL CORTEX OF SCHIZOPHRENIA PATIENTS

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Background: Abnormalities in the arquitecture and neuroplasticity of the prefrontal cortex, specially of its inhibitory networks, may play an important role in the etiology of schizophrenia. The polysialylated form of the neural cell adhesion molecule (PSA-NCAM) may influence these structural changes through its anti-adhesive properties. PSA-NCAM is expressed by interneurons in the rodent and human prefrontal cortex, participates in

neurite outgrowth and synaptogenesis and changes in its expression occur in parallel to neuronal remodeling in certain regions of the adult brain. Methods: Using immunohistochemistry and optical densitometry we have studied the expression of PSA-NCAM, of the general synaptic marker synaptophysin and of GAD67, a marker of inhibitory neuropil elements. We have analysed layers II to VI of the middle frontal gyrus, using postmortem sections from the Stanley Neuropathology Consortium. Our sample consisted of 15 cases of schizophrenia patients and 15 unaffected controls. Results: PSA-NCAM and GAD67 were expressed in neuronal somata and in the neuropil of the human dorsolateral prefrontal cortex, with different levels of expression in each layer. PSA-NCAM expression was significantly decreased in the schizophrenic group in layers II ($P = .03$), III ($P = .02$) and IV ($P = .04$) and a trend was detected in layers V ($P = .06$) and VI ($P = .06$). GAD67 was also significantly decreased in layers II and VI of schizophrenic patients, ($P = .01$ and $P = .007$, respectively), and marginally in layers III ($P = .09$) and V ($P = 0.08$). Conclusion: .
ID: 985841

GENETIC NEUROPATHOLOGY OF SCHIZOPHRENIA

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Background: There have been a number of postmortem human brain studies of putative schizophrenia candidate genes in patients and controls. In a number of these studies, differences in candidate genes have been complimented by studies finding associations of allelic variation with expression of transcripts which are brain and/or primate specific and preferentially expressed in fetal human brain. Methods: Association studies of allelic variation involving genotyping (by Taqman or Illumina SNP chips) with expression (by qRT-PCR or Illumina microarray chips) have been performed on prefrontal cortex (PFC) and hippocampus of patients with schizophrenia ($n = 40$) and controls ($n = 70$) as well as in a developmental series ($n = 276$) ranging in age from week 14 in the fetus to 80 years of age. Results: Differences between patients and controls in PFC and/or hippocampus have been seen in DISC1, KCNH2, GAD1 and NRG3 ($P < .05$ to 1E-12). Allelic variation in each of these 4 genes as well as 3 other genes (NRG1, COMT and GRM3) is associated with transcripts preferentially expressed in fetal human brain ($P < .05$ to 1E-15). There are, moreover, thousands of SNP-expression associations in PFC in our developmental series ($P <$1E-9–1E-79). Conclusion: Postmortem human brain tissue is critical for elucidating the mechanisms by which allelic variation in genes increases risk for schizophrenia. Moreover, fetal human brain may be particularly important in the genetic neuropathology of schizophrenia.
ID: 979654

MICROARRAY ANALYSIS OF POST-MORTEM HIPPOCAMPUS FROM MATCHED COHORTS OF SUBJECTS WITH SCHIZOPHRENIA, BIPOLAR DISORDER, AND MAJOR DEPRESSIVE DISORDER

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Background: Microarray studies have the power to elucidate changes in multiple signaling systems simultaneously by interrogating transcript expression across the genome. Previous microarray studies of post-mortem brain samples from subjects with schizophrenia have largely focused on prefrontal cortex, as much is known about the dysfunction of this region in disease. The present study sought to explore gene expression changes in hippocampus in order to better understand changes previously observed in frontal cortex and to look for new pathways that might provide intervention points for novel therapeutics. Methods: RNA was isolated from hippocampus of control subjects and subjects with schizophrenia, bipolar disorder, and major depressive disorder ($n = 19$ from each group) matched for gender and as closely as possible for age and hybridized to U133_Plus2 Affymetrix chips. Intensities were normalized by RMA and subjected to pairwise comparison followed by Benjamini and Hochberg False Discovery Rate correction (FDR). Results: Schizophrenia was the only psychiatric condition evaluated in which significant gene expression changes were observed with FDR adjusted $P < .05$ (4507 genes total), illustrating the specificity of the observed gene expression dysregulation to schizophrenia. Markers that have been observed to decline in the prefrontal cortex in schizophrenia, such as GAD67, parvalbumin and somatostatin, were robustly down-regulated in hippocampus. Pathway analysis showed enrichment of down-regulated genes involved with pathways related to GABA A receptor lifecycle, glutamate metabolism and mitochondrial function, while up-regulated genes implicated a number of inflammatory pathways. Additional gene sets of interest, such as the DISC1 interactome, showed significant enrichment in the hippocampal dataset from subjects with schizophrenia. Conclusion: Hippocampus appears to be a site of robust alterations in gene expression in subjects with schizophrenia, but not bipolar disorder or major depression.
ID: 979670

COMMON GENETIC VARIATION IN NEUREGULIN 3 (NRG3) REGULATES NRG3 EXPRESSION AND INFLUENCES RISK FOR SCHIZOPHRENIA

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Background: The NRG-ErbB signaling pathway is critical to neurodevelopment and several genes in the network have been associated with schizophrenia. NRG3 is a specific ligand for ErbB4 and is the most recent signaling partner to be implicated in the disorder. Previous fine mapping of the 10q22–23 locus in schizophrenia has identified strong evidence of association between delusion severity and polymorphisms in intron 1 of NRG3, in particular rs10748842. The biological mechanisms remain unknown. Methods: Family based samples were used for clinical genetic investigation of NRG3 polymorphisms. DNA was available from 350 families with an affected offspring. The samples were ascertained as part of the Clinical Brain Disorders/National Institute of Mental Health (NIMH) Sibling Study. Main effect analyses of single SNPs were conducted using the family-based association test (FBAT). To isolate, clone and sequence full length NRG3 cDNAs, adult and fetal human brain cDNA libraries were generated. Expression levels of NRG3 transcripts were measured using quantitative real time RT-PCR in dorsolateral prefrontal cortex (DLPFC) derived from 245 normal individuals, 42 fetal subjects and 113 individuals with schizophrenia. Effects of risk genetic variation on NRG3 eQTLs were examined. NRG3 EGF-domain bioactivity was investigated in human embryonic kidney cells and human B-lymphoblasts. Results: At the clinical genetic level, distorted transmission of alleles in intron 1 of NRG3 (including rs10748842) was observed in our family-based sample and we confirm association to patient delusion- and positive symptom severity. Molecular cloning and sequencing in human brain revealed that NRG3 undergoes complex splicing, generating >15 alternative isoforms. Disease state and rs10748842 were associated with increased brain expression of novel NRG3 isoforms that contain a unique developmentally regulated 5' exon (from $P = 1.097$E-12 to $P = 1.445$E-15). We demonstrate that rs10748842 resides within a DNA ultraconserved element. Biochemical studies of NRG3 in human cells demonstrate that the NRG3 EGF-domain activates the AKT pathway and has differential physiological properties to that of NRG1. Conclusion: Our observations strengthen the evidence that NRG3 is a schizophrenia susceptibility gene, provide quantitative insight

into NRG3 transcription traits in the human brain and reveal a probable mechanistic basis for disease association.
ID: 983424

THE DUPLICATED α7 NICOTINIC RECEPTOR GENE, CHRFAM7A, IS A DOMINANT NEGATIVE REGULATOR OF THE FULL-LENGTH GENE, CHRNA7

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Background: The α7 nicotinic receptor gene, CHRNA7, is a replicated candidate gene for schizophrenia. Expression of CHRNA7, as measured by [125I]-α-bungarotoxin binding is decreased in postmortem hippocampus, cortex, and the reticular nucleus of the thalamus, the regions that have been thus far examined in schizophrenic subjects, compared to controls. mRNA and protein for CHRNA7 are low in schizophrenic non-smokers, but normal in schizophrenic smokers. Thus, the low bungarotoxin binding is not explained. The CHRNA7 gene is partially duplicated in humans. Exons 5–10 were duplicated centromeric to CHRNA7 by 1.6 Mb, interrupting a partial duplication of a gene on chromosome 3, ULK4. The chimeric gene is expressed in brain and more abundantly in the periphery. A 2bp deletion in exon 6 of CHRFAM7A is associated with schizophrenia. Methods: The partially duplicated gene, CHRFAM7A, with and without the 2bp deletion in exon 6, were cloned into the oocyte expression vector pcDNA 3.1. Xenopus oocytes were injected with 2ng of the full-length gene, CHRNA7, in pcDNA3.1. Clones of CHRFAM7A were also injected alone. Subsequent experiments coexpressed CHRNA7 with either CHRFAM7A or CHRFAM7A with the 2bp deletion. For clones expressed alone, equimolar amounts of empty vector were injected. Ooctyes were stimulated with 5sec pulses of 200mM acetylcholine. Current was recorded with an automated two-electrode voltage clamp. Effects of the duplicated gene clones on transcription of CHRNA7 were performed by real-time PCR. Results: Compared to the full-length alpha 7 gene, CHRNA7, the duplicated gene clones did not form a functional receptor alone. However, mean acetylcholine stimulated current was markedly reduced by cotransfection with CHRFAM7A and further reduced (52%) if the 2bp deletion was present. There was no effect of cotransfection on transcription of the CHRNA7 gene. Conclusion: Co expression of CHRFAM7A with the full-length gene, CHRNA7, in oocytes suggests that the gene duplication functions as a potent dominant negative regulator of alpha 7 nicotinic receptor function. The 2bp deletion, in exon 6 of CHRFAM7A, further decreases function, consistent with low levels of alpha 7 receptor binding and function in schizophrenic subjects.
ID: 979146

DEVELOPMENTAL TRAJECTORY OF THE ENDOCANNABINOID SYSTEM FROM INFANCY TO ADULTHOOD

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Background: Postmortem data implicate changes in the cannabinoid CB_1 receptor (CB_1R) in schizophrenia pathogenesis. Endogenous ligands for CB_1R, or endocannabinoids, regulate brain development and modulate GABA and glutamate release in mature brain. Since schizophrenia is a disorder of aberrant neurodevelopment, we aimed to assess the developmental trajectory of the endocannabinoid system in normal human brain. Methods: Tissue from the middle frontal gyrus of subjects aged 39 days to 49 years was analysed for mRNA and protein expression using quantitative RT-PCR, *in situ* hybridization and Western blotting. mRNA targets were in three categories: (1) the cannabinoid receptor (CNR1 or CB_1R), (2) synthetic enzymes for the two major endocannabinoids (NAPE-PLD for anandamide and DAGLα for 2-arachidonylglycerol [2-AG]), and (3) hydrolytic enzymes (FAAH for anandamide breakdown and MGLL and ABHD6 for 2-AG hydrolysis). Results: CNR1 mRNA is highest at birth and decreases throughout human postnatal life. In contrast, mRNA encoding enzymes for synthesis and hydrolysis of anandamide increased steadily from the neonatal period to adulthood, suggesting that anandamide takes more prominence as humans grow and mature. Enzymes related to the other main cortical endocannabinoid 2-AG also show some increase early in life, but mRNA expression is steadier across the lifespan: a mild inverted U-shaped pattern gently peaks at school age for DAGLα and an early peak in the hydrolytic enzyme MGLL appears in infancy. However, mRNA encoding the other 2-AG hydrolysis enzyme, ABHD6, increases steadily until adulthood suggesting that control of 2-AG signaling may be regulated by different mechanisms depending on the age of the individual. Our work suggests that the relative contribution of each endocannabinoid to the modulation of neurotransmission within human prefrontal cortex may differ throughout life. Conclusion: These data represent the most comprehensive assessment of human endocannabinoid system development to date and provide crucial evidence of the dynamic regulation of this system during life. Further work is needed to determine how cannabis exposure during critical developmental periods may perturb this system and result in increased risk for schizophrenia in vulnerable individuals. However, our data suggest that production and breakdown of endocannabinoids is developmentally regulated during postnatal brain maturation and any disruption to this normal process by exogenous cannabis may be detrimental.
ID: 938107

L-FICOLIN-MASP COMPONENTS OF THE COMPLEMENT SYSTEM IN SCHIZOPHRENIA

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Background: Adversity in utero underlies the abnormal neurodevelopment in schizophrenia. Accumulating evidence suggests that prenatal exposure to infection (eg rubella, influenza, and toxoplasmosis) contributes to the etiology of schizophrenia. The lectin pathway of the complement system is the first line defense of innate immunity against invading microorganisms. Different target-recognition protein complexes activate the lectin pathway: mannan-binding lectin (MBL) complexed with MBL-associated serine proteases (MASPs), and L-, H- or M-ficolins combined with MASPs. All of them have MASP-2 as the key component for triggering the complement cascade. Our recent study showed that schizophrenic patients have high MBL-MASP-1 and MBL-MASP-2 complex activities. Methods: In this study, we investigated L-ficolin and MASP-2 serum levels (ELISA), the activities of L-ficolin bound MASP-1 (enzymic assay) and MASP-2 (C4 fixation assay) in 103 chronic schizophrenic patients (SP) in the acute phase of the disease and 127 healthy volunteers (HV). In addition, available DNA samples of 94 SP and 83 HV were tested for the D120G SNP of the MASP2

gene, as heterozygosity for this allele significantly influences the concentration of MASP-2. Results: Median concentration of L-ficolin in healthy Armenians was similar to those reported for other Caucasian populations (3.66 mg/L, 95% CI 3.25–4.49). SP (5.08 mg/L, 95% CI 4.59–5.60) had ~40% increase in serum [L-ficolin] (Mann-Whitney 2-tailed $P < .002$; 95% CI 1.6–.3). L-Ficolin-(MASP-1) activity was not detectable. Although there was only a modest increase in total MASP-2 median level (SP: 289 ng/mL (95% CI 248.1–334.2) vs. HV: 275 ng/mL (95% CI 238.1–304.8); Mann-Whitney 2-tailed $P < .36$; 95% CI –57.6–22.9), SP had significantly higher activity of L-ficolin-(MASP-2) complex (one-tailed median test $P < .05$; SP vs. HV: 7.44 vs. 6.47 AU). Only one SP out of 177 subjects investigated was a heterozygote for the MASP2 gene D120G polymorphism. Conclusion: The results implicate complement lectin pathway alterations in schizophrenia. It seems that changes of the lectin pathway in schizophrenia involve not only the MBL-MASP component over-activation reported previously, but also alterations of L-ficolin-(MASP-2) on protein concentration and activity levels. Besides, our result on L-ficolin-(MASP-1) implies that, unlike MBL, L-ficolin has higher affinity for MASP-2 than MASP-1.
KRM acknowledge the Royal Society-NATO fellowship #16312/03B/LD.
ID: 988250

DISRUPTED-IN-SCHIZOPHRENIA-1 (DISC1) MODULATES INNATE IMMUNE SIGNALING PATHWAYS VIA NF-KB

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Background: We generated transgenic mice which express truncated human Disrupted-In-Schizophrenia-1 (mutant DISC1) in forebrain neurons. We previously reported that difference of cytokine expression in fetal mouse brain, especially basal level of IL-1beta in mutant DISC1 is higher than control mice. Many reports have shown that schizophrenia is associated with abnormal cytokine expression in brain. In addition, several groups have reported that DISC1 is involved in several signaling pathways such as GSK3-beta, ERK and AKT. Transcription factor NF-kB is a major molecule to transduce immune signals, and is downstream of AKT. Recently some groups have reported that NF-kB pathway is activated in schizophrenia patients. Thus, we hypothesized that DISC1 modulated cytokine expression via NF-kB-dependent cytokine signaling pathway. Methods: We used neuronal cell line Neuro2a transfected with mutant DISC1 or GFP as a control. We stimulated cells with a pro-inflammatory cytokine, TNF-alpha, and then measured NF-kB activation by luciferase reporter assay. We also evaluated expression of a signaling molecule, I-kB which regulates NF-kB translocation. Results: We found that mutant DISC1 affected recovery of I-kB expression level even after 60 minutes post stimulation with TNF-alpha, suggesting a sustained activation of NF-kB-dependent cytokine signaling pathway. No changes were observed in the GSK3-beta pathway. Using 2 copies of NF-kB binding sites construct as a reporter, we found a higher activity of NF-kB in cells transfected with mutant DISC1 than GFP-transfected cells. We are currently analyzing upstream factors which may activate NF-kB, as well as downstream genes whose transcription is initiated by NF-kB. Conclusion: Our studies suggest that disturbances in DISC1 functions could modulate the innate immune signaling pathways, contributing to neuroimmune abnormalities observed in schizophrenia patients.
ID: 979780

GENETICALLY COMPROMISED NEURONS AND ASTROCYTES SHAPE NEUROIMMUNE DYSFUNCTIONS IN SCHIZOPHRENIA

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Background: It has been proposed that immune response by pregnant women may be a common pathogenic process that affects fetal brain maturation. Both neurons and astrocytes contribute to innate immune response in the brain and their dysfunction in genetically predisposed organisms would likely exacerbate immune activation to affect neurodevelopment. We focused on Disrupted-In-Schizophrenia 1 (DISC1) as its variants and mutations have been associated with schizophrenia. We evaluated how selective disruption of the DISC1 function in neurons or astrocytes affected cytokine production and synergistically produce schizophrenia-like brain and behavioral pathology in adult mice. Methods: Pregnant mice were treated with saline or Poly I:C at embryonic day 9. Levels of cytokines were measured in fetal and adult brains, expression of mutant human and endogenous mouse DISC1, LIS1, NDEL1, gp130, Grb2, and GSK-3β were assessed in cortical samples from newborn mice. Volumetric brain abnormalities and various domains of the mouse behavior repertoire were evaluated in adult male mice. In addition, we assessed the NF-κB-dependent signaling pathway in neuronal N2a cells that expressed mutant DISC1. We also generated a new mouse model of selective and inducible expression of mutant DISC1 in astrocytes to explore their contribution to neuroimmune dysfunctions in schizophrenia. Results: Prenatal interaction produced depression-like responses and altered pattern of social behavior that were associated with decreased volumes of amygdala and periaqueductal gray matter and density of spines on dendrites of granule cells of the hippocampus. Prenatal interaction modulated secretion of inflammatory cytokines in fetal brains, levels of mutant human and endogenous mouse DISC1 and GSK-3β. Expression of mutant DISC1 in N2a cells inhibited recovery of IκBα levels after treatment with 10ng/mL of TNF-α and produced significantly greater NF-κB-dependent transcription activation. Interactions between immune activation and mutant DISC1 in astrocytes are being investigated. Conclusion: Prenatal immune activation interacted with mutant DISC1 to produce the neurobehavioral phenotypes that were not seen in untreated mhDISC1 mice and that resemble aspects of major mental illnesses. Mutant DISC1-altered activation of the GSK-3β and NF-κB pathways in neurons and/or astrocytes could contribute to the neurobehavioral abnormalities, resembling major mental diseases.
ID: 978991

INFECTIOUS AND IMMUNE MODELS OF SCHIZOPHRENIA: OLD PROBLEMS, NEW SOLUTIONS

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Background: Infections contribute to some cases of schizophrenia. However, the mechanisms of whereby microbes affect neurodevelopment remain unclear. Both microbial and host heterogeneity may be responsible for variable outcomes of infections in predisposed individuals. Animal models based on combinations of microbial, immune and genetic factors may shed more light on the contributions of infections to schizophrenia. Thus, we studied the neurobehavioral effects of prenatal immune activation and early postnatal parasitic infection in wild-type and mutant DISC1 mice. Methods: We compared the neurobehavioral effects of two Type II strains of *Toxoplasma gondii* (*T. gondii*), Prugniaud (PRU) and ME49, on attraction to cat odor, locomotor activity, anxiety, sensorimotor gating, and spatial working and recognition memory 2 and 7 months post-infection (mpi). In addition, we analyzed the effects of prenatal immune

activation on the brain and behavior development in mutant DISC1 mice. Pregnant mice were treated with saline or Poly I:C at embryonic day 9. Levels of cytokines were measured in fetal brains, expression of mutant human and endogenous mouse DISC1, gp130, Grb2, and GSK-3β were assessed in cortical samples from newborn mice. Volumetric brain abnormalities and domains of the mouse behaviors were evaluated in adult mice. Results: At 2 mpi, mice infected with either strain exhibited significantly more attraction to cat odor than uninfected animals did, but only PRU-infected mice exhibited this behavior 7 mpi. PRU-infected mice had significantly greater body weights and hyperactivity while ME49-infected mice exhibited impaired spatial working memory. No differences in parasite antibody titers were seen between PRU- and ME49-infected mice. Prenatal interaction produced abnormal affective and social behaviors and associated smaller amygdala and periaqueductal gray matter, and decreased density of spines on dendrites of hippocampal granule cells. Mutant DISC1 modulated Poly I:C-induced secretion of cytokines in fetal brains, and levels of endogenous mouse DISC1 and GSK-3β. Conclusion: The present data suggest the effect of T. gondii infection on mouse behavior is parasite strain-dependent and genetic predisposition to schizophrenia may modulate the behavioral consequences of immune activation produced by in utero infections. The present mouse models may facilitate a better understanding of the contribution of microbes to schizophrenia and related conditions.
ID: 979024

EXPRESSION OF IMMUNE MOLECULES (MHC CLASS I AND COMPLEMENT C3) IN POSTMORTEM BRAINS OF PATIENTS WITH SCHIZOPHRENIA

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Background: A role for the immune system has been hypothesized in the pathophysiology of schizophrenia, but further experimental evidence to support this concept is awaited. Novel functions of molecules originally identified in the immune system have been recently reported. These molecules include proteins of the classical complement pathway (C1q and C3) and MHC class I complex. They are expressed in developing or mature brains and have distinct roles in brain development, neuronal differentiation, and synaptic development and plasticity. Thus, in this study, we hypothesized that these molecules might be aberrantly expressed in brains from patients with schizophrenia. Methods: To address this question, we examined the levels of C3 expression (mRNA via real-time PCR) and MHC class I expression (protein by Western blotting) in the frontal cortices from 35 schizophrenia patients, 35 subjects with bipolar disorder, and 35 normal controls (obtained from the Stanley Medical Research Institute). Results: We observed a lower C3 mRNA expression in brains from patients with schizophrenia and bipolar disorder compared to that in normal controls. In subjects with bipolar disorder, the difference from the controls reaches statistical significance (ie $P < .05$). In terms of MHC class I, we found a statistically significant association between schizophrenia (vs normal control) and log-transformed values of the MHC class I protein expression, adjusting for smoking status. Non-smoking SZ brains ($n = 4$) had a decreased level of MHC class I proteins. We conducted a bootstrap (random) sampling up to 1000 replicates of the data to account for the small sample size of the non-smoking SZ and the finding was still statistically significant. Conclusion: These results, even within the limit of our sample size, suggest a potential role of nicotine in modulating the expression of MHC class I molecules. We will discuss these observations in association with possible regulation of synaptic mechanisms via complements and MHC class I proteins.
ID: 978667

DIFFERENTIAL EXPRESSION OF STRUCTURAL SYNAPTIC ELEMENTS IN THE LEFT SUPERIOR TEMPORAL CORTEX OF SCHIZOPHRENIA PATIENTS

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Background: Irregular cytoarchitecture and synaptic pathology are common features of schizophrenia. On the molecular level, several lines of research have established contributions of the GABAergic, glutaminergic system, and recently myelination-related events to the pathophysiology of the disease, taking into account that there are certainly more than only a few genes involved in the development and progression of schizophrenia. However, in this study, our attention has been drawn to genes related to cytoskeletal and synaptic elements. Methods: In a post-mortem study, genome-wide microarrays (Illumina) have been used for expression profiling in the left superior temporal cortex of 10 schizophrenia patients and 10 healthy controls. Array data were further confirmed with selected genes by qRT-PCR. Results: In the list of downregulated genes, there are a number of synapse-specific genes, ie synaptotagmin6 and syntaxin12. Others, like STX16 and STX2 (EPIM) are upregulated. Intriguingly, genes confirmed by qRT-PCR preferentially belonged to structural genes, such as collagens 4 and 15A1, gelsolin, myosin6, laminin C3, spectrin beta and scaffold attachment factor B2 the products of which, like actin, are major intra- and extracellular structural elements of the synapse. Conclusion: The turnover time of actin in dendritic spines is approx. 44 sec. This highlights the dynamics of cytoskeletal elements in neuronal fiber endings. It also underlines the pivotal role of genes expressed in neurons that control remodeling of dendritic spine or synaptic cytoskeleton. Moreover, it has been largely overlooked in the past that structural elements of the extracellular matrix play pivotal roles in axon guidance, synapse formation and stabilization. Typically, these (gylco)proteins like collagen or laminin are products from glial cells which highlights the close interrelationship between neurons and glial cells in establishment and maintenance of higher tasks of the brain like cognition and memory. Very likely, it is the interplay between all genes of the pre- and postsynaptic sites that determines synaptic strength or weakness. It is hypothesized, that abnormal expression of these and related genes has a major impact on the development and progression of schizophrenia.
This work was supported by the European Commission under the Sixth Framework Programme (BrainNet Europe II, LSHM-CT-2004-503039).
ID: 977664

DYSFUNCTION OF CLATHRIN MEDIATED ENDOCYTOSIS CONTRIBUTES TO SYNAPTIC PATHOLOGY IN PSYCHOTIC DISORDERS: A REVIEW OF THE EVIDENCE.

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Background: Psychotic disorders such as schizophrenia and bipolar affective disorder have long been conceptualized as disorders of synaptic function. Evidence suggests abnormalities in both pre- and postsynaptic processes such as vesicle recycling and neurotransmitter-receptor traffick-

ing. However, it is unclear which molecular mechanisms or pathways are causally involved in such pathology. Findings from studies in postmortem schizophrenia brain hint at Clathrin Mediated Endocytosis (CME) as a potential mechanism contributing to psychosis pathophysiology. Methods: We reviewed the literature for evidence supporting or rejecting the hypothesis of CME dysfunction in psychotic disorders. Preliminary findings from current proteomic investigations of our own group are also presented in this context. Results: Evidence from postmortem brain studies, and particularly from the proteomic literature, supports dysregulation of key CME proteins in psychotic disorders. In our own proteomic investigations of postmortem brain, we have recently extended this evidence base for CME key protein AP-2 and a number of CME accessory proteins. However, not all proteomic investigations of postmortem brain show abnormal CME protein expression, and a number of studies have specifically failed to demonstrate deficiencies in key CME players. Conclusion: Current evidence suggests a role of CME in schizophrenia pathophysiology. Dysfunction of CME may partly explain functional deficits of the synapse which have been observed in the disease. Further investigations will be necessary to confirm findings in larger postmortem samples, and to specify the cellular location of observed protein abnormalities.
ID: 979483

GLUTATHIONE UNGLUED: OXIDATIVE STRESS AND GLUTATHIONE/GLUTAMATE METABOLISM

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Background: Glutamate is the principal excitatory neurotransmitter of the brain and mediates diverse physiologic and pathologic processes. Multiple studies have also suggested a role for deficient glutamate neurotransmission in schizophrenia, particularly via NMDA glutamate receptors. While the release of glutamate from neurotransmitter vesicles has been intensively studied, comparatively less is known how overall neuronal glutamate levels are regulated prior to synaptic release as well as the impact of cellular stress upon neurotransmission. Glutathione is a tripeptide composed of the amino acids glutamate, cysteine, and glycine. Glutathione is abundantly present at millimolar concentrations in neurons, and its synthesis and metabolism is governed by a collection of enzymes known as the gamma-glutamyl cycle. Glutathione participates in a variety of cellular processes, including antioxidant and drug detoxification pathways. Multiple lines of evidence have also identified decreased glutathione levels in patients with schizophrenia, utilizing live patients (magnetic resonance spectroscopy of brain, cerebrospinal fluid) as well as autopsy specimens. Oxidative stress and defense by the glutathione pathway may be highly relevant to schizophrenia pathophysiology and interneuron dysfunction. Methods: We propose that glutathione may be a potentially important glutamate reservoir that contributes to baseline neuronal glutamate levels. We measured glutamate levels in neurons after treatment with molecular inhibitors that target enzymes of the glutathione metabolic cycle (BSO, 2I4C, and acivicin). Results: We find that 2I4C and acivicin, agents that block liberation of glutamate from glutathione, result in 25%–50% decreases in glutamate levels in PC12, HT22 and rat primary cortical neurons (DIV 21). BSO, which prevents synthesis of glutathione from glutamate, has the reverse effect, significantly increasing glutamate levels and decreasing glutathione. Reduced glutamate levels are not the result of cytotoxicity as cell viability was not substantially altered via treatment. We studied oxidative stress in transgenic mice expressing dominant negative Disrupted in Schizophrenia 1 (DISC1) under the CaMKII promoter. These animals demonstrate increased oxidative stress in the cortex as measured by protein carbonyls. Conclusion: This model suggests potential bridges between two independent lines of research, that of diminished glutathione levels and glutamatergic dysfunction in schizophrenia.
ID: 979752

POTENTIAL EFFECT OF PDE4B SPLICE VARIANT EXPRESSION ON PDE4 INHIBITOR ACTIVITY IN HUMAN, RAT AND MURINE CELL BASED FUNCTIONAL ASSAYS

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Background: The PDE4 family of phosphodiesterases contains 4 gene members (PDE4A, PDE4B, PDE4C and PDE4D) and regulates cAMP hydrolysis in the cell. PDE4 has been associated with a number of CNS diseases including schizophrenia, depression and neurodegenerative disorders. While all PDE4 genes are expressed in CNS, PDE4 isoforms A, B and D are widely distributed in human brain. Recent literature reports have identified PDE4B activity as one of the molecular mechanisms associated with schizophrenia. Studies in PDE4 isoform specific knockout mice with Rolipram (a nonselective PDE4 inhibitor) suggest that, in part, the antipsychotic effects of rolipram are attributed to the inhibition of PDE4B isoform. Here we profiled the inhibitory effects of rolipram, compound 1 (PDE4D selective inhibitor) and compound 33 (a reported PDE4B selective inhibitor) in several assays including murine and human PBMC LPS induced TNFalpha release, human stem cell derived neurons, B35 rat neuroblastoma cell line, and rat primary cortical cell cAMP assays. Methods: PBMC LPS TNFalpha release assay Human and murine PBMCs with and without compound were stimulated over night with 100 ng/mL LPS RPMI plus 10% FBS. Plates were centrifuged at 1000 rpm for five minutes. Cell supernatant was diluted and TNFalpha was determined by ELISA (R&D Systems) cAMP assay. Assay was performed by homogeneous time resolves fluorescence Cisbio cAMP dynamic 2 kit. Results: Results showed that rank order potency for compounds tested did not change when comparing different assays. The data also showed compound 33 was 13 fold more potent at inhibiting TNFalpha release in murine LPS stimulated PBMCs vs. the assay performed with human PBMCs. Moreover, we found compound 1was two fold more potent over compound 33 at inhibiting TNFalpha release in murine PBMCs (Table 1). Western blot data with PDE4B isoform specific antibody showed PDE4B2 to be the predominant species expressed in human peripheral monocytes, human stem cell derived neurons, B35 rat neuroblastoma cells and rat primary cortical cells (Fig. 1). Conclusion: Conclusion: The data showed that rank order potency for compounds tested did not change across assays. However, changes in compound potency were evident between assay and species. Current western blot data shows PDE4B2 to be the predominant isoform expressed cell types tested thus far. We are investigating the possibility that changes in compound potency are due to 4B splice variants.
ID: 969642

MOLECULAR ALTERATIONS ASSOCIATED WITH THE COMT VAL158MET POLYMORPHISM IN SCHIZOPHRENIA

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Background: Schizophrenia is an illness associated with several risk genes and environmental risk factors. One of the putative risk genes, COMT (catechol-o-methyl transferase), influences prefrontal cortex (PFC) structure and function, a brain region known to be involved in the pathophyisology of schizophrenia. The COMT val158met single nucleotide polymorphism (SNP), the result of a (GA) base substitution in the coding region of COMT, alters its activity such that the COMT val/val variant is more active than the met variants. Since COMT is a dopamine catabolic enzyme, the COMT val/val genotype is expected to be associated with increase in

dopamine metabolism and lower synaptic dopamine. The aim of this study was to determine the influence of the COMT val158met genotype on the dopamine (DA) and glutamate (Glu) signaling pathways in schizophrenia PFC. Methods: Human post mortem dorsolateral prefrontal cortex tissue samples from a cohort of control and schizophrenia cases (n = 24–26; val 10–12, met carriers 14 per group) were obtained from our brain collection, the Dallas Brain Collection. Quantitative real time PCR was performed to determine the influence of the COMT val/met SNP on specific DA and Glu markers. Two analyses were conducted. First, we compared COMT val/val control cases with COMT met carrier controls to determine the influence of the val/met snp in the control human DLPFC. The second analysis compared control val/val and schizophrenia val/val cases to identify differentially regulated disease-associated molecular targets in the putative risk gene groups. Results: We find that COMT val/met SNP is associated with a differential regulation of DARRP32, NR2A, GluR1 and mGluR7 in the control DLPFC. There were no changes in D1–D5 receptor or TH mRNA levels. Disease-associated alterations were found in COMT, D1 and TH mRNA levels as well as in NR2A, NR2B and mGluR4 mRNA expression. Conclusion: These data suggest that the COMT val/met SNP influences both the dopamine and glutamate neurotransmitter systems in the human DLPFC. Further, the data suggest that the putative risk COMT val allele has a differential effect on these neurotransmitter systems in schizophrenia. This may have important implications in the pathophysiology and treatment of schizophrenia
ID: 978432

CORTICAL MU OPIOID RECEPTOR MRNA EXPRESSION IN SCHIZOPHRENIA AND ACROSS DEVELOPMENT

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Background: Prefrontal cortical (PFC) dysfunction in schizophrenia has been linked to disturbances in GABA neurons, including parvalbumin- and somatostatin-containing cells. Interestingly, the endogenous opioid system modulates parvalbumin and somatostatin neuron function in a manner that could directly impact GABA-related disturbances in schizophrenia. For example, activation of the mu opioid receptor (MOR) suppresses both the activity of, and GABA release from, parvalbumin and somatostatin neurons. Thus, alterations in PFC MOR signaling, especially if they arise during development, could contribute to cell type-specific disturbances of GABA neurotransmission in schizophrenia. Methods: We used quantitative PCR to measure mRNA levels for MOR and other opioid markers, including the delta opioid receptor (DOR) and proenkephalin, in the PFC from (1) 42 schizophrenia subjects and 42 matched healthy comparison subjects; (2) 18 monkeys chronically exposed to either haloperidol, olanzapine, or placebo; and (3) 49 monkeys ranging in age from 1 week to 11.5 years. qPCR was performed using the comparative threshold cycle method with four replicate measures per target gene, and mRNA levels were normalized using three reference genes. Results: We found higher mRNA levels for MOR (+27%), but no differences in DOR or proenkephalin mRNAs, in schizophrenia subjects relative to comparison subjects. Higher PFC MOR mRNA levels in schizophrenia appeared to be predominantly attributable to higher mRNA levels of the exon 4-containing MOR-1 splice variant. Higher MOR mRNA levels in schizophrenia also appeared to be related to some predictors and measures of disease severity, but were not a consequence of exposure to substances of abuse, psychotropic medications, or other potential confounds. Finally, MOR mRNA levels markedly declined through early development, stabilized shortly before adolescence, and substantially increased with age across adulthood in monkey PFC. Conclusion: The combination of higher MOR mRNA levels in schizophrenia and a normal decline in MOR mRNA levels before adolescence suggests that a developmental pause or impeded maturation of PFC MOR mRNA expression may occur in the disorder. Higher MOR mRNA levels, if accompanied by a corresponding increase in protein levels, may lead to suppression of GABA release from, and somatic hyperpolarization of, parvalbumin and somatostatin neurons, which together may impair the functioning of these neurons in schizophrenia.
ID: 946424

COGNITIVE AND SERUM BDNF CORRELATES OF BDNF VAL66MET GENE POLYMORPHISM IN PATIENTS WITH SCHIZOPHRENIA AND NORMAL CONTROLS

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Background: Studies suggest that the functional polymorphism of brain-derived neurotrophic factor gene (BDNF Val66Met) may mediate hippocampal cognitive functions. Few studies have reported its role in determining cognitive deficits in schizophrenia and whether peripheral BDNF levels may be useful to assess cognitive measures in schizophrenia. Methods: Six hundred and fifty-seven schizophrenic inpatients and 445 healthy controls were recruited. The performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the BDNF Val66Met polymorphism and serum BDNF levels were compared in both groups. Patient psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS). Results: Visuospatial/constructional abilities significantly differed by genotype but not genotype × diagnosis. The Met allele was associated with poor visuospatial/constructional performance in schizophrenia patients and healthy controls. On attention performance, there were significant genotype and genotype × diagnosis effects. Met allele-associated attention impairment was specific to schizophrenia patients but not healthy controls. Decreased serum BDNF levels and the degree of cognitive impairment in schizophrenia were dependent on the presence of the BDNF Val66Met polymorphism. Variation in BDNF was not associated with increased risk for schizophrenia; however, patients with the Met variant allele had an earlier age of onset. Conclusion: Our findings demonstrate the association between the BDNF Met variant and poor visuospatial/constructional performance. Furthermore, the BDNF Met variant may be specific to attentional decrements in schizophrenic patients, and also associated with earlier age of onset of schizophrenia. The association between decreased BDNF serum levels and cognitive impairment in schizophrenia is dependent on the BDNF Val66Met polymorphism.
ID: 978869

ALTERED LEARNING AND MEMORY PLASTICITY IN SCHIZOPHRENIA: INCREASED P(SER831)-GLUR1 LEVELS IN CA3 IN A MOUSE MODEL AND IN HUMAN CA3 TISSUE

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Background: The hippocampus is one of the brain regions reliably altered in schizophrenia that may mediate symptoms. Imaging studies show that hippocampal volume is decreased, perfusion is increased and task-activation is reduced in schizophrenia often selective for CA3 or CA1; moreover,

the hippocampal dysfunction correlates with the magnitude of psychosis. Postmortem brain studies report reduced adult neurogenesis in dentate gyrus (DG); and, mossy fiber synapses from DG onto CA3 neurons are decreased in number. Furthermore, subunits of the NMDA and AMPA receptors are reduced in DG tissue in schizophrenia tissue. These lines of evidence suggest that glutamatergic transmission from DG onto CA3 neurons is reduced in schizophrenia and that resultant plasticity changes could occur in CA3 and be involved in the expression of psychosis. Our model posits that there is a reduced threshold for LTP in CA3 and an increase in glutamate synaptic strength; these changes could pathologically increase ''pattern completion'' and generate false associations, some with psychotic content, and altered memory formation (1). In this study, we examined the protein levels of LTP-related molecules in CA3 to test the downstream effects of the impaired DG function in schizophrenia. Methods: We screened hippocampal CA3 subfield tissue from eleven pair of schizophrenia and normal cases using Western blots. Results: From this preliminary sample we found a trend toward increased NR2B (P = .08, d = .64) and increased P(Ser831)-GluR1 (P = .13, d = .55) in schizophrenia CA3. It is known that increases in P(Ser831)-GluR1 and NR2B can represent increased glutamate synaptic strength.. To test whether these LTP-associated changes in CA3 could result from reductions in mossy fiber signaling, we measured LTP markers in NPAS3 knockout mice, an animal model of schizophrenia psychosis with impaired neuronal signaling in DG . We found P(Ser831)-GluR1 increased in CA3 in the NPAS3 knockout mouse (P <.05), a finding which parallels the human SZ data. Conclusion: Our results suggest that increased LTP in CA3, associated with reduced DG glutamate signaling, could mediate a dimension of schizophrenia, ie, psychosis. We are generating conditional DG-NR1 knockout mice to test more directly whether reduced DG glutamatergic transmission is associated with increased CA3 LTP and how this increased LTP could be further modulated by environmental risk factors for schizophrenia.
ID: 978840

18. Cognitive Neuroscience

ASTROCYTE DYSFUNCTION MOUSE MODEL IN MENTAL ILLNESSES

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Background: Dysfunctions of astrocyte contribute to major mental illnesses. Several studies have demonstrated alterations in expression of astrocyte glutamate transporters and layer-specific reductions in astrocytes of the prefrontal cortex in schizophrenia and depression. Although DISC1 (Disrupted-in-Schizophrenia 1) has been recognized as a promising candidate psychiatric genetic risk factor, practically all in vitro and in vivo experiments have been focused on neuronal functions of DISC1. A recent report has detected expression of DISC1 in mouse and human glial cells, including astrocytes, supporting studies of the normal and abnormal functions of DISC1 in astrocytes. Methods: We have generated double transgenic mice with a selective expression mutant human DISC1 (mhDISC1) in astrocytes as evidenced by biochemical and immunohistochemical in vitro and in vivo assays. Results: Astrocytic expression of mDISC1 did not produce gross neurodevelopmental abnormalities in transgenic mice but was associated with elevated anxiety in female but not male adult mice. Mutant DISC1 has a dominant-negative effect and leads to impairment of astrocytes functioning and ensuing neurobehavioral abnormalities. Conclusion: We propose that our mouse model of inducible expression of mhDISC1 in astrocytes is a valuable experimental system to advance our knowledge of the molecular mechanisms whereby mutant DISC1 may affect astrocytes functions in major mental illnesses
ID: 979770

INTERACTION OF MUTANT DISC1 AND PRENATAL IMMUNE ACTIVATION: TIMING OF THE NEUROBEHAVIORAL EFFECTS OF MUTANT DISC1

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Background: Gene-environment interactions are involved in the pathogenesis of mental diseases. We evaluated interaction between mutant human Disrupted-In-Schizophrenia-1 (mhDISC1) and maternal immune activation implicated in schizophrenia and mood disorders. Methods: Pregnant mice were treated with saline or polyinosinic:polycytidylic acid (Poly I:C) at gestation day 9. In mutant mice DISC1 express only prenatally, only postnatally and continuously (both prenatally and postnatally). In mice with pre and postnatal expression we measure levels of inflammatory cytokines in fetal and adult brains, expression of mhDISC1, endogenous DISC1, LIS1, NDEL1, gp130, Grb2, GSK-3β and GFAP were assessed in cortical samples of newborn mice. Tissue content of monoamines, volumetric brain abnormalities, dendritic spine density in the hippocampus and various domains of the mouse behavior repertoire were evaluated in adult male mice. Results: Prenatal interaction produced anxiety, depression-like responses, and altered pattern of social behaviors. These behaviors were accompanied by decreased reactivity of the HPA axis, attenuated 5-HT neurotransmission in the hippocampus, reduced enlargement of lateral ventricles, decreased volumes of amygdala and periaqueductal gray matter and linear density of spines on dendrites of granule cells of the hippocampus. Prenatal interaction altered secretion of inflammatory cytokines in fetal brains, levels of mhDISC1, endogenous mouse DISC1, and GSK-3β. The behavioral effects of GEI were observed only if mhDISC1 was expressed throughout the life span. Conclusion: The findings suggest that prenatal immune activation interacts with mhDISC1 to produce neurobehavioral phenotypes that were not present in unchallenged mhDISC1 mice and that resemble aspects of mood disorders. Prenatal and postnatal expression is required for phenotype development and changes of this expression (especially postnatal expression) can give us new way to develop treatment. We propose that our DISC1 mouse model is a valuable system to study the molecular pathways underlying gene-environment interplay relevant to major mental illnesses.
ID: 979292

EMOTION DIFFERENTIATION DEFICITS IN SCHIZOPHRENIA

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Background: Deficits in recognizing negative emotions among schizophrenia subjects are well documented. However, few studies have examined whether schizophrenia subjects have difficulty differentiating among such emotions (eg, fear, anger). Also, some studies have found that healthy females were more accurate than males when recognizing emotions (1). The aim of this study was to use behavioral data from an emotion recognition (ER) task to examine whether schizophrenia subjects have deficits when differentiating between negative emotions and whether these deficits are influenced by gender. Methods: Schizophrenia subjects (SCZ: n = 21) and healthy controls (CON: n = 20) completed an ER task requiring them to view four facial expressions (ie, fear, anger, sadness, disgust) and then select the correct choice when paired with each of the other three emotions. ANOVA was used to examine whether there were between-group differences for performance accuracy and response times when differentiating among the negative emotions. Gender was included as a fixed-factor to examine group*gender interactions. Results: SCZ had a lower performance accuracy than CON on the ER task (P = .042), and SCZ needed more time than CON to differentiate between sadness and fear (P = .002) and sadness and anger (P = .022) when viewing a sad face, and between anger and sadness (P = .022) and anger and disgust (P = .013) when viewing an angry face. Significant interactions were found between group and gender such that male SCZ responded faster than female SCZ when differentiating between fear and sadness (P = .024) and fear and disgust (P = .001) when viewing a fearful face, between anger and sadness when viewing an angry face (P = .002), and between disgust and anger (P = .001) when viewing a disgusted face. There was no significant group*-gender interaction for performance accuracy. Psychopathology and cognition were also measured, but did not differ between male and female SCZ. Conclusion: Our results suggest that schizophrenia subjects have difficulty differentiating among facial expressions of anger, fear, sadness, and disgust. Also, females with schizophrenia may be particularly impaired as they take longer to differentiate among negative emotions than males with schizophrenia. These deficits may cause problems in correctly interpreting reactions and motivations of others, thus, leading to adverse social consequences.
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ID: 976668

MEDIAL TEMPORAL LOBE AND BASAL GANGLIA MEDIATED LEARNING IN CHRONIC SCHIZOPHRENIA PATIENTS, THEIR SIBLINGS AND HEALTHY VOLUNTEERS. A 45-YEAR FOLLOW-UP WITHIN THE NORTHERN FINLAND 1966 BIRTH COHORT STUDY

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Background: Neurocognitive impairments are core feature of schizophrenia. The most studied cognitive deficits in schizophrenia include attention, working memory, verbal declarative memory, and executive function (Ivleva et al 2010). Similar but milder neurocognitive deficits have also been found in biological relatives of schizophrenia patients (Ivleva et al 2010). Acquired equivalence is a cognitive phenomenon in which prior training to treat two stimuli as equivalent increases generalization between them. The learning of stimulus response pair is mediated by basal ganglia (BG) and stimulus generalization is mediated by medial temporal lobe (MTL), especially hippocampus (Myers et al 2003, Keri et al 2005). Methods: The NFBC 1966 have been followed since mid-pregnancy up to date. It is based upon 12 068 pregnant women and their 12 058 live-born children. It includes information concerning pregnancy and delivery, subjects' development, socio-demographic factors, genetic data, education and illness related factors. We performed the modified Rutgers acquired equivalence (AE) task for 80 psychotic subjects, 30 siblings and 120 controls. Results: Preliminary results of the behavior data (n = 18 schizophrenia and 68 controls) showed significant impairment in both BG mediated learning and MTL mediated stimulus generalization in schizophrenia group compared to normal controls. Conclusion: In previous studies BG dependent learning has been intact in schizophrenia patients while stimulus generalization has been impaired (Keri et al 2005, Shohamy et al 2009). Our population-based sample with also very ill patients might provide valuable data and new insight in the learning among people with chronic and severe schizophrenia.
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ID: 979580

DYSFUNCTION IN A DISCRETE CORTICALSTRIATAL CIRCUIT REFLECTS LIABILITY TO SCHIZOPHRENIA

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Background: We tested the hypothesis that schizophrenia is associated with dysfunction in a specific corticostriatal circuit by examining two skill learning circuits in 3 studies. A motor skill circuit originating in the supplementary motor cortex and includes the supplementary motor area, putamen, globus palidus and thalamus was studied using the Serial Reaction Time task (SRT). A cognitive skill circuit involving the caudate nucleus/dorsolateral prefrontal cortex and ventral striatum/orbitofrontal cortex was studied using the Procedural Classification Task (PCT). Methods: Patients and relatives of patients with schizophrenia and controls were trained on both the SRT and PCT. We assessed development of automaticity using a dual task paradigm. Results: Patients with schizophrenia were impaired at learning on the PCT. Controls showed the greatest gain in performance within the first session while patients improved slightly across all three sessions and never reached the level of controls.

In contrast, patients were not impaired at learning on the SRT. These results suggest that patients with schizophrenia may have dysfunction in a specific corticostriatal sub-circuit. The differential deficit noted above was not due to psychometric differences between the two tasks. We examined the development of these two circuits in normal children and adolescents. Paralleling the results of the first study we found developmental differences in cognitive but not motor skill learning. While children tended to have slower reaction times on the SRT, they benefited as much as adolescents from the sequenced trials. In contrast, adolescents learned faster and achieved higher levels of accuracy on the PCT than the children. Both children and adolescents automated the task well. These results provide additional evidence of the independence of these two circuits. A third study tested the hypothesis that deficient cognitive skill learning is associated with liability to schizophrenia. Non-Affected siblings of patients with childhood onset schizophrenia and controls performed the PCT before and after training while in the fMRI. Siblings of COS patients performed more poorly than controls very early and late in practice and showed reduced activation in the caudate nucleus/dorsolateral prefrontal cortex compared to controls. Conclusion: Taken collectively these studies indicate that the dysfunction in the cognitive skill circuit that supports performance on the PCT may be associated with liability to schizophrenia.
ID: 979395

CANNABIS EXPERIENCES, COGNITION AND SCHIZOTYPY.

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Background: Background: Clinical and population-based studies point towards an association between cannabis and psychotic experiences. However whether this association is directly causal or mediated by and interacting with other risk factors is still open for debate. In the general population those high on psychosis proneness (or schizotypy) are more likely to self report psychotic-like experiences after smoking cannabis (eg Barkus et al, 2006). Aims: Here we explore how other psychosis risk factors operate to increase risk for psychotic experiences after cannabis. Methods: Method: We recruited participants on the immediate experiences subscales from the Cannabis Experiences Questionnaire (CEQ), as well as a group of participants who were cannabis naive or had not used in the last two years (controls). 40 participants had above average scores on the Psychosis-Dysphoric subscale (PD) and 36 participants with below the mean scores on PD but above the mean on Pleasurable experiences. There were 33 controls. Participants completed a battery of psychological measures and cognitive tasks. Psychological measures included stress reactivity, schizotypy and other personality traits. The cognitive tasks covered domains of cognition such as learning, working memory and spatial working memory. Results: Results: Groups did not differ significantly on age and sex. There were differences in the personality profile of the two groups. The three groups had subtle differences in cognitive performance in the domains of working memory and learning. These differences were not attributable to IQ or other drug exposure. Conclusion: Conclusions: In identifying risk factors for psychotic experiences and sensitivity to after effects from cannabis use personality traits, emotional reactivity and subtle cognitive deficits may be used as markers. It is possible cognitive deficits are a reflection of a biological vulnerability involved in conferring risk for psychosis.
ID: 977449

CALCYON UP-REGULATION IN ADOLESCENCE IMPAIRS RESPONSE INHIBITION AND WORKING MEMORY IN ADULTHOOD

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Background: Calcyon regulates activity dependent internalization of AMPA glutamate receptors and long term depression of excitatory synapses. Elevated levels of calcyon are consistently observed in brains from schizophrenic patients, and the calcyon gene is associated with attention deficit hyperactivity disorder. Executive function deficits are common to both disorders, and at least for schizophrenia, the etiology appears to involve both heritable and neurodevelopmental factors. Methods: Here, we show with calcyon overexpressing CalOE transgenic mice that lifelong calcyon upregulation impairs executive functions including response inhibition and working memory, without producing learning and memory deficits in general. As response inhibition and working memory, and the underlying neural circuitry continue to mature into early adulthood, we functionally silenced the transgene during postnatal days 28–49, a period corresponding to adolescence. Results: Remarkably, the response inhibition and working memory deficits including perseverative behavior were absent in adult CalOE mice with the transgene silenced in adolescence. Suppressing the calcyon transgene in adulthood only partially rescued the deficits, suggesting calcyon upregulation in adolescence irreversibly alters development of neural circuits supporting mature response inhibition and working memory. Brain regional immunoblots revealed a prominent down-regulation of AMPA GluR1 subunits in hippocampus, and GluR2/3 subunits in hippocampus and prefrontal cortex of the CalOE mice. Silencing the transgene in adolescence prevented the decrease in hippocampal GluR1, further implicating altered fronto-hippocampal connectivity in the executive function deficits observed in the CalOE mice. Conclusion: Treatments that mitigate the effects of high levels of calcyon during adolescence could preempt adult deficits in executive functions in individuals at-risk for serious mental illness.
ID: 986939

COMPARING LEARNER STATUS AFTER DYNAMIC ASSESSMENT WITH THE WCST, CFT AND CVLT

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Background: Learning potential as measured with dynamic assessment methods combines instruction with test administration. The extent to which an individual can take advantage of the instruction to improve performance provides the index of learning potential. Most often learning potential in schizophrenia is assessed using the Wisconsin Card Sorting Test; however, it is unknown the extent to which learning status as determined by the WCST is applicable to other areas of cognitive functioning. The purpose of this study was to determine if learning potential status on the WCST was related to learning potential status on measures of verbal memory (CVLT) and visual memory (CFT). Methods: A cross-sectional design examined learning potential in 88 individuals with schizophrenia or schizoaffective disorder. The dynamic assessment of the WCST was administered and learner status was determined using the methods previously described by Schoettke et al A training protocol was developed for both the CVLT

and CFT and like the WCST, learner status was based on an algorithm taking into account the standard error of prediction based on established reliabilities of the measure. Results: Spearman Correlations indicate no relationship between learner status on the WCST and the CVLT (r = .08) and CFT (r = .18). There were more mismatches (60%) than matches (40%) for learner status. Utilizing a Friedman two-way analysis of variance by ranks, there was no difference in learner status for the three different cognitive domains suggesting there are similar numbers of high scorers, learners and non-learners across the three measures. These results indicate that learning status in one cognitive domain is not related to learning status in other cognitive domains. Learner status may be a better predictor when the area of cognition that is dynamically assessed is more closely related to the area of living that is the target of rehabilitation. Conclusion: These results indicate that learning status in one cognitive domain is not related to learning status in other cognitive domains. Learner status may be a better predictor when the area of cognition that is dynamically assessed is more closely related to the area of living that is the target of rehabilitation.

Frequency of Learner Status

	High Scorer	Learner	Nonlearner
WCST	19 (23%)	34 (42%)	29 (35%)
CFT	13 (15%)	36 (41%)	39 (44%)
CVLT	18 (21%)	39 (44%)	31 (35%)

ID: 978881

METACOGNITION, THEORY OF MIND AND NEUROCOGNITION AS INDEPENDENT PREDICTORS OF SOCIAL FUNCTION IN SCHIZOPHRENIA

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Background: Research suggests that deficits in the ability to process complex social information are a barrier to recovery from schizophrenia and may mediate the impact of other aspects of illness such as neurocognition upon functioning. Less is known though about what kinds of deficits in theory of mind and metacognition affect performance in complex social tasks. This study sought to examine this issue by exploring whether metacognition, theory of mind and neurocognition were independently related to performance on a laboratory test simulating a social interaction. Methods: Participants were 82 adults with SCID confirmed diagnoses of schizophrenia or schizoaffective disorder in a non-acute phase of illness. Emotion recognition in a social interaction was assessed with the Bell Lysaker Emotional Recognition Scale. Theory of Mind Tests included the Eyes and Hinting Tests. Metacognition was assessed using the Metacognition Assessment Scale. Neurocognition was assessed using the Wisconsin Card Sorting Test and the Vocabulary subtest of the WAIS III. Results: A stepwise multiple regression revealed that 50% of the variance in performance on the Bell Lysaker Emotional Recognition Scale was predicted by the Vocabulary subtest (R^2 = .24); the Eyes test (R^2 = .12); the Metacognition assessment scale (R^2 = .06); the Hinting test (R^2 = .04); and the Wisconsin Card Sorting Test (R^2 = .04). Conclusion: Results suggest that difficulties detecting emotions in social interactions may stem from a range of different phenomenon including lower pre-morbid intelligence, deficits in Theory of Mind, poorer capacities for metacognition and reduced flexibility in abstract thought.
ID: 961964

JUMPING TO CONCLUSIONS: ASSOCIATIONS WITH METACOGNITION INDEPENDENT OF SYMPTOM SEVERITY IN SCHIZOPHRENIA

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Background: Jumping to conclusions refers to a reasoning style in which persons arrive at conclusions relatively quickly in the presence of relatively little data. It is of interest in psychiatric research in the face of increasing data that suggest it is a risk factor for the formation of delusions in psychosis. One issue yet to be explored concerns the roots of this reasoning bias and, in particular, whether it may be related to deficits in metacognition or the ability to think about thinking. Do persons, for instance, who have limited abilities to think about their own thinking have more of a tendency to jump to conclusions? Methods: To explore the link between metacognition and jumping to conclusions we assessed Jumping to Conclusions using the Beads Test and Metacognition using the Metacognition Assessment Scale. To rule out the possibility that results were the effect of symptom severity, symptoms were assessed using the Positive and Negative Syndrome Scale. Participants were 40 adults with a schizophrenia spectrum disorder in a non-acute phase of illness. Results: Partial correlations controlling for positive, negative and disorganized symptoms on the PANSS revealed that greater levels of metacognition were correlated with a lesser tendency to jump to conclusions (ie a higher average number of beads requested before reaching a conclusion; r = .39, P <.05). Conclusion: Results are consistent with the possibility that deficits in metacognition influence or are influenced by reasoning biases. One possible implication is that treatments which target metacognition may have an influence on reasoning biases in persons with severe mental illness.
ID: 979684

MODELLING COGNITIVE SYMPTOMS IN THE DVD-DEFICIENT RODENT MODEL OF SCHIZOPHRENIA

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Background: Schizophrenia is a poorly understood but very disabling group of brain disorders with cognitive dysfunction a core symptom of this disease. There is a clear imperative to develop animal models that may reflect aspects of the cognitive deficits associated with schizophrenia. Based on clues from epidemiology, we have proposed that low prenatal vitamin D may be a risk factor for later development of schizophrenia. There is now robust evidence from in vitro and whole animal studies showing that low vitamin D levels during early life adversely affect brain development and adult behavior. Methods: Female rats were fed a vitamin D deficient diet from 6 weeks prior to conception until birth, when they were transferred to a diet containing vitamin D. Control rats were fed a vitamin D containing diet throughout the experiment. Six-month old DVD-deficient and control Sprague Dawley rats were assessed on selected cognitive domains using a 5 choice serial reaction time task and a 5 choice continuous performance task in an operant chamber. Brief flashes of light signaled the rat to either respond or withhold responding to receive a food reward. Measures such as hit, miss, false alarm and correct rejection were recorded. At the end of the experiment dopamine, serotonin, glutamate and GABA were measured in brain tissue using HPLC. In a separate experiment, DVD-deficient and control rats were also assessed for working memory using a de-

lay match to position task in an operant chamber. Results: DVD-deficient rats demonstrated mildly enhanced impulsivity and while they were normal on all measures of vigilance on response trials, their lack of inhibition on withhold trials was observed immediately and persisted throughout testing. Reduced glutamate levels in the striatum were correlated with impaired performance on the 5C-CPT. DVD-deficient rats had normal working memory as demonstrated by the delay match to position task. Conclusion: We show that DVD-deficient rats have impaired behavior on tasks that assess attention and vigilance, which are analagous to human continuous performance studies, but have normal working memory. One interpretation of these data is that DVD-deficient rats have reduced glutamatergic input from the cortex to the striatum which results in altered acquisition of a new response while inhibiting a previously learned response. These results provide specific targets to further investigate the influence of low pre-natal vitamin D on brain function.
ID: 978163

JUDGMENTS OF SIMILARITY AND DIFFERENCE RELATING TO THE OBJECT OF THE ACTION, AGENCY, AND OTHER SOCIAL COGNITIVE DEPENDENT MEASURES: A COMPARISON OF SCHIZOPHRENIC AND NON-DIAGNOSED RESPONDENTS ACROSS THREE WESTERN CULTURES

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Background: Prior research suggests that persons with schizophrenia are less likely to be affected by prior learning, perhaps mediated through the hippocampus, than are persons without schizophrenia. This may well contribute to one of the hallmark symptoms of schizophrenia, disorganized thought. We decided to test this idea through a social cognition context. Specifically, we were interested in determining just how influential social cognitive schemata were in the judgments of people with schizophrenia. For example, we hypothesized that persons with schizophrenia would be more inclined to make less consistent judgments about an object of action (eg, a written essay being interesting, well-written, and strongly argued) than persons without schizophrenia. Methods: 154 persons in three western cultures (North America, Netherlands, and United Kingdom) agreed to assist us: 63 non-diagnostic controls, 73 with schizophrenia, and 18 with other diagnoses. Subjects read and filled out questionnaires about each essay answering questions about the essay itself; agency; person-disposition; and external constraints. Most also completed the Oxford-Liverpool Schizotypy Inventory, along with giving reactions and socio-demographic information. Results: Results showed mixed support for the hypothesis. It seemed to depend on the kind of culture, the kind of essay, and the kind of social cognition dependent measure that characterized the judgment-making context. For example, in the North American and United Kingdom samples, essay 1 judgments, showed the predicted effects, with persons with schizophrenia showing significantly less inter-correlated measures of the essay being judged well-written, strongly argued, and interesting, than persons without schizophrenia. However, in the United States sample regarding essay 3 judgments, there were no such differences between persons with schizophrenia compared to persons without schizophrenia. And in the United Kingdom sample of essay 2 judgments, the predicted results were reversed! Conclusion: We would conclude that our hypothesis received some support, but appeared to depend on several complex interactions of culture, diagnostic group, and essay. Control analyses relating to symptom severity and to select socio-demographic variables, while not clarifying a possible necessary factor that would explain diverse findings, nonetheless allowed us to determine more precisely some of the conditions under which the effect might emerge
ID: 979999

CONTRIBUTIONS OF EARLY-STAGE VISUAL PROCESSING TO EMOTION RECOGNITION DEFICITS IN SCHIZOPHRENIA

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Background: Patients with schizophrenia (SCZ) show low-level visual processing deficits, with preferential magnocellular (M) pathway dysfunction reported in several studies, as well as emotion recognition deficits. This study examined contributions of visual pathway dysfunction to emotion recognition deficits by altering stimulus properties and examining event-related potentials (ERPs). Methods: SCZ and controls received two behavioral tasks: (1) contrast sensitivity and (2) behavioral emotion recognition in which the contrast of faces was altered to bias processing towards the M pathway (4 and 12% contrast) or to provide mixed M and parvocellular (P) stimuli (96% contrast). Ability to identify happy, sad, fearful, and neutral expressions was determined. The same faces were used in an ERP study in which participants were asked to perform an implicit task (press to a flower) to maximize sensory responses. Results: Basic visual processing deficits were seen in the contrast sensitivity task. Behavioral responses as well as amplitude of the dorsal visual stream P1 ERP component in the emotion studies showed contrast response functions indicative of M processing for both groups (eg, steep increase at low contrast with plateau at higher contrast), with SCZ showing deficits in behavioral emotion recognition and P1 amplitude. Contrast sensitivity was significantly related to P1 amplitude. SCZ did not show a deficit in the ventral stream N170 component, but did show decreased amplitude of the later P250 component. The P250 is thought to be related to affective processing and like the P1, was found to have a dorsal visual stream source. Behavioral emotion recognition, P1 and P250 amplitude results showed that controls were able to perform relatively well at the low contrast whereas SCZ needed 96% contrast (ie,. P contributions) to achieve similar levels of performance as controls at M-biased low-contrast. Conclusion: These results provide evidence that M-biased visual pathway information contributes to emotion recognition in controls and that SCZ show a deficit in using this information. The P1 deficit in SCZ reflects impairment at even the earliest stages of emotion processing that contribute to impaired later-stage processing. Thus, results provide evidence for a contribution of early-stage visual processing to emotion recognition deficits in SCZ and suggest that a bottom-up approach to remediation may be effective. Supported by R37MH49334 and P50MH086385.
ID: 977417

THE PRIMACY OF COGNITIVE DISTURBANCES IN MARIJUANA ABUSE: NEUROBIOLOGICAL PERSPECTIVES

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Background: Although about 7 million people in the US population use marijuana at least weekly, there is a paucity of scientific data on possible persistent neurocognitive effects of marijuana use and their potential correlations to neuroimaging deficits. Methods: A battery of neurocognitive tests was given to heavy marijuana abusers abstinent for at least 25 days. In addition, we determined if 25-day abstinent MJ users would show persistent dose-related alterations in performance and brain activity using PET H(2)(15)O during the Iowa Gambling Task-IGT (a decision-making task). Eleven heavy MJ users and 11 non-drug users participated. The MJ group resided in an inpatient research unit at the NIH/NIDA-IRP

for 25 days prior to testing to ensure abstinence Results: As joints smoked per week increased, performance decreased on tests measuring memory, executive functioning, and psychomotor speed. When the group was divided into light, middle, and heavy users, heavy users performed significantly below the light group on 5 of 35 measures. Duration of use had little effect on performance. There was a dose-related association between increased MJ use and lower IGT performance and alterations in brain activity. The MJ group showed greater activation in the left cerebellum and less activation in the right lateral orbitofrontal cortex (OFC) and the right dorsolateral prefrontal cortex (DLPFC) than the Control group. Heavy MJ users showed less activation in the left medial OFC and greater activation in the left cerebellum than the Moderate group. Brain activity and task performance were similar between the Moderate MJ users and the Control group. Conclusion: Very heavy use of marijuana is associated with persistent decrements in neurocognitive performance even after 28 days of abstinence. The neuroimaging findings suggest that heavy MJ users might have persistent decision-making deficits and alterations in brain activity. Thus, Heavy MJ users might focus on immediate reinforcing aspects of a situation (ie, getting high) while ignoring negative consequences. Thus, faulty decision-making could make an individual more prone to addictive behavior and more resistant to treatment. These findings will be compared and contrasted to published observations in schizophrenic patients and co-morbid patients.
ID: 979478

COGNITIVE INHIBITORY DEFICITS IN AT-RISK FOUR YEAR-OLDS

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Background: The offspring of parents with psychosis have been shown to have cognitive inhibitory defects identifiable by six years of age. It is unclear, however, whether these deficits are present and can be detected even earlier in life. This lack of clarity is primarily due to the lack of a clear method to measure problems in cognitive inhibition in preschool aged children. Our research attempts to assess a method to measure cognitive inhibitory deficits in preschoolers using the known relationship between maternal Axis I disorders and deficits in offspring cognition. We examined four-year-olds whose mothers had a history of Axis I mood and affective disorders when compared to controls by utilizing a Chimeric Animal Stroop task, a childhood adaptation of the traditional neuropsychiatric Stroop task. Methods: Participants were four-year-olds of mothers with and without Axis I mood or affective disorders. Incongruent (mis-matched animal heads and bodies) and control (clown faces with animal bodies) pictures were presented randomly over two blocks separated by one block of matching pictures. Reaction times, type of stimulus presented, and responses (correct, incorrect, or no response) were recorded. To account for variability in participation across blocks, the block where each child had the best participation (least percentage of no response answers) was utilized for analysis. Results: When children responded within the allotted three second time window, children whose mothers had an Axis I mood or affective disorder were significantly less likely to give a correct response to incongruent (mismatched) stimuli ($P = .016$). When considering all opportunities to respond, children whose mothers were affected with Axis I disorders were more likely to give an incorrect response ($P < .01$), and there was a trend of a lower percentage of correct responses overall ($P = .06$). No statistically significant differences were noted between the children's average reaction times. Conclusion: The association between maternal Axis I disorders and cognitive inhibitory deficit is already identifiable by four years of age. More research is needed to further determine potential specific etiologies, and further adaptation of the Chimeric Animal Stroop may produce even more robust detection in this preschool aged population. This method may be useful to study preschoolers vulnerable to later onset of psychosis.
This research was supported by the NIMH, grant number MH068582 (Robert Freedman, PI).
ID: 976555

PREFRONTAL CORTICAL DEFICITS AND IMPAIRED COGNITION-EMOTION INTERACTIONS IN SCHIZOPHRENIA

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Background: Despite schizophrenia patients' reports of diminished experience of emotion on interview and self-reported anhedonia and amotivation, their emotional experience in the presence of an emotional stimulus (ie, "in the moment") appears largely intact. In this study, we used a theoretical model emphasizing the emotion-cognition interactions and tested the hypothesis that schizophrenia patients' in-the-moment emotional reactivity is spared, but that they have a deficit in the neural substrates of cognitive control processes (such as those implemented by the dorsolateral prefrontal cortex, DLPFC) which are needed to maintain and report on an emotional response following the offset of the emotional stimulus. Methods: We used slow event-related fMRI to examine the brain activity of 23 schizophrenia patients and 24 healthy comparison subjects during trials in which they viewed affective images and, after a delay, they were asked to rate the emotion experienced while viewing the image. Performing this task required DLPFC-dependent cognitive control processes because of the delay between each image and the ratings, and by requiring ratings of emotional experience on dimensions consistent, as well as inconsistent with the overall affective valence of the eliciting stimulus. Results: In the presence of emotion stimuli, the brain activity of schizophrenia patients was similar to that of comparison subjects. During the delay, patients showed decreased activation in a network of brain structures which included the DLPFC, and other prefrontal, limbic and paralimbic areas; their ratings of emotional experience differed from healthy subjects on dimensions inconsistent with the stimulus valence. In patients, the delay-related DLPFC activity to Pleasant stimuli correlated negatively with clinical measures of anhedonia. Conclusion: Taken together, these results suggest that schizophrenia is characterized by a failure of cognitive control circuitry to support the critical link between affect and goal-directed behavior, and that the failure of this mechanism may contribute to a greater degree than previously thought to the affective deficits noted clinically in this disorder.
ID: 987678

TOWARDS A COGNITIVE RESOURCE LIMITATIONS MODEL OF DIMINISHED EXPRESSIVITY IN SCHIZOTYPY & SCHIZOPHRENIA

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Background: Diminished expression of emotion is a pernicious feature of schizophrenia-spectrum pathology that is poorly understood. We tested the hypothesis that diminished expressivity reflects a cognitive resource issue - that is, as cognitive resources are depleted, expressivity becomes dramatically diminished in individuals with schizophrenia-spectrum pathology. Methods: Data from two studies are presented here. In the first study, we employed acoustic analysis of natural speech procured during experimentally-manipulated low and high cognitive-load dual attention tasks in individuals with psychometrically-defined schizotypy and controls. In the second study, we employed acoustic analysis of natural speech procured during separate abstract (presumably requiring considerable cognitive

resources) and free (requiring fewer cognitive resources) speech conditions from stable outpatients with schizophrenia and affective disorders. Results: For both studies, all groups showed significantly decreased expressivity as a function of increased task demands. For both studies, negative traits/symptoms were associated with an exaggerated reduction in expressivity from low to high-load conditions. Moreover, in the first study, individuals with the most extreme reductions in diminished expressivity were those from the schizotypy group with the poorest cognitive performance on the high-load task. Conclusion: These findings suggest that diminished expressivity occurs as a function of limited cognitive resources in individuals with negative symptoms/traits.
ID: 978493

"SOCIAL FUNCTIONING AND COGNITION IN PATIENTS WITH SCHIZOPHRENIA, THEIR UNAFFECTED SIBLINGS AND HEALTHY CONTROLS: IMPACT ON QUALITY OF LIFE"

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Background: Patients with schizophrenia show deficits in many cognitive domains and social functioning, social skills, and self management skills in their daily life activities. The present study evaluated the relationship between general-social cognition, mental state and social functioning, and impact on quality of life. Methods: 22 patients with chronic disorder of schizophrenia were evaluated and compared with 19 first-degree relatives and 19 healthy controls. The assessments used were: Cognitive Screening: Word Accentuation Test, MCCB (Matrics Consensus Cognitive Battery) Social Functioning: UPSA (University of California Performance Skills Assessment), TABS (Test of Adaptive Behaviour in Schizophrenia), SSPA (Social Skills Performance Assessment), Mental State: Beck and Hamilton, Severity of Symptoms: Scale for Positive and Negative Syndrome of Schizophrenia, Quality of life: SF-36. Results: Patients showed significant differences from controls and siblings in MCCB total score ($P < .001$), whereas siblings showed significant differences compared to controls in MCCB total score ($P = .009$). Siblings differences were significant for patients ($P < .001$)and controls ($P = .022$) in TABS. Conclusion: Results suggest that the performance of nonpsychotic siblings is located between patients and healthy controls, suggesting that social performance measures are (or associated with) intermediate phenotypes of the disease. General and social cognition have a complex relationship with social functioning and quality of life.
ID: 978873

SYNERGISTIC DISRUPTION OF PREPULSE INHIBITION BY PRENATAL IMMUNE CHALLENGE AND RESTRAINT STRESS

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Background: Gestational immune challenge with viral antigen poly-inosinic/cytidylic acid (polyIC) has been well established as a neurodevelopmental model of schizophrenia. Also, it has been reported that oxidative stress is a phenomenon present in psychiatric disorders like schizophrenia. To gain a better understanding of the interaction between these two phenomena in the context of schizophrenia pathophysiology, we are developing a two-hits model (prenatal immune challenge (PIC) followed by juvenile restraint stress (RS)). Methods: C57BL/6 gestational mice were injected intraperitoneally with saline (100 μL) or with polyIC (20 mg/kg) at gestational day 12 (G12). Offsprings was submitted, or not, to a restraint stress for 2 hours, on three consecutive days, from postnatal days 33–35 (PN33–35). Twenty-four hours after the last period of restraint stress, PPI was assessed. Results: Our preliminary validation of this model revealed a synergistic effect of PIC and RS with respect to prepulse inhibition of acoustic startle (PPI) disruption. PIC and RS independently decreased in PPI and a synergistic effect of restraint stress was observed in offsprings of PolyIC-injected mice. Conclusion: These findings support the hypothesis that maternal immune activation interacts with RS in the development of sensorimotor gating deficit relevant to schizophrenia pathophysiology. Although RS elicits numerous and complex neurochemical and behavioral effects, our future work will assess the involvement of oxidative phenomena by (1) direct quantification of oxidative biomarkers and (2) investigation of the effect of antioxidant treatments. Further work will also be necessary to assess neurochemical abnormalities in dopaminergic and GABAergic neurotransmission. This two-hits animal model can be useful to study mechanisms responsible for behavioral and neurochemical abnormalities relevant to schizophrenia as well as to evaluate different potential therapies.
ID: 979385

ODD SPEECH OF SCHIZOTYPAL PERSONALITY DISORDER QUANTIFIED ON SINGLE WORD LEVEL

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Background: Odd speech is one criterion for schizotypal personal disorder (SPD). Previous data showed decreased pitch variability and increased pause proportion at the whole sentence level. This line of inquiry continues examining a single word, ''adorable''. The goal is to delineate specific speech pattern abnormalities in antipsychotic-naïve SPD subjects for targeted future social remediation work. Methods: Eighteen healthy comparison (HC) subjects were age and PSES matched with 19 SPD subjects recruited from the community. Tape-recordings of ''The puppies are adorable'' were analyzed with Praat software. The intensity wave form from ''adorable'' was isolated, normalized for duration and amplitude. This was quantified by the mean-squared error between the group average waveform and each individual's wave form. Pseudo-color intensity maps from individuals were generated. In a separate analysis, pitch variability and duration were compared between groups using ANOVA. Attack, the rise in intensity over time, was also compared for 10%–90% slope of syllable ''dor'' using ANOVA. Verbal fluency to letter ''c'' was measured and used in correlation analyses. Results: Intensity maps of SPD subjects suggest more variation than HC (effect size .8). For SPD, better executive function correlated with more normal intensity maps, a relationship not present in HC (Fisher Z for difference in correlation coefficients = .05). SPD subjects showed statistically significant less pitch variation and longer duration (effect size .8) compared with HC. There was no difference in attack. Conclusion: SPD subjects' odd speech can be quantified on the single word level. Efforts at cognitive/social remediation will be challenging given SPD subjects' impaired executive functioning and the multiplicity of deficits.
ID: 986769

EFFECT OF EARLY CANNABIS USE ON COGNITION IN SCHIZOPHRENIA AND PSYCHOTIC BIPOLAR DISORDER

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Background: Cannabis use is a risk factor for schizophrenia, particularly, early cannabis use. Cannabis is known to produce transient psychotic symptoms in otherwise healthy persons. In addition, cannabis use has been shown to worsen negative symptoms, and alter cognitive function in individuals with schizophrenia. Cannabis exposure has been associated with impaired cognitive performance in chronic users. However some studies suggest that schizophrenia patients with a lifetime history of cannabis use may have better cognitive functioning compared with schizophrenia patients without co-morbid cannabis use. In bipolar disorder, lifetime cannabis use has been associated with increased risk of suicide attempts, mixed episodes, and poor social functioning. However, to our knowledge, no studies have previously examined an effect of early cannabis use on cognitive function in individuals with psychotic bipolar disorder. This preliminary study will examine the effect of early cannabis use (before 18 years) on cognitive performance in individuals diagnosed with schizophrenia, and bipolar disorder with lifetime psychotic features. Methods: To date, we have collected 43 individuals with schizophrenia and 25 individuals with psychotic bipolar I disorder, including 16 individuals with early cannabis use (9 from schizophrenia group and 7 from bipolar group) and 9 individuals with late cannabis use (5 from schizophrenia group and 4 from bipolar group); they were enrolled in an ongoing study of psychosis. These volunteers completed 10 standardized neuropsychological tests that tapped 4 cognitive domains: working memory (WM), declarative memory (DM), executive function (EF) and attention (ATTN). Results: Average *T* scores in the 4 domains of WM, DM, EF, and ATTN, contrasting the early vs. late cannabis users (with probands pooled across diagnosis) show no differences between the 2 groups in WM, EF or ATTN, all tapping predominantly frontal lobe function. However, the declarative memory domain *T* score trended lower in the early cannabis users [40.4 +/−16.9] than in late cannabis users [48.3 +/−14.1] ($d' = .51$). We will seek additional subjects for this analysis and examine the individual tests representing the DM domain separately Conclusion: Low declarative memory performance may characterize early cannabis users (<18yo), with little evidence of alteration in frontal lobe task performance; this suggests that hippocampally-dependent functions might be particularly vulnerable with early cannabis use.
ID: 979865

COGNITIVE IMPAIRMENT AND SUBJECTIVE TIME IN SCHIZOPHRENICS

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Background: An experimental study was conducted to compare time perception of short durations, including intra- and interindividual variability of subjective duration judgments, in schizophrenic and in healthy males. Methods: The psychological methods of reproduction, and of verbal estimation in subjective seconds, were used. Results: It was found 1) that the means of the reproductions do not differ between the 2 groups, 2) the schizophrenics verbally estimated all durations longer and less veridical than the healthy subjects, 3) the variability of the estimates between, as well as within, subjects is much greater in schizophrenics than in the healthy group, 4) also the estimates by the schizophrenic group showed an approximately linear function of responses vs. the reference durations in log-log coordinates, in agreement with Stevens′ power law. Conclusion: Schizophrenics are described in terms of distraction and of chaotic and disorganized behavior. This important aspect of schizophrenic symptomatology typically results in cognitive impairment. The impairment may be at the root of the deviant, though fairly consistent, estimations by the schizophrenic subjects. This vulnerability entails that the schizophrenics seem to be unable to translate perceived time into numbers (seconds), probably because of their general difficulty in being able to quantify. To be more specific, it appears that the better understanding of the cognitive processes and the vulnerability factors of experiencing time and of time-structuring behavior is important knowledge as to how the schizophrenics individuals orient themselves in time and space. The conclusion is that our result does not support the view of general time distortion as such in schizophrenia.
ID: 987889

JUMPING TO CONCLUSIONS AND PSYCHOSIS

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Background: Individuals with delusions have a tendency to jump to conclusions (JTC). This means that they request less information before making a decision, and are therefore more likely to reach an inaccurate decision. This construct is often measured using a probabilistic reasoning task, called "The Beads Task." Using data from a case-control study of first-episode psychosis, we aim to compare data-gathering style between patients suffering their first episode of psychosis and non-clinical controls. Methods: As part of the Genetics and Psychosis (GAP) study we collected JTC data on 64 patients with a first episode of psychosis and 57 non-clinical volunteers from the local population. We used 2 versions of the Beads Task: 85:15 and 60:40. In both versions, participants are required to seek information in order to make a decision. Jumping to conclusions was defined on the beads task as making a decision after 2 or fewer items. We also evaluated the accuracy of the answer, on the basis of the patient's choice (right or wrong inference at the task). Results: 43.8% ($n = 28$) of cases compared with 24.6% ($n = 14$) of controls reported a JTC reasoning bias at the ratio 85:15, $P = .027$. 34.4% ($n = 22$,) of cases compared with 8.8% of controls ($n = 5$) reported a JTC reasoning bias at the ratio 60:40, $P = .001$. Moreover, in the ratio 60:40, 7.0% ($n = 15$) of cases compared with 23.4% ($n = 4$) of controls made inaccurate inferences, $P = .027$. Conclusion: JTC reasoning bias was significantly more prevalent in cases than controls, in both versions of the task, showing that the most difficult task (60:40) leaded to more errors than the less difficult one. Furthermore, the inaccuracy of the inference was higher in patients than controls, confirming that seeking for less information leads to wrong conclusions. The symptomatic and neuropsychological correlates of JTC will be examined in further analyses with the complete sample.
ID: 979520

PARANOIA VS. TRUST: EVIDENCE FOR A REDUCED SENSITIVITY TO SOCIAL REWARD IN NON-AFFECTIVE PSYCHOSIS

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Background: Psychosis is associated with severe social dysfunction. Its core symptoms, such as paranoid delusions, are characterized by hostility and a fundamental loss of trust in others. The impairment of basic trust has long been regarded as a primary deficit of the illness. Yet, little research has incorporated the social interactive quality of psychotic symptoms. The cur-

rent study aimed to elucidate the underlying mechanisms of disturbed interpersonal trust and reciprocity over the psychosis continuum. Methods: A multi-round trust game was used to investigate group differences in 1) trust, 2) the effects of positive contextual information and 3) the development of pro-social behavior during 20 consecutive real-time social interactions. The sample consisted of 29 patients with non-affective psychosis, 24 first-degree relatives of patients with non-affective psychosis, 35 healthy control subjects and 176 students who participated as counterparts (trustee) in the trust game. The association between group status and trusting behavior (amount invested) as a function of the trustees' reciprocity (amount repaid) were analyzed by means of multilevel regression analyses and a contingency model. Results: Controls showed the highest investment, patients the lowest. The invested amounts of relatives were intermediate. Controls did not differ significantly from relatives, but both made significantly higher investments than patients ($P < .05$). Positive contextual information about the degree of cooperativeness of the trustee significantly increased the investments of controls and relatives but had no effect on patients ($P < .05$). Controls and relatives showed more pro-social and mutually trusting interactions than patients. Patients were more likely to answer benevolent repayments of their trustee by decreased investments ($P < .05$) Conclusion: Non-affective psychosis is associated with a compromised ability to engage in trusting and trust building behavior and a reduced sensitivity to positive information about an anonymous game partner. These effects seem to be due to the disorder rather than vulnerability factors. The loss of basic trust and the insensitivity to positive information about other persons may drive the instantiation and manifestation of psychotic symptoms and are likely to contribute to the devastating effects of psychosis on daily life social functioning of psychotic patients.
ID: 945064

IS FRONTO-PARIETAL DYSCONNECTIVITY THE CORE CORRELATE OF DISEASE EXPRESSION IN EARLY ONSET SCHIZOPHRENIA?

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Background: Abnormalities in fronto-parietal networks are thought to underpin core aspects of cognition in schizophrenia. Current models postulate that the dorsolateral prefrontal cortex (DLPFC) mediates task-rules representation and maintenance and modulates activity in the posterior parietal cortex; within the latter both task relevance and stimuli features are integrated into unified representations of "salience" or "priority" used for competitive stimulus selection. Methods: Data presented arise from 3 different studies comparing cognitive, brain functional and diffusion tensor imaging data relating to cognitive control of attention and working memory in relation to fronto-parietal connectivity Results: Adolescents with schizophrenia ($n = 50$) compared with their unaffected first degree relatives ($n = 100$) and controls ($n = 93$) showed evidence of deficits in bottom-up control of sustained attention in terms of target sensitivity (Cohen's $d = 0.8$). Twenty of these patients, when compared with matched controls, showed evidence of reduced dorsolateral prefrontal cortical (DLPFC) activation during a working memory task. The DLPFC deficit was associated with abnormalities in its interaction with parietal cortices evident both in terms of white matter tract and functional connectivity. Conclusion: Abnormal fronto-parietal integration during adolescence may disrupt the formation and maintenance of task-relevant salience maps which may relate to the emergence of psychotic symptoms and persistence of cognitive deficits in schizophrenia.
ID: 975470

CROSS-SPECIES TOOLS TO EVALUATE POTENTIAL TREATMENTS FOR COGNITION DEFICITS IN SCHIZOPHRENIA

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Background: The MATRICS Program developed a consensus regarding the nature of the cognitive impairments in schizophrenia and how they might best be assessed and treated. This presentation will focus on how preclinical scientists can develop and refine animal tests to identify novel pro-cognitive agents having potential utility in the treatment of antipsychotic-treated schizophrenia patients. Attention/vigilance is commonly assessed in humans using the continuous performance test (CPT), which requires a response to signal events and an inhibition of response to non-signal events. Signal detection theory (SDT) is used to evaluate performance in the CPT. A recently developed rodent 5-choice (5C)-CPT requires both responses to target stimuli and the inhibition of responses to other stimuli, thereby enabling the use of SDT in assessing vigilance. Methods: Initial validation of the 5C-CPT as tested in an extended session challenge, tests in dopamine D4 receptor mutant mice challenged with a variable stimulus duration or an extended inter-trial interval session; and tests of the 5-HT2C antagonist SB242084. The predictive validity of the 5C-CPT was assessed by testing the effects of nicotine on vigilance in C57BL/6J mice. Results: C57BL/6J mice exhibited higher levels of vigilance than DBA/2J mice and a less pronounced vigilance decrement. Shorter stimulus durations degraded performance by increasing false alarm responses and D4-deficient mice had poorer vigilance. No difference in premature responses was observed. A 5-HT2C antagonist-induced increase in premature responses was observed, with no effect on false alarms. Nicotine induced a significant improvement on performance of C57BL/6J mice, consistent with observations in humans. Conclusion: The use of target and non-target stimuli in the mouse 5C-CPT enabled the: a) use of SDT to assess vigilance; b) identification of a vigilance decrement over time in 2 strains of mice; c) differentiation of impulsivity in response to non-target stimuli and motor impulsivity; and d) identification of nicotine-induced improvements in vigilance. These effects are consistent with human studies using the CPT. Hence, these studies suggest that the 5C-CPT enables vigilance testing in mice and is therefore available for use in efforts to develop and assess pro-cognitive compounds having efficacy that may translate from rodent to human CPT testing.
ID: 977268

TEMPORAL FRAGMENTATION IN SCHIZOPHRENIA?

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Background: The psychic life of patients with schizophrenia appears to be fragmented in time and space, but it is unclear how fragmentation in time relates with fragmentation in space. We base our approach on previous results showing that (1) patients with schizophrenia benefit from automatic grouping when using unambiguous stimuli, but are impaired at re-grouping distinct elements together. (2) Patients are impaired at reporting an asynchrony between stimuli. They detect asynchronies at an implicit level, but are unable to perceive a succession between asynchronous events, as if fragmenting events in time excessively. We question whether this is due to impaired spatial organization. Methods: Two squares were displayed on a screen, either simultaneously or with an asyn-

chrony. 19 patients and matched controls pressed on a right or left response key according to the simultaneity/asynchrony of the stimuli. This allows to evaluate both the explicit response and an implicit bias: when 2 squares are displayed asynchronously on opposite sides, the response can be biased to the side of the first or second square. We explored the impact of attention and spatial grouping by contrasting respectively divided vs. focused attention (4 possible locations vs. 2), and connected vs. unconnected stimuli. Results: We replicated previous results, with opposite biases in patients and controls. The profile of results in controls suggests that their responses are influenced by a sense of succession, with a bias to the side of the second square increasing as the location of the second square is predictable. In contrast patients do not benefit from the predictability of the second square location. At the shortest SOAs, when asynchronies are not detected, patients' responses were biased to the side of the first square, instead of the second square like controls. This effect was the largest when there was only 2 possible locations for connected squares. Conclusion: The bias to the side of the first stimulus suggests a fragmentation of events, inasmuch patients appear to be influenced by the stimulus which is displayed alone for a short time, rather than by the stimulus appearing last. This bias is the largest when spatial difficulties are erased (only 2 locations and connected stimuli), suggesting that the origin of this effect is temporal rather than spatial. We will discuss the possibility of a time anticipation impairment in patients. Acknowledgments: This research was supported by a grant from the University Hospital of Strasbourg.
ID: 979170

SOCIAL TRAIT JUDGMENT AND AFFECT RECOGNITION FROM STATIC FACES AND VIDEO VIGNETTES IN SCHIZOPHRENIA

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Background: Previous research has shown impairment in affect recognition in individuals with schizophrenia (SZ). Poor affect recognition has been associated with more severe symptoms and poor social functioning. Few studies have examined the quality of social judgments made by individuals with SZ, with mixed findings. Research in nonclinical populations suggests healthy people can accurately judge many social traits of others from brief exposure to nonverbal cues. The current study examined the quality of social judgments made by schizophrenic outpatients from both photos of emotional faces and short videos, rich with nonverbal cues. Methods: Outpatients with SZ and demographically matched healthy controls (HC) participated in affect recognition and social trait judgment tasks. Forty-two stimuli from the Karolinska Directed Emotional Faces were used for affect recognition from static photos, and 35 video clips of 15s each selected from The Awareness of Social Inference Test comprised the vignettes. Sound was removed from the video. Participants viewed each face and video clip, and made judgments about the emotional state, attractiveness, trustworthiness, approachability, and intelligence of the actor(s). Clinical symptoms (SANS, SAPS), current mood (PANAS), empathy (IRI), and social functioning (SFS) data were assessed and the Eyes test was given to index the Theory of Mind (ToM). Results: SZ patients were impaired compared with HC on affect recognition for both static and video stimuli. This impairment was significantly correlated with increased positive symptoms. SZ patients were able to identify faces, which suggests that affect recognition impairment is not due to a general deficit in face recognition. Additionally, increased schizotypy in the HC significantly correlated with poor affect recognition. Social judgments made from correct video trials indicate that patients tend to overrate attractiveness, approachability, and intelligence compared with HC. The relationship between these findings and social functioning and ToM remains unclear. Conclusion: These results indicate that SZ is associated with impaired affect recognition and abnormal social trait judgment. Considering the importance of accurate social trait judgment in everyday interactions and the potential role of impaired trait judgment in paranoid ideation, our finding of anomalous social trait judgment in SZ patients is intriguing. Acknowledgments: Supported in part by NARSAD and R01 MH073028.
ID: 978993

CLINICAL AND CROSS TASK CORRELATIONS OF CNTRACS TASK PERFORMANCE

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Background: The NIMH has made major investments in the development of tools for the assessment of treatment effects on cognition with the MATRICS and CNTRACS initiatives. The rationale for CNTRACS is clear: basic cognitive neuroscience has provided new opportunities to interrogate brain and behavior with the promise of leading toward a much more specific understanding of the deficits in schizophrenia and the development of more specific treatment targets. We performed inter-task correlations to determine if the tasks being developed as part of CNTRACs were relatively independent of each another. If uncorrelated, performance cannot be explained on the basis of the ''generalized deficit'' that confounds the interpretation of many cognitive findings. In addition, we examined the relationship of performance on these tasks to measures of function and symptoms. Methods: We examined the cross-task and clinical correlations between the main dependent measures from the CNTRACS tasks. Clinical measures included the BPRS, UPSA, and SLOF. Patient sample sizes varied for some of the measures, with all major analysis including at least 160 participants Results: All of the CNTRACS tasks discriminated patients from controls with effect sizes ranging from a low of $d = .27$ on the CCE to highs of $d = .99/.98$ on the RISE and DPX. To put into context, a $d = .84$ was observed in this sample on the UPSA Brief. The correlations between CNTRACS tasks ranged from $r = -.02$ to .21, suggesting minimal overlap in the abilities being measured. Modest, but significant correlations were observed with the UPSA for the D′ score from the DPX and the RISE Item and Associative Recognition memory scores. The DPX correlated significantly with the SLOF. None of the tasks correlated with severity of positive symptoms. DPX performance correlated with the severity of negative and disorganization symptoms. Conclusion: The CNTRACS tasks reveal significant impairments in 4 relatively independent cognitive processes thought to be mediated by different neural systems We observed statistically significant but limited overlap with symptom severity, coupled with significant correlations with proxy measures of community functioning. Given the lack of cognitive construct overlap, it is reasonable to expect that treatment effects could impact the varying systems measured by these tasks in a detectable, differential fashion.
ID: 977092

LEARNING FROM LOSSES BUT NOT FROM GAINS: A NEUROBEHAVIORAL RECIPE FOR AVOLITION IN SCHIZOPHRENIA

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Background: : Negative symptoms are defined by the absence of normal function. However, there must be a productive mechanism that leads to this absence. Here, we test a reinforcement learning account suggesting that negative symptoms result from a failure to learn from rewards while loss avoidance learning is preserved. We also test whether the value of rewards themselves or rather the learning that occurs from reward "prediction errors" is deficient. Methods: Case-control design. All subjects performed a probabilistic reinforcement learning paradigm involving stimulus pairs. The correct choice for 2 stimulus pairs resulted in the receipt of monetary reward. The correct choice for 2 other stimulus pairs resulted in the avoidance of a loss. A transfer phase followed learning. Setting: A tertiary care research outpatient clinic. Patients: A total of 47 clinically stable patients with a diagnosis of schizophrenia or schizoaffective disorder and 28 healthy volunteers participated. Patients were divided into high and low negative symptom groups. Results: High negative symptom patients demonstrated impaired learning from rewards but intact loss avoidance learning, and showed no preference for rewarding stimuli when presented with loss avoidance stimuli in the transfer phase. Low negative symptom patients did not differ from controls on any measure. Conclusion: Negative symptoms appear to result from a specific type of reinforcement learning abnormality: Patients do not represent the expected value of rewards but do learn to avoid punishments and from the positive prediction errors associated with loss avoidance. This framework offers the potential to understand the origins of negative symptoms at a specific, mechanistic level.
ID: 975612

THE IMPACT OF WORKING MEMORY CAPACITY LIMITATIONS ON THE OPERATION OF OTHER COGNITIVE SYSTEMS IN SCHIZOPHRENIA

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Background: In this symposium, we will present the results from an ongoing research program on the nature and consequences of WM impairment schizophrenia. Methods: A series of case-control experiments examining visual change detection, visual search, and target detection using behavioral and ERP methods. Results: Patients demonstrate visual WM capacity deficits across stimulus types (colors, orientations, locations). These deficits are not reliably amplified by increasing delay intervals suggesting impairment occurs at the encoding stage. Preliminary ERP evidence suggests that the basic neural machinery involved in WM storage, indexed by contra-lateral delay activity, is intact in schizophrenia, only failing as capacity is exceeded. Surprisingly, patients show normal precision of successfully encoded representations. Thus there is a limitation in the amount of information that can be stored, with no degradation of the fidelity of stored representations. Reduced WM capacity should impact other cognitive systems that require the rapid updating of WM representations including selective attention and executive control. We examined performance in a visual search task where subjects received a cue indicating the color of the item to be searched at varying intervals before the onset of the search array. This requires participants to rapidly encode the target color in WM to form a search template that serves to guide and limit search to the most task relevant items. Patients showed dramatic, SOA dependent slowing when target colors varied on a trial by trial basis, with minimal time-dependent impairment when the target color was held constant. Thus, slowing in the ability to update the search template caused marked slowing in simple visual search. We also examined the ability of patients to rapidly update a rule to be used to guide response selection. In this 1–2 AX CPT task, the number 1 cue defines A-X as the target sequence whereas the number 2 defines B-Y as the target. Thus, on every trial, the rule must be updated and maintained to guide response selection. In 2 separate experiments we have documented deficits in this critical control process with patients missing more targets and making more false alarms to both 1 BY and 1 AY foils. This suggests a dual impairment in updating rules and in inhibiting preponent responses. Conclusion: WM impairments in schizophrenia have a cascading impact on the operation of other cognitive systems.
ID: 975618

EARLY VISUAL PERCEPTION AND SOCIAL COGNITION IN SCHIZOPHRENIA

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Background: To better understand the nature of disability in schizophrenia it is important to identify the key determinants of outcome. Relatively few models of outcome have included perceptual measures, even though visual perceptual processing measures have considerable explanatory potential. In this presentation we will discuss 2 lines of evidence that show the importance of early visual processing deficits in schizophrenia for variables that mediate outcome, including social cognition and functional capacity. Methods: Data will be presented from 2 studies. One study included a large sample of schizophrenia patients and administered 2 visual masking tasks: 1 early stage task of masking of object formation, and 1 of later stage masking by object substitution (ie 4-dot masking). We used structural equation modeling (SEM) to examine the associations between these masking tasks and 2 types of mediating variables: social cognition and functional capacity. The second study employed the Bubbles Task to isolate visual information needed to recognize visual objects (ie faces). In this study we examined how groups differed in the extraction of salient information about emotions displayed on faces. This information was then correlated with performance on a task of social perception. Results: In the first study, the SEM analyses showed good model fit when the visual masking tasks were connected to social cognition and to functional capacity. In the Bubbles Task, patients used high spatial frequency information from the eye region significantly less often than controls when identifying fear. Among the schizophrenia patients, those who utilized the eye region more (ie more like controls) performed better on the social perception task. Conclusion: The first study showed that impairment in very early visual processes (first 500 ms of visual processing) lead to problems with social cognition and functional capacity. The second study showed that schizophrenia patients employ an atypical strategy of using salient visual information to recognize emotional faces, and that the more the strategy departs from normal, the greater the impairment on a social perception task. Taken together the results from these 2 studies provide support for the importance of bottom up visual processing for downstream effects that have functional significance.
Acknowledgments: This study was supported by NIH grant MH043292.
ID: 976871

TRUST VS. PSYCHOSIS: ELUCIDATING THE UNDERLYING MECHANISMS OF DISTURBED SOCIAL REWARD LEARNING

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Background: Paranoid delusions are characterized by an elementary lack of trust in others. However, the lack of trust has not actually been incorporated in cognitive models of paranoia so far. Trust is a necessary component of successful social interactions and has been shown to be inherently rewarding. The purpose of this study was to use game-theoretical approaches to study the behavioral and neural mechanisms underlying disturbed development of trust in psychosis. Methods: Functional magnetic resonance imaging data was acquired on 20 patients with paranoid delusions and 20 healthy controls while they were participating in a multiple-round trust game. The hypotheses were: (i) psychosis is associated with lower investments and lack of reciprocity during a trust game; and (ii) these behavioral abnormalities are associated with abnormal activation in reward-related brain areas. Results: Compared with controls, patients invested significantly less during the first round of the trust games, and were less often engaged in mutually reciprocative interaction, suggesting a behavioral index of reduced trust in patients. At the neural level, we found a reduced brain reward response within striatal and orbitofrontal cortices, and anterior insula in patients. Conclusion: This provides preliminary evidence for the hypothesis that aberrant sensitivity to social reward underlies the basic loss of trust in psychosis.
ID: 979838

BRAIN IMAGING AND NEUROCOGNITIVE MARKERS FOR AN INDIVIDUALIZED PHARMACOLOGICAL TREATMENT OF SCHIZOPHRENIC DISORDERS

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Background: Clinical studies on neuroleptic treatment response converge to suggest that most second-generation antipsychotics (SGAs) are equally effective (or non-effective). As a consequence, evidence-based choice of treatment almost exclusively focuses on the prevention of side effects while the individual therapeutic response of a patient is often uncertain. Many schizophrenic patients do not respond sufficiently to the first antipsychotic substance that is chosen in this "trial-and-error" way. In order to enhance the treatment success, it is necessary to develop diagnostic tools that permit to characterize the phenotype of individual schizophrenic patients in more detail, and - based on these tools - to improve the prediction of the patient's individual response to different SGAs. Methods: Functional neuroimaging and experimental neuropsychological testing is applied in order to detect and validate prognostic markers, which may allow for an individualized and optimized pharmacological therapy of schizophrenia that orientates to the phenotype of individual patients as specified by testable brain dysfunctions. Results: Findings from a series of preclinical and clinical studies will be presented. Using functional neuroimaging in healthy subjects, several neural networks underlying different sub-components of working memory have been identified, and the corresponding brain-behavior relationships have been validated by lesion studies. In samples of schizophrenic patients, different neurocognitive phenotypes with regard to selective dysfunctions of these neural networks have been observed. Furthermore, genetic polymorphisms of serotonergic and dopaminergic neurotransmission have been shown to selectively and differentially affect the capacity of these neurofunctional subsystems of working memory. Conclusion: From these studies hypotheses can be derived about the prognostic value of circuit-specific deficit patterns for predicting the individual response of schizophrenic patients to treatment with the D2-/D3-antagonist amisulpride vs. with other neuroleptics with additional 5-HT2A-antagonistic effects. These hypotheses are currently tested in a prospective clinical study.
ID: 985435

VISUOSPATIAL ATTENTION IN SCHIZOPHRENIA: DEFICITS IN BROAD MONITORING

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Background: Although attention is widely thought to be dysfunctional in people with schizophrenia (PSZ), studies using the most common attentional orienting paradigm have found no patient deficit in the ability to select 1 location and withdraw attention from others. Here we test whether the deficit lies not in the ability to focus attention narrowly, but in the ability to maintain a broad focus that encompasses multiple locations. Methods: PSZ (N = 29) and healthy control subjects (HCS, N = 26) were tested in a visuospatial attention paradigm in which a target stimulus was presented in 1 of 4 peripheral target locations. A central cue indicated that attention should be focused on 1, 2, or all 4 possible target locations. Central fixation was verified by eye-tracking. Results: When only 1 or 2 locations were cued, both PSZ and HCS responded faster when the target appeared at a cued than uncued location, confirming prior observations that PSZ are unimpaired at focusing attention spatially. However, increases in the number of validly cued locations had a much more deleterious effect on response speed and omission errors for PSZ than for HCS, with particular impairment in trials with 4 cued locations. Remarkably, PSZ responded more slowly when all 4 locations were cued than when 1 or 2 locations were cued and the target appeared in an uncued location, indicating impairment specific to broad spatial monitoring rather than disengaging and shifting attention. Conclusion: This study changes the view of attentional orienting in schizophrenia, demonstrating that deficits arise when broad monitoring is required rather than when attention must be focused narrowly. This may reflect a deficit in the ability to maintain a state of "diffuse watchfulness," a function ascribed to the default network of resting brain function, which reportedly displays abnormal activity in PSZ (Whitfield-Gabrieli et al. 2009, Proc Natl Acad Sci 106:1279–1284). Performance of the present task when all 4 locations have to be monitored depends on default network activity (Hahn et al. 2007, Cereb Cortex 17:1664–1671), which is modulated by nicotine (Hahn et al. 2007, J Neurosci 27:3477–3489). Preliminary results will be presented showing that transdermal nicotine (14 mg/24 hrs) reduced reaction time and omission errors in PSZ. These effects tended to be particularly pronounced in trials with 4 cued locations that require broad spatial monitoring. Supported by NIMH MH065034 and ADB Contract # N0 1DA-5-9909.
ID: 947366

PATTERNS OF DEFICITS IN BRAIN FUNCTION IN BIPOLAR DISORDER AND SCHIZOPHRENIA: A CLUSTER ANALYTIC STUDY

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Background: Historically, bipolar disorder (BPD) and schizophrenia (SCZ) have been considered distinct nosological entities, with each disorder having a different etiology and pathogenesis. The validity of maintaining such a distinction between SCZ and BPD is unclear, however. A cluster analytic study was carried out to empirically identify homogeneous neurocognitive subgroups based on discrete patterns of neurophysiologic and cognitive deficits and to examine these bio-cognitive subtypes in relation to formal clinical diagnoses. Methods: 22 SCZ patients, 21 BPD patients, and 29 controls were clustered based on a wide range of neurophysiological and cognitive traits, spanning from early pre-attentive stages of information processing to higher level complex cognitive processes. The various domains of brain function included auditory event related potentials (ERP) of P50 sensory gating, N100, P200, P300, mismatch negativity (MMN), gamma and beta response, smooth pursuit eye movements (SPEM), and thought disorder. Results: The cluster solution based on the K-means algorithm indicated the presence of 3 distinct groups: 1 group of individuals exhibited severe functional abnormalities, with the lowest scores on 14 out of 16 measures. 59% of SCZ ($n = 13$), 43% of BPD ($n = 9$) patients and 14% controls ($n = 4$) were classified in this group. Individuals in the second group exhibited larger gamma and beta activity, faster processing speed, and better SPEM. 41% of controls ($n = 12$), 36% of SCZ ($n = 8$) and 43% of BPD ($n = 9$) patients were classified in this group. The bio-cognitive functions tapped by these tasks correspond to early stage sensory information processing and error monitoring. The third group of individuals exhibited better performance in sensory gating, N100, MMN and P300 ERP responses, and higher cognitive function (lowest thought disorder score). 45% of controls ($n = 13$), 4% of SCZ ($n = 1$) and 14% of BPD ($n = 3$) patients were classified in this higher functioning group. These tasks tap inhibitory function and higher complex cognitive processes. Conclusion: In summary, regardless of formal diagnosis, a sub-group of SCZ or BPD patients exhibited greater functional abnormalities. Individuals in this group are hypothesized to have greater genetic loading for psychotic illness than those with fewer deficits. About a third of patients showed preserved early-stage sensory processing. Only a small proportion of patients were classified in the bio-cognitive subtype that probed inhibitory and higher cognitive function.
ID: 979855

NEUROCOGNITIVE FUNCTIONING IN TWINS DISCORDANT FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: This study was designed to elucidate neurocognitive endophenotypes for schizophrenia and bipolar disorder and to clarify the extent of overlap in these features between the 2 syndromes. Methods: Twin pairs discordant for schizophrenia or bipolar disorder as well as healthy control pairs were identified from the Swedish Twin Registry. As part of an on-going study, we administered a neuropsychological test battery in a sample of 36 schizophrenia probands, 24 unaffected co-twins of schizophrenia probands, 25 bipolar disorder probands, 15 unaffected co-twins of bipolar disorder probands, and 70 control subjects. Univariate mixed model analyses were performed on diagnostic group accounting for dependency of observations within twin pairs and including age and gender in the model as covariates. Results: Verbal working memory was sensitive to genetic loading for schizophrenia and bipolar disorder. Measures of processing speed and verbal fluency were impaired in schizophrenia probands and - to a lesser extent - their unaffected co-twins relative to control subjects. Additionally, although no variables showed genetic loading specific to bipolar disorder, unaffected co-twins of bipolar disorder probands showed a general pattern of neurocognitive performance superior to control subjects. Psychomotor performance was impaired in patients, regardless of diagnosis. Conclusion: The findings suggest that deficits in verbal working memory may be an effective endophenotypic marker for schizophrenia and bipolar disorder. In addition, results show evidence that processing speed and verbal fluency are related to genetic liability specific to schizophrenia. No impairment was specific to bipolar disorder. However, results indicate that unaffected bipolar co-twins show a pattern of enhanced neurocognitive performance relative to healthy control subjects.
ID: 986809

RAPID BENEFICIAL EFFECTS OF OLANZAPINE ON METACOGNITION OF HEALTHY PARTICIPANTS

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Background: Recent studies suggest that contrary to what has been widely held, the antipsychotic effects of neuroleptics begins within hours of drug administration. Accordingly, neuroleptics induce a rapid change of the neurocognitive mechanisms involved in the production or in the maintenance of psychotic symptoms. However, neurophysiological studies have failed to reveal any rapid effect of antipsychotics that could beneficial to neurocognition. This failure could be due to the particular neurocognitive mechanisms explored so far, which did not include metacognition about meaningful items, a type of reflective thinking. Methods: 47 healthy subjects were tested in a double-blind cross-over placebo-controlled study. We used 2 new primed semantic-categorization tasks and a classical oddball task as a reference. These tasks were performed 12–18 hours after administration of 2.5 mg of olanzapine vs. placebo. We measured the frontal slow positive waves (FSPWs) of the event-related brain potentials (ERPs) elicited by target words, which are known to index metacognition. Results: Although our participants felt significantly less energetic, response times collected in the 3 protocols were not significantly longer in the medication than in the placebo condition. In the new tasks, FSPWs depended on semantic congruency, as in previous studies. Most importantly, FSPWs were larger after olanzapine than after placebo in both new tasks, whereas none of the other components of the ERPs obtained in the 3 tasks were found to differ. Conclusion: The larger FSPWs suggest that, in healthy individuals, neuroleptics could boost the metacognitive processes elicited by meaningful stimuli, such as words.
ID: 986815

USING COMPUTATIONAL PATIENTS TO EVALUATE ILLNESS MECHANISMS IN SCHIZOPHRENIA

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Background: Various malfunctions involving working memory, semantic representations, prediction-error signaling, hippocampal functioning and dopamine neuromodulation have been associated with disorganized speech and delusional beliefs in schizophrenia. Computational models may provide insights into underlying mechanisms and tie together explanations of seemingly disparate symptoms and experimental findings. Methods: DISCERN is a multimodular artificial neural network capable of narrative learning and recall. For this study, the network learned "autobiographical" and "impersonal" crime stories, each associated with an emotion code. Eight illness mechanisms were simulated: (i) working memory (WM) disconnection, (ii) WM underactivation, (iii) WM inefficiency, (iv) semantic network distortion, (v) semantic network overactivation, (vi) semantic network hyperpriming, (vii) hyperarousal, and (viii) amplified prediction error signaling while learning narratives. Twenty healthy controls and 37 patients with schizophrenia or schizoaffective disorder matched for age, gender and parental were also studied. Illness mechanisms were contrasted to determine which best matched narrative breakdown profiles evidenced by the 2 subject groups when recalling thematically related stories heard 7 days previously. Illness mechanisms were further assessed to ascertain whether narrative behavior emerged suggesting fixed delusions. Results: All mechanisms were equivalent in matching the narrative breakdown profile of healthy controls. However, exaggerated prediction-error signaling while learning narrative memories was statistically superior to other mechanisms in matching the narrative breakdown profile of patients. These simulations also systematically confused "autobiographical" agents with "impersonal" crime story agents to model fixed, self-referential delusions. Conclusion: The selective advantage of the prediction-error model in matching the patient narrative breakdown profile suggests that this mechanism captures specific aspects of pathophysiology underlying schizophrenia rather than nonspecific sources of error-proneness demonstrated by human subjects overall. This illness mechanism predicts that narrative memories are intermingled and corrupted while incorporated into long-term storage, thereby producing speech disorganization and delusional narratives fixed in memory. Implications regarding the illness prodrome, dopaminergic neuromodulation, and hippocampal dysfunction will be discussed.
ID: 977380

CONTRIBUTIONS OF THE LATERAL PREFRONTAL CORTEX TO THE DAILY EXPERIENCE OF PSYCHOTIC-LIKE SYMPTOMS

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Background: It has been proposed that intact lateral prefrontal cortex (LPFC) function may protect individuals with schizophrenia-spectrum characteristics from the progression to frank psychosis. However, the exact mechanism by which the LPFC exerts protective influence for those at risk for psychosis is unknown. One hypothesis is that the LPFC engages cognitive control mechanisms to manage the stress-induced exacerbation of psychotic-like symptoms. Methods: Here we tested a basic model of this diathesis-stress interaction. We expected that among healthy individuals with personality-based risk for psychosis, deficits in LPFC (middle frontal gyrus, BA 9/46) would predict the exacerbation of psychotic-like symptoms after a stressful event. Healthy adults with high ($N = 19$) and low ($N = 19$) levels of schizotypal traits completed a structural and functional MRI scan as well as an online daily diary for 3 weeks. The fMRI task assessed neural activity during a "go/no go" response inhibition task. After the scan, participants reported each day (for 21 days) whether they had a stressful event (including minor hassles, such as getting stuck in traffic, etc.) and rated the extent to which they experienced psychotic-like symptoms, including mild hallucinations, odd bodily sensations, dissociative experiences, self-referential thoughts, external agency, and paranoia. Results: The results show that severity of psychotic-like symptoms are predicted by a 3 way interaction between schizotypy, left LPFC activity during the response inhibition task, and the occurrence of a stressful event. Specifically, after the occurrence of a stressful event, high schizotypy individuals with low left LPFC activity had higher levels of self-referential thoughts, dissociative experiences, and sensations of external control. The severity of psychotic-like experiences was also predicted by the interaction of schizotypy and left LPFC gray matter volume (GMV). Specifically, high schizotypy individuals with lower left LPFC GMV had higher levels of psychotic-like experiences. The relationship between schizotypy and left LPFC GMV strongly predicted daily severity of psychotic-like experiences regardless of the occurrence of stressful events. Conclusion: Overall, the results suggest that among people with a latent personality risk for psychosis, intact LPFC structure and function can help control the daily expression and stress-induced exacerbation of psychotic-like symptoms.
ID: 979326

STOP SIGNAL TASK PERFORMANCE AND SUBCORTICAL VOLUMES IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

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Background: Response inhibition (RI) is an important aspect of cognitive control. The underlying RI brain circuitry entails contributions from inferior frontal, supplementary motor, and striatal brain regions. Few studies have examined RI in schizophrenia. Methods: In the current study, we examined RI in 39 patients with schizophrenia or schizoaffective disorder and 42 age- and sex-matched healthy controls using the stop signal paradigm in which the primary task is a choice RT task. On 25% of trials a stop-signal following the imperative stimulus signals the participant to withhold response on that trial. The duration of the interval between the imperative stimulus and stop signal (stop signal delay, SSD) is actively titrated to induce, ideally, a 50% rate of RI success. Stop Signal Reaction Time (SSRT) is calculated as the difference between mean RT and average SSD. Longer estimated SSRTs are taken to indicate poorer RI. Participants also had anatomical MRI scans, and subcortical brain volumes were segmented using FSL software's FIRST program. Results: Patients showed longer SSRTs ($P < 1 \times 10^{-6}$), and increased RI failure rate ($P < .001$) and choice errors ($P < 1 \times 10^{-6}$) than controls. They also showed reduced left accumbens and hippocampal volumes. Patients were more

likely than controls to adopt the maladaptive strategy of delaying responses to avoid making a false alarm ($P < .001$). Within patients, these "waiters" showed reduced volumes of amygdala, putamen, and thalamus bilaterally, as well as right pallidum. Conclusion: These results show that patients with schizophrenia show poor performance and adopt maladaptive strategies on a RI task, and that these maladaptive strategies are associated with volume reductions in subcortical brain regions associated with response inhibition performance.
Supported by grants R01 MH064783 and R21 MH084031 to MJH
ID: 979421

ASSOCIATIONS BETWEEN SUPERIOR TEMPORAL AND PREFRONTAL GYRUS THICKNESS WITH 100 MS PAIRED-CLICK MEASURES

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Background: The biggest effect-size finding in a recent study examining 100 ms superior temporal gyrus (STG) paired-click activity in a large sample of controls and patients with schizophrenia (Sz) was smaller STG (M100) responses to the first click (S1) in Sz (Smith et al., 2010). The present study examined whether STG gray-matter abnormalities would be observed in a subset of this sample and the relationship of STG abnormalities to S1 source strength. Although second-click (S2) aberrations were not observed, top-down influence of prefrontal cortex (PFC) activity on S2 gating is possible. Methods: Paired-click measures (whole-cortex magnetoencephalography) and 1.5T structural MRI were available for 52 patients with Sz and 53 controls. Bilateral cortical thickness measures were obtained, using Freesurfer (parcellation method), of Heschl's gyrus (HG), planum temporal (PT), and the lateral aspect (LA) in STG and pars triangularis, orbital inferior, opercular inferior, and middle frontal gyrus in PFC. Results: Patients had decreased LA thickness bilaterally ($P = .04$). No group differences were observed for PFC regions. Hierarchal regression examined relationships between STG and PFC gray matter and S1 and S2 amplitudes. Left LA thickness predicted larger S1 amplitudes in both groups ($P = .003$). For S2, a Group X left PFC interaction ($P = .05$) showed that greater pars triangularis thickness predicted reduced left S2 source strength only in Sz ($P = .04$). Conclusion: Consistent with the literature, thinner STG gray matter was observed in patients with Sz. Although HG and PT are thought to be the primary generators of the M100 STG response, only LA thickness predicted M100 S1 source strengths. Given the decreased S1 response and thinner LA cortex in Sz, present findings suggest additional generators on STG that influence encoding processes. Results also suggest a top-down influence (PFC to STG) on gating processes in Sz, indicating that, although normal gating in Sz was observed in these subjects, the mechanisms to achieve normal gating may differ in Sz.
ID: 977834

NEUROCOGNITION AND BRAIN STRUCTURE ENDOPHENOTYPES ACROSS THE PSYCHOSIS DIMENSION

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Background: This study sought to characterize cognitive endophenotypes of psychosis within traditional diagnosis and psychosis dimension in a family sample of schizophrenia (SZ) and psychotic bipolar I disorder (BD). Methods: 44 probands with SZ (SZP), 32 probands with BD (BDP), 30 first-degree relatives of SZP (SZR), 25 first-degree relatives of BDP (BDR), and 28 healthy controls (HC) were recruited. Standardized clinical, neuropsychological measures, and an inferential memory (Acquired Equivalence) test were administered. Results: The analysis of cognitive measures by traditional DSM-IV diagnoses revealed no differences between SZP and BDP, or between SZR and BDR in the domains of working memory (WM), declarative memory (DM), executive function (EF) and attention (AT). Relatives overall showed higher cognitive performance compared with probands, as expected. However, when we segmented the probands and relatives along the psychosis dimension, independent of diagnostic group, results revealed lower cognitive performance in probands compared with relatives without psychosis spectrum disorders, whereas relatives with psychosis spectrum disorders showed an intermediate level of performance across all cognitive domains. SZP showed lowed inferential memory performance compared with HC, whereas no differences emerged between either SZP and BDP, or SZR and BDR. Conclusion: In this study, cognitive performance did not distinguish probands or their first-degree relatives within traditional DSM-IV diagnostic groups (SZ and BD), but distinguished probands and relatives with and without lifetime psychosis independent of diagnostic categories. These data support the notion that SZ and BD present a clinical continuum with overlapping cognitive features defining the psychosis phenotype.
ID: 942106

OSCILLATORY HIERARCHICAL DISTURBANCES IN SCHIZOPHRENIA: RELATION TO SYMPTOMS AND COGNITION

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Background: Auditory MMN and N1 are among the best described biomarkers of schizophrenia (SZ) and index distributed cortical dysfunction. Brain rhythms underlying generation of these rhythms show hierarchical organization with faster rhythms (eg beta/gamma) showing entrainment to underlying slower activity (eg delta/theta). This study applies oscillatory hierarchical modeling to ERP and fMRI biomarkers of SZ. Methods: Data are presented from 3 datasets ($n = 20–25$ pts/ctls each). Dataset 1 evaluated oscillatory hierarchical deficits underlying impaired long-latency auditory N1 to unattended tones. Dataset 2 evaluated deficits underlying impaired function in an attention-dependent visual continuous performance (CPT) task. Dataset 3 evaluated auditory sensory function relative to underlying rsfMRI measures. Oscillatory analyses were conducted on wavelet transformed continuous EEG data, within the delta (2–4), theta (4–8), alpha (8–12), beta (12–28) and gamma (30–80) Hz frequency ranges. Results: Deficits in long-latency N1 generation reflected primarily impaired

phase-reset of underlying theta rhythms (P = .002), potentially driven by reduced stimulus entrainment of underlying low frequency delta rhythms (P = .005). Impaired delta generation correlated closely significantly with impaired negative symptoms, including blunted affect (r = .61, P = .008) and lack of spontaneity (r = .65, P = .005). On the CPT, deficits in alpha desynchronization reflected impaired stimulus processing, while deficits in beta desynchronization reflected motor preparation. In rsfMRI studies, reduced coupling in auditory regions along with impaired MMN generation correlated with impaired auditory sensory function. Conclusion: Cognitive deficits, in SZ reflect, at least in part, reduced entrainment of brain activations to underlying rhythm of presented stimuli. Furthermore, oscillatory biomarkers, such as theta/delta coupling, produce greater between-group effect size differences than do their time-domain counterparts. Although oscillatory analyses of SZ, to date, have focused primarily on impairments of high frequency (gamma) generation, present findings suggest significant deficits as well as within slower oscillatory bands, including resting state, delta, theta, alpha, and beta activity, reflecting symptom-related impaired communication among, as well as within, distributed brain regions.

Funding: R37MH49334. R01MH064783, P50MH086385.

ID: 977339

CONTEXT PROCESSING IMPAIRMENT IN SCHIZOPHRENIA: ELECTROPHYSIOLOGICAL AND GENETIC ASPECTS

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Background: As treatment of positive symptoms of schizophrenia improves, the focus of much research has centered on treatment-resistant cognitive deficits commonly found in this disorder. Behavioral data provide evidence for a specific deficit of context processing in individuals with schizophrenia (Cohen & Servan-Schreiber, 1992). Evidence has also been found of a moderate deficit of context processing abilities in unaffected first-degree relatives of individuals with schizophrenia, indicating a genetic component (MacDonald et al., 2003). Electrophysiological components associated with context processing in healthy individuals have been investigated (Dias et al., 2003), but similar research has been scant in individuals with schizophrenia (Javitt et al., 2000) and non-existent in family studies. Methods: This study consisted of individuals with schizophrenia, their healthy first-degree relatives, and control individuals completing a novel context processing task, the Stimulus Response Reversal Task. Green and red squares are used as cue stimuli to indicate the response set for a following probe, the word ''right'' or ''left.'' Green cue trials are considered ''low cognitive load,'' as the response set is to use the hand corresponding to the probe. Red cue trials are considered ''high cognitive load,'' as the participant is required to overcome the prepotent response and use the hand opposite to the probe word to respond. This task allows relatively simple comparisons of prepotent vs. conflicting responding. Behavioral and electrophysiological data will be analyzed to investigate context processing deficits and associated patterns of brain activation in these samples. Results: We hypothesize that the control group will demonstrate a large difference in activation (P300 and Selection Negativity components) between green vs. red cues, likely indicating cognitive preparation to overcome a prepotent response following red cues. We also predict that this between-cue activation difference will be moderately decreased in the relative sample and very small or absent in the schizophrenia sample. Conclusion: These results would suggest the presence of poor representation and maintenance of contextual information in the schizophrenia and relative samples. Additionally, support of our hypotheses would identify specific neural patterns associated with poor context processing ability and offer further evidence of a genetic relationship of the context processing impairment in schizophrenia.

ID: 979516

REDUCED POSTERIOR NASAL VOLUME: A NEURODEVELOPMENTAL ABNORMALITY IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Abnormalities in nasal volume are thought to signify a marker of embryological dysmorphogenesis in schizophrenia, as nasal structures mature in conjunction with the palate and ventral forebrain. Posterior nasal volume decrement has been observed in schizophrenia though not in unaffected first-degree family members suggesting this may be an environmentally-mediated abnormality. The aim of the current study was to further examine the nature of this deficit in individuals at clinical high risk for developing psychosis. Methods: Measurements of nasal cavity were acquired using an acoustic rhinometer in adolescents and young adults at clinical high risk (CHR) for psychosis (n = 10), as well as demographically-matched schizophrenia patients (n = 12) and healthy low risk controls (n = 11). Two measurements were obtained for each nostril, and mean values were calculated for total right and left nasal volume. Nasal volume was further divided into anterior and posterior compartments based on the inferior turbinate boundary. Factors thought to influence nasal volume differences, including height, race, and smoking history, were included as covariates in the analysis. Results: There was a statistically significant main effect of group on total nasal volumes, with patients showing reduced nasal volumes compared with controls and CHR individuals showing intermediate volumes between patients and controls. A significant interaction of group, nostril, and nasal compartment was observed. CHR individuals showed a statistically significant decrement in right posterior nasal cavity volume compared with the control group. Patients showed significantly lower right and left posterior nasal cavity volumes compared with controls, and significantly lower left posterior nasal cavity volume compared with the CHR group. In patients, nasal volume indices were not associated with schizophrenia symptoms, illness duration, age of onset, pack-years, or antipsychotic medication usage. Conclusion: Collectively, these findings lend further support for posterior nasal volume decrement as a specific developmental craniofacial abnormality observed in schizophrenia patients and at risk individuals. Aberrant nasal volume size may be a neurodevelopmental marker of disruption in embryological development that could have predictive utility in identifying individuals transitioning to psychosis.

This study was funded in part by NIH Grants MH63381 (PJM), MH59852 (BIT), K08MH079364 (MEC), and a NARSAD Independent Investigator Award (PJM).

ID: 975458

THE EFFECT OF FREQUENCY MODULATION OF ABSTRACT TONES ON AFFECTIVE PROSODY IN SCHIZOPHRENIA

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Background: Schizophrenia patients show decreased ability to identify emotion based upon tone of voice (''emotional prosody''). Acoustic features of stimuli giving rise to these deficits have yet to be determined. This study uses abstract tones to explore mechanisms of auditory emotion processing deficits in schizophrenia. Methods: 41 patients and 41 controls were asked to identify the emotional valence (happy, sad, angry, fearful, or neutral) of 38 tones that differed in fundamental frequency (F0), frequency modulation (F0SD) and absence or presence of high frequency energy (HF500). A subsample completed a tone-matching, a verbal affective prosody tasks and a mismatch negativity (MMN) paradigm. Results: In the base condition, both groups showed a highly significant ($P < .0001$) non-uniform pattern of response across levels of F0 and F0SD. Stimuli with highest F0 and F0SD frequencies were preferentially identified as happy, while stimuli with lowest F0 and F0SD frequencies were preferentially identified as sad. Stimuli with low F0 and mid-range F0SD were identified as angry. Patients showed less modulation of response across frequency change, leading to a highly significant between-group difference in response pattern to maximally identifiable stimuli ($d = 1.5$). In addition, significant correlations were observed between response pattern to abstract stimuli and both tone matching ($r = .40$) and voice emotion recognition tasks ($r = .48$). Correlations remained significant even following covariation for between-group differences in global cognitive performance. Significant MMN was generated to these abstract tones, with between group differences. A model of MMN amplitude to abstract stimuli and cohort predicted performance on F0 and F0SD dependent items on the affective prosody task, but not voice intensity (eg loudness) item performance. Conclusion: While patients with schizophrenia were able to utilize changes in acoustic properties to distinguish emotions, they still demonstrated significant less sensitivity to changes in tonal frequency than did controls. Moreover, response patterns for abstract tones strongly predicted response accuracy for identifying auditory emotion in speech, suggesting that early sensory processing deficits may underlie impaired auditory emotion recognition in schizophrenia.
ID: 976244

ENHANCED CUE-INDUCED RELAPSE TO COCAINE SEEKING IN THE NEONATAL VENTRAL HIPPOCAMPAL LESION (NVHL) RAT MODEL OF SCHIZOPHRENIA

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Background: Patients with schizophrenia are up to 5 times more likely to have substance use disorders than people without mental illness. It is commonly believed that this co-morbidity is due to self-medication. However recent studies suggest that this vulnerability may be due to a common pathophysiology. One of the most comprehensively studied animal models of schizophrenia is the neonatal ventral hippocampal lesion (NVHL) model; this early neuroanatomical manipulation causes medial prefrontal cortex (mPFC)-related deficits that have also been proposed to exist in schizophrenia. Environmental cues are critical for relapse behaviors in both humans and experimental animals, and the cue-induced reinstatement model has also been shown to be dependent on an intact mPFC. We therefore hypothesized that NVHL rats would show enhanced reinstatement induced by cocaine-associated cues. Methods: At postnatal day 7–9, male Long-Evans pups (15–20 g) received either bilateral excitotoxic lesion of the ventral hippocampus via injection of ibotenic acid or sham surgery. Upon reaching adulthood, NVHL and SHAM rats went through catheter surgery and were then trained to self-administer cocaine for 3-hour/day for 10 days. Each lever press resulted in a cocaine infusion which was paired with a tone and a light stimulus. Extinction training, where lever press had no programmed consequences, took place for 3 hour/day for a minimum of 7 days followed by a session of cue-induced reinstatement testing in which lever presses led to cue presentations but not cocaine. Results: We found that NVHL had normal acquisition and intake of cocaine compared with SHAM controls. However, compared with SHAM controls, NVHL rats had an increased lever press responding on day 1 of extinction as well as increased lever responding to the cues during the reinstatement session. Conclusion: These data suggest that NVHL rats are more vulnerable to cue-induced relapse. Additional studies using this animal model could shed light on the mechanisms involved in the prevalence of schizophrenia and drug addiction.
ID: 978440

ILLUSORY CONTOUR PERCEPTION IN SCHIZOPHRENIA: IMPAIRED OR INTACT?

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Background: People with schizophrenia are impaired at integrating Gabor elements into a global shape and are also less adept at utilizing collinear Gabor elements when detecting a central low-contrast target (Uhlhaas & Silverstein, 2005; Must, Janka, Benedek, & Kéri, 2004). Prior studies have not made it clear whether similar deficits would obtain with spatially broadband stimuli, such as those that elicit the appearance of illusory contours. We addressed this question with a ''fat/thin'' shape discrimination paradigm (Ringach & Shapley, 1996) that is well-established in basic vision but untested in the field of schizophrenia. Methods: Two clinically-stable patients and 8 healthy controls participated in a 30 minute computerized experiment. On each trial, a monitor briefly displayed 4 sectored circles or ''pac-men'' that were individually rotated to create 1 of 2 stimulus types. In the control conditions, the pac-men appeared disconnected, and the task was to indicate whether they were rotated rightward or leftward. In the integration conditions, ''illusory'' contours connected the pac-men and the task was to determine whether the resulting shape was ''fat'' or ''thin.'' On half of the trials of the integration and control conditions, distractor lines—which are known to degrade illusory shape perception—accompanied the pac-men. These lines always appeared at the same location and never provided any information about the target identity (eg, whether it was fat or thin). Task difficulty was determined by the degree that the pac-men were individually rotated (with larger rotations making discrimination easier). A Bayesian adaptive staircase procedure adjusted the rotation angle on each trial to simultaneously estimate threshold and slope (Kontsevich & Tyler, 1999). Results: The effect of the distractor lines for healthy controls marginally depended on the presence of illusory contours ($P = .065$). More specifically, distractor lines tended to raise thresh-

olds in the illusory condition ($P = .058$) but not in the control condition ($P > .6$). The same interaction was marginally lessened among patients ($P = .085$). Conclusion: These results, although preliminary, suggest that a staircase-controlled fat/thin discrimination task offers a promising and efficient means to assess illusory contour perception in schizophrenia. It can shed new light on the impaired neural mechanisms in schizophrenia, and help decide whether contour linking is a spatially broadband deficit.
ID: 979070

DEFICITS IN LEARNING-DEPENDENT PREDICTIVE PERCEPTION AND THEIR RELATIONSHIP TO COGNITIVE IMPAIRMENT AND REALITY DISTORTION IN SCHIZOPHRENIA

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Background: Cognitive deficits play a key role in the onset of schizophrenia. Cognitive impairment precedes the onset of psychosis in a subgroup of patients and accounts for considerable dysfunction. Yet cognitive deficits as currently measured are not significantly related to hallucinations and delusions. Part of this counterintuitive absence of a relationship may be caused by the lack of an organizing principle of cognitive impairment in schizophrenia research. Methods: We have reviewed literature on healthy brain function as well as perception and cognition in schizophrenia. Results: A review of the literature suggests that prediction based on past experience plays a significant role in healthy perception. Deficits in learning-dependent predictive perception appear to play a central role in many of the perceptual and cognitive deficits associated with schizophrenia. Conclusion: Impairment in learning-dependent predictive perception may represent the core deficit in schizophrenia and may underlie many of the cognitive deficits and the symptoms that present as reality distortion (delusions, thought disorder and hallucinations). As deficits in learning dependent predictive perception are proposed to lie more proximal to the biological causes of schizophrenia than deficits in standard cognitive constructs, tests that more directly probe LDPP may be especially sensitive predictors of conversion in individuals at high-risk for schizophrenia. The accurate identification of cognitive processes that precede the onset of psychosis will not only be useful for clinicians to predict which young people are at greatest risk for schizophrenia, but will also help elucidate the neurobiology of psychosis onset, thus leading to new and effective treatments for preventing schizophrenia and other psychoses.
ID: 979866

TOWARD COGNITIVE AND SYSTEMS NEUROSCIENCE MODELS OF PSYCHOSIS

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Background: The purpose of this presentation is to place the presentations within a broader context of emerging themes related to the neurobiology of schizophrenia. Methods: The rational development of novel antipsychotic medications depends on an understanding of how neural systems represent the symptoms of psychosis. Results: Ideally, this understanding should inform our understanding of how structural and neurochemical developmental abnormalities contribute to the development of these symptoms. Each of the presentations in this session, by Drs. Keefe, Hoffman, and Corlett constitute a serious conceptual and experimental effort to address this gap. Conclusion: This presentation will examine areas of convergence across the presentations that point toward broader strategies for developing novel treatments for these symptoms.
ID: 979617

BODY MOVEMENT SYNCHRONY DURING SOCIAL INTERACTION IN PATIENTS WITH SCHIZOPHRENIA IS RELATED TO SYMPTOMS AND SOCIAL FUNCTIONING

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Background: In schizophrenia and other severe mental disorders nonverbal behavior in social interactions is both prominently affected, as well as strongly related, to outcome. Empirical research in this field, however, has been scarce. Novel computerized methods can now be used to objectively examine nonverbal behavior in schizophrenia. Methods: Motion energy analysis (MEA) refers to a method by which objective measures of body movement can be extracted from video recordings. In the present study, videotaped role-play scenes with 42 stabilized outpatients were analyzed. Each patient interacted in 14 short scenes with an investigator who portrayed an interpersonal partner. Correlations between movement parameters and psychopathology ratings from independent PANSS interviews were calculated. Results: Both reduced movement activity and slowness of movement were correlated with negative symptoms and with specific general symptoms, eg depression and motor retardation. Positive symptoms were generally not related to movement parameters with the exception of suspiciousness being correlated with reduced head movements. There were clear signs of "social contagion" in the interactions, ie in patients with lower movement rates investigators also showed reduced movement. Lower movement synchrony between patients and investigators was associated with symptoms and social functioning, even after controlling for patients' levels of movement. Conclusion: MEA measures of nonverbal behavior in schizophrenia patients seem to be strongly and specifically linked to psychopathological symptoms. The clear and strong relationships between movement, movement synchrony, symptoms and social functioning suggest targeting body movement in various forms of therapeutic interventions. Normalizing body movement and movement synchrony should be considered a critical goal for the therapy of schizophrenia.
ID: 977523

CONTEXTUAL MODULATION OF FACIAL AFFECT RECOGNITION IN SCHIZOPHRENIA

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Background: Difficulties in recognizing emotion expressed in the human face is the most consistent social cognitive finding in schizophrenia. Although studies typically examine recognition of facial expressions in isolation, social situations provide powerful constraints on our perception, especially for ambiguous expression. In this study, we examined the effect of situational context on facial affect recognition in schizophrenia. Methods: Thirty schizophrenia patients and 23 normal controls received a facial affect recognition task. The task consisted of 2 conditions: a situational context condition and a no context condition. For the situational context condition, a face was shown that displayed either surprise or a neutral emotion. The face was preceded by a sentence describing either a fear-relevant event or a surprise-relevant event (the sentence "frame"). Subjects were asked to rate how fearful or surprised the face appeared on a 9-point Likert scale. In the second condition (no context), 3 types of faces (fear, surprise, neutral) were presented without any sentence frame and subjects rated the faces on how fearful or surprised the face appeared using the same Likert

scale. Results: When rating emotional faces in the absence of any sentence frame, the 2 groups were rated the surprise and neutral faces comparably, but not the fearful faces - for these faces, patients rated them as less fearful than controls. To assess the influence of the sentence frames on context, we calculated the difference in ratings between a surprise face with, and without, a surprise frame. Patients showed non-significantly less context modulation than controls (between-group effect size = .40). Conclusion: When recognizing surprise expression in isolation, schizophrenia patients and controls showed comparable ratings. However, when surprise facial expressions were presented with different types of sentence frames, patients showed a smaller modulation (non-significant at this sample size) relative to controls. Schizophrenia patients appear to be less influenced by situational context that constrains the interpretation of facial expression. Less contextual modulation in schizophrenia suggests that patients may not benefit from situational context, or "top-down" social cues when interpreting ambiguous social stimuli, such as ambiguous facial expression.
ID: 979619

BOTTOM-UP DEFICITS IN AUDITORY PROCESSING AND SHORT-TERM AUDITORY PLASTICITY IN SCHIZOPHRENIA

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Background: Schizophrenia (SZ) patients show marked auditory processing impairments, which are linked to impaired phonological reading ability. Consistent with this correlation, tone matching deficits are also reported in developmental dyslexia, but with a specific pattern characterized by failure to form a "perceptual anchor" during fixed repetitive stimulus presentation. In this study, we evaluated SZ patients in a fixed vs. roving tone matching paradigm previously shown to be sensitive to tone matching dysfunction in dyslexia (Ahissar et al, Nat Neurosci, 2006). Methods: A two-down/one-up staircase procedure was used to determine auditory thresholds for each subject. Step size began at 40 Hz and decreased to 5 Hz. There were 2 trial types. In Fixed trials, the first tone was always 1,000 Hz and the second tone varied based upon performance. In Roving trials, the first tone was chosen at random from 250–4000 Hz and the second tone was chosen based on performance. Subjects responded with which tone in each pair was higher in pitch. Results: Both groups performed better on fixed than roving trials ($P < .0001$). SZ ($n = 32$) performed worse than controls ($n = 42$) across both tasks ($P < .004$), with no significant group X task interaction ($P = .88$). Controls improved over time in the fixed task ($P < .0001$) whereas SZ did not ($P = .77$). In contrast, neither group showed significant improvement over time in the roving condition. Both groups showed more reversals in the roving than fixed condition ($P < .0001$), but there was no significant between-group difference or group X task interaction, suggesting similar levels of task engagement. Conclusion: This is the first study to evaluate effects of using fixed vs. roving tone matching conditions in SZ. In this task, dyslexia patients show deficits only in the fixed condition but not in the roving condition. In contrast, SZ showed equivalent deficits across conditions, suggesting more global cortical impairments and auditory tone matching deficits. SZ also failed to improve over time in the fixed condition, suggesting failures in short-term neuroplasticity. Overall, these findings are consistent with prior reports of impaired early auditory processing in SZ. In addition, these findings highlight similarities as well as differences in performance between SZ and dyslexia patients, consistent with prior reports of impaired phonological processing and reading ability in SZ.
Funding: R37MH49334, P50MH086385.
ID: 979370

SCHIZOPHRENIA AND SOCIAL COGNITION ACROSS 3 WESTERN CULTURES: EFFECTS OF SOCIAL CONSTRAINT ON THE ATTRIBUTIONS OF AGENCY AND PERSON-DISPOSITION

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Background: Previous research has suggested that schizophrenia makes it difficult to discern relevant information for making judgments across a wide variety of decision-making contexts. The present study attempted to test this within a standard social cognition context, where making a proper behavioral judgment would depend on attending to relevant social constraint information. It was hypothesized that persons without schizophrenia will indicate that Agency and Person-disposition are higher under low social constraint than high social constraint, whereas persons with schizophrenia will not be affected by such information when making similar judgments. Methods: A total of 154 persons across 3 western cultures (North America, Netherlands, and United Kingdom) gave informed consent. There were 63 normal controls, 73 with schizophrenia, and 18 patient controls. Subjects read 3 health-related essays, allegedly written under low constraint (writers could write about whatever they chose, etc.) or high constraint (writers could only write what they had been instructed to write, etc.). The order of constraint information, among other factors, was random (either before or after the essay). Subjects then answered questions about Agency (eg, the degree to which the writer chose to write the essay); Person-disposition (eg, how much the personal vision of the writer was reflected in the essay); etc. The Oxford-Liverpool Schizotypy Inventory was then administered, followed by debriefing and socio-demographic assessment. Results: A series of 3 Way ANCOVAs (controlling for gender and age) examined main effects of constraint, diagnostic group, and culture, and any interaction effects on attributions of Agency and Person-disposition. As hypothesized, results showed quite consistent and significant interaction of constraint and diagnostic group, confirmed with post-hoc 2-sample *t* tests conducted within cultures, diagnostic groups, and essays. Persons without schizophrenia were more likely to be affected by constraint information than persons with schizophrenia. Conclusion: While these results appear robust across 3 different Western cultures, and 3 different essays - suggesting the presence of a neurological deficit (eg, hippocampal or thalamic-related), there is the possibility that the method was simply too complex for the schizophrenia group, thus explaining the results; evaluations of the credibility of this and other alternatives supported the major conclusion.
ID: 979455

VALIDATION OF NEUROPHYSIOLOGICAL BIOMARKERS IN SCHIZOPHRENIA: 12 MONTH STABILITY AND NEUROGENETIC CORRELATES

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Background: Endophenotypes are quantitative, laboratory-based biomarkers that are not apparent to the naked eye and are thought to represent intermediate links in the pathways between genetic variation and the clinical expression of the disorder. Mismatch negativity, P3a, P50 and N100 component amplitudes and gating measures are event-related potential (ERP) biomarkers reflecting the earliest stages of sensory information processing. These measures reflect the activation of distributed neural networks and are not prominently influenced by attentional and motivational artifacts that may confound the assessment of some higher

cognitive operations in clinical populations including schizophrenia. Methods: Subjects included 341 schizophrenia patients (SZ) and 205 nonpsychiatric comparison subjects (NCS) tested on a comprehensive neurophysiological, clinical, cognitive and functional assessment battery. Biomarker stability was assessed in a subset of 163 SZ and 58 NCS comparison subjects who underwent identical testing procedures separated by 1 year (mean = 364.57, SD = 23.83, days). A custom 1,536 SNP array was used to identify candidate genes contributing to the expression of these endophenotypes in a subset of 219 (127 SZ and 92 NCS) individuals. Results: The majority of neurocognitive and neurophysiological measures demonstrated moderate to substantial 1-year stability in both nonpsychiatric comparison subjects and schizophrenia patients with average ICCs across all measures exceeding 0.75. Indeed, 37 of 42 reliability assessments in the present study exceeded 0.60. Specifically, MMN and P3a exhibited substantial stability (ICCs > 0.87 in both SZ and NCS). P50 and N100 component amplitudes were also significantly stable (ICCs range 0.61 to 0.89 in both groups). Genetic association analyses revealed significant associations (all empirical *P*'s < .01) with several synapse-related genes, including BDNF, GRIN3A, DISC1, CTNNA2, NRG1, and ERBB4, with MMN/P3a associations being particularly strong. Conclusion: Neurophysiological measures of sensory information processing are robust, reliable, and functionally relevant endophenotypes that allow for the examination of distributed neural and genomic networks that may underlie the clinical, cognitive, and functional impairments of schizophrenia patients. Deficits in neurocognitive/neurophysiological function may be directly related to impaired synaptic integrity in schizophrenia.

Supported by MH079777, MH065571, MH042228

ID: 980007

ALTERED EMOTIONAL MODULATION OF ASSOCIATIVE MEMORY IN PATIENTS WITH FIRST EPISODE PSYCHOSIS: AN EVENT-RELATED FMRI STUDY

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Background: The medial temporal lobe (MTL) plays a central role in memory for associations. There is considerable evidence of abnormalities in MTL structure and function in psychosis, which may explain why memory for associations is one of the cognitive functions most affected in psychosis. Emotion may enhance the likelihood that information is remembered and this effect reflects the influence of the amygdala on encoding processes occurring in the MTL. However it remains unclear how emotion affects associative memory in psychosis. This event-related fMRI study attempted to identify neural correlates of the influence of emotions on associative memory in patients with first episode psychosis (FEP) and healthy controls. Methods: Eighteen FEP patients and twenty matched controls were instructed to memorize 90 pairs of standardized pictures during a scanned encoding phase. Each pair was composed of a scene and an unrelated object. Trials were either neutral, positive or negative as a function of the emotional valence of the scene. Results: At the behavioral level, controls, but not FEP patients, exhibited better performance for both emotional conditions relative to neutral trials. Between-group comparisons revealed that both groups performed equally well on neutral associations, but that FEP patients demonstrated lower performance than controls on emotional associations. Within the MTL, amygdala and entorhinal activations were elicited by emotional associations, whereas posterior parahippocampal activation was elicited by neutral associations in controls. Between-group comparisons revealed that FEP patients showed lower activity in both the amygdala and the entorhinal cortex, but similar activity in the parahippocampal gyrus relative to controls. Conclusion: This fMRI study indicates that emotional enhancement of associative memory seen in controls is related to amygdala and the entorhinal cortex activity. By contrast, FEP patients cannot benefit from such an enhancement, suggesting that emotional modulation processes are selectively altered in psychosis.

ID: 947509

PROSPECTIVE MEMORY IN PATIENTS WITH EARLY-STAGE SCHIZOPHRENIA AND THEIR UNAFFECTED FIRST-DEGREE SIBLINGS

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Background: Prospective memory (PM) is the ability to remember to carry out intended actions in the future. Besides being severely impaired in schizophrenia, PM deficit had been proposed to be a trait marker and prevalent in psychometrically-defined schizotypal personality disorder. Little is known about PM performance in unaffected first-degree siblings of patients with schizophrenia. Further evidence is therefore needed to support PM as an endophenotype for schizophrenia. Methods: This study recruited 40 patients with early-stage schizophrenia (duration of illness: 19.5 months; 93% receiving second-generation antipsychotics; mean dosage: 50.4% of BNF-recommended maximum dose), and their 46 unaffected siblings through a well-established early intervention programme for psychosis in Hong Kong, and 43 healthy subjects from nursing schools. Participants were matched in age and education. Time-based, event-based, activity-based PM, IQ, and other neurocognitive functions were assessed by computerized or standardized tools. Results: MANCOVA controlling for IQ found significant between-the-group differences in PM performances in semantic time-based (F[2,124] = 4.45; P = .015), semantic event-based (F = [2,124] = 7.06; P < .001). Planned pair-wise comparison between patients with schizophrenia and healthy subjects found significant effect size in semantic time-based (P = .015; Cohen's d = 1.06) and semantic event-based PM (P < .01; Cohen's d = 1.15). An examination of the effect size also indicated there were modest difference between unaffected siblings and healthy subjects in semantic time-based (Cohen's d = 5.7) and semantic event-based PM (Cohen's d = 5.1). Perceptual PM was intact in patients with early-stage schizophrenia. Patients with schizophrenia and healthy subjects did not differ in all other neurocognitive functions. Conclusion: Patients with early-stage schizophrenia performed worst in PM tasks, their unaffected siblings lied intermediate between the patients and healthy subjects. PM has the familial association property of an endophenotype. In early-stage schizophrenia, PM can be differentially affected while other neurocognitive functions are intact. Semantic PM task is more demanding than perceptual PM task to patients with schizophrenia, it may be related to semantic memory deficit in schizophrenia.

ID: 977285

METACOGNITION AND THEORY OF MIND AS PREDICTORS OF INSIGHT IN SCHIZOPHRENIA

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Background: Many persons with schizophrenia experience poor insight or unawareness of the symptoms and consequences of their illness. As a result they may be at risk for treatment non-adherence and a range of negative outcomes. One recent theory has suggested that poor insight in schizophrenia reflects in part deficits in metacognitive capacity, or the ability to think about thinking, both one's own and the thinking of others. Is has been suggested that with a limited ability to form complex representations of one's own thoughts and the thoughts of others, many with schizophrenia struggle to construct a coherent account of the challenges that the disorder entails. Methods: To assess the possibility that deficits in metacognitive capacity may underlie impairments in insight we gathered concurrent assessments of neurocognition using the Wisconsin Card Sorting test, Theory of Mind tests using the Hinting Test and the Bell Lysaker Emotion Recognition Test (BLERT), metacognitive capacity using the Metacognition Assessment Scale (MAS) and insight using the abbreviated Scale to Assess Unawareness of Mental Disorder (SUMD). Participants were 82 adults with a schizophrenia spectrum disorder in a post acute phase of illness living in the community. Results: Univariate correlations controlling for neurocognition revealed that better performance on the Hinting Test, BLERT and higher ratings of metacognition on the MAS were significantly correlated with better total ratings of insight on the SUMD. Higher MAS ratings were more closely linked with the awareness of symptoms component of insight. BLERT scores were most closely linked with awareness of treatment need component of insight, while performance on the Hinting Test was most closely linked with the awareness of consequences of illness component of insight. Performance on the Hinting test and the MAS captured unique portions of the variance (R^2 = .18 and .10, respectively) in total insight in a stepwise multiple regression. Conclusion: Results suggest impairments in different forms of metacognition may be linked to difficulties with differing forms of insight in persons with schizophrenia. These associations may be independent of concurrent impairments in neurocognition. Impairments in insight may reflect deficits in reflecting about mental states rather than the failure to accept a specific account of psychiatric challenges
ID: 975639

ASSESSMENTS OF SELF-REFLECTIVITY AND THEORY OF MIND: ASSOCIATIONS WITH SYMPTOMS AND FUNCTION

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Background: Research suggests that many with schizophrenia experience a range of deficits in metacognition including difficulties recognizing their own mental states and the mental of others. It is unclear to what extent deficits in the ability to detect one's own mental states vs. the mental states of others are semi-independent and whether they have unique clinical and functional correlates. Methods: To explore this issue we assessed awareness of one's own mental state using the Beck Cognitive Insight scale (BCIS) and the Mastery subscale of the Metacognition Assessment Scale (MAS) as rated from the basis of a semi structured narrative interview. Concurrently, we assessed awareness of the thoughts and feelings of others using the Bell Lysaker Emotional Recognition Scale, the Eyes Test, the Hinting Test and Picture Arrangement Subscale of the WAIS III. Positive, negative and cognitive symptoms were assessed using the Positive and Negative Syndrome Scale and Social Functioning was assessed using the Quality of Life Scale. Participants were 88 adults with schizophrenia spectrum disorders in a non-acute phase of illness. Results: Analyses were performed in 2 phases. First a principal components analysis was performed followed by a varimax rotation of all 6 metacognitive measures. Second, factor scores were correlated with assessments of symptoms and social function. Results of the factor analysis revealed 2 factors with eigen values above one. The first factor, which was composed of the 4 assessments of awareness of others mental states, accounted for 40% of the variance. The second factor, which was composed of the MAS mastery score and BSIC total, related to self-reflectivity and accounted for 17% of the variance. Univariate correlations revealed that the factor score linked with awareness of others mental states was correlated with negative and cognitive symptoms ($r = -.32$ and $-.32$ respectively; $P < .025$). The factor score linked with self reflectivity was correlated with positive and cognitive symptoms ($r = -.25$; $P < .025$ and $-.40$; $P < .001$; respectively) as well as quality and quantity of social relationships ($r = -.36$; and .38; $P < .001$; respectively). Conclusion: Results suggest that the capacity for awareness of one's own mental state may be semi-independent of the capacity for the awareness of the mental states of others and may have unique links with symptoms and function.
ID: 979546

DEFICITS IN THE ABILITY TO RECOGNIZE ONE'S OWN AFFECTS AND THOSE OF OTHERS: ASSOCIATIONS WITH NEUROCOGNITION, SYMPTOMS AND SEXUAL TRAUMA AMONG PERSONS WITH SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Research suggests that many with schizophrenia experience a range of deficits in metacognition including difficulties recognizing the emotions of others as well as their own emotions. Unclear is to what extent these metacognitive deficits are related to other features of the illness. Methods: To explore the correlates of deficits in the ability to recognize one's own emotions and those of others we concurrently assessed awareness of one's own emotions and those of others and then classified participants with a schizophrenia spectrum disorder in a non acute phase of illness as: i) unaware of their own emotions and those of others (n = 30); ii) aware of their own emotions but unaware of the emotions of others (n = 50); or iii) aware of their own emotions and aware of other's emotions (n = 17). We then compared these groups on concurrent assessments of neurocognitive function, symptoms, history of sexual trauma and diagnosis of schizophrenia vs. schizoaffective disorder. Results: ANCOVA controlling for education found that the group with impairments in both their ability to recognize their own emotions and those of other people demonstrated greater impairments in verbal memory, processing speed and executive function and higher levels of disorganization symptoms than those in the other 2 groups. The group unaware of their own emotions and unable to recognize emotions of other people had lesser levels of emotional discomfort and a lower frequency of a diagnosis of schizoaffective disorder than the other groups. The group aware of their own emotions and not those of others had a significantly higher report of childhood sexual abuse. Conclusion: Results suggest different forms of metacognitive deficits may be uniquely related to different aspects of illness in schizophrenia.
ID: 960867

THE EFFICIENT MEASUREMENT OF DIFFERENTIAL DEFICITS IN GOAL REPRESENTATION

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Background: Context processing is a form of goal representation in which the context of a cue stimulus must be represented and maintained to provide top-down support for a subsequent action. Neuroimaging studies have implicated dorsolateral prefrontal cortex (DLPFC) in context processing performance, and dopamine agonist D-Amphetamine may serve to improve this function. While context processing tasks, such as expectancy variants of the AX task, have often been used in experimental studies in schizophrenia, the current study was designed to optimize a variant of the task known as the dot pattern expectancy (DPX) task for clinical assessment and medication trials. Methods: Individuals with schizophrenia recruited from 5 different sites were compared with controls on 5 versions of the DPX task. In this task, a particular probe dot pattern was defined as a target only when it followed a valid cueing dot pattern (an A-then-X rule). The different versions systematically varied prepotency of the A-then-X trials, and the delay between the cue and the probe. An ongoing study is examining test-retest reliability of the optimized version of each measure. Results: An impairment in goal maintenance was observed across all versions (d = 1.0), however a specific deficit was in this mechanism was most evident when A-then-X trials were frequent (70% of trials) and the delay between cue and probe was short (3 seconds) (interaction d = .5). This effect eroded when the task was shortened by removing trials. Analyses of trial sequences showed that patients' failures of context processing occurred irrespective of the number of AX trials that had come beforehand, whereas the AY difficulty control condition was significantly more difficult for patients following 3 or more AX trials. Additionally, the internal consistency of the task, which has a 10 minute running time, was acceptable for clinical purposes. Retest results will also be discussed. Conclusion: A new generation of context processing tasks may allow the evaluation of this cognitive construct in a manner suitable for clinical assessment and medication trials. Specific deficits observable using this task increases the likelihood of developing a clinically useful biomarker of changes in DLPFC functioning.
ID: 976548

BRUTE FORCE ESTIMATION OF TESTS' DISCRIMINATING POWER: A SIMULATION AND INDEPENDENT COMPONENTS ANALYSIS APPROACH

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Background: NIMH's Research Domain Criteria (RDoC) initiative is predicated on our ability to distinguish deficits across various domains of cognitive functioning. However, a prominent feature of schizophrenia is a pattern of widespread impairments known as the generalized deficit. Unfortunately, tasks that measure this generalized deficit show larger or smaller effect sizes depending on the tasks' discriminating power and irrespective of their putative domain of cognitive functioning. Contrary to a large literature, we have shown discriminating power results from many interacting psychometric properties (Kang & MacDonald, 2010). Here we show how independent components analysis (ICA) within a simulation model can strengthen inferences about the domains of cognitive functioning impaired in patients, and thereby address a central challenge to the RDoC initiative. Methods: Simulations mimicked task performance on free response and binary forced-choice tasks of different length (2–100 items), difficulty (1%–99% correct), variability and internal consistency. The advantage of the simulation method was that the size of the generalized deficit and specific deficits could be assigned and varied in each case. We discovered that discriminating power changes depending on the size of the specific deficit, thereby necessitating an ICA procedure that estimates and then combines the fixed component of a task's discriminating power and its variable component. Results: Brute force estimation of a fixed level of discriminating power results in an increasingly inaccurate correction as patients become more impaired. Thus, it appeared that there was no invariant estimation of discriminating power. Estimates that combined the ICA-derived fixed and variable components of discriminating power accounted for over 96% of variability in discriminating power across both free-response and forced-choice tasks in large groups (n = 10,000). Crucially, these estimates accounted for over 83% of variability in discriminating power in small cross-validation samples (n = 40), a sample size thought to be too small for item-response theory analysis. We will also present results on cross-validation with empirical data. Conclusion: The RDoC initiative must control for the generalized deficit problem to characterize how schizophrenia differs from other mental disorders. Brute force correction for this confound is one of the tools that can facilitate this new way of thinking about psychopathology.
ID: 988038

OLFACTION AND COGNITION IN HEALTHY SUBJECTS AND SCHIZOPHRENIA: SEX MATTERS

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Background: Smell may be the ideal sensory modality to probe the links between perception, cognition and behavior. Odor stimuli have unfiltered input into the prefrontal cortex and direct access to the circuitry for behavioral motivation. Methods: We measured associations between scores of olfaction and cognition in healthy subjects and schizophrenia patients of both sexes. We tested the threshold for detecting a standard odor (STT) and used the 40-item University of Pennsylvania Smell Identification Test (SIT). Results: The means for STT and SIT were similar in all 4 groups, but their associations with specific cognitive tasks differed both between patients and controls and by sex. Less sensitivity for odor detection, ie higher STT, was related to better attention in controls, but with slower processing speed in cases. Only cases showed sex differences in the links between cognitive tasks and lower STT scores, ie greater acuity at detecting the standard odor: this was correlated with higher nonverbal intelligence in males vs. better delayed-recall and visual memory in females. SIT was generally related to better verbal comprehension in all groups, particularly in female cases and controls. Cases again showed sex effects: higher SIT was correlated with better working memory in males, but with worse working memory in females. Conclusion: The associations between olfaction and cognition we observed in schizophrenia may be disease related, or these observations may indicate more fundamental associations between cognitive domains and olfactory processes that are unmasked in schizophrenia because of abnormalities in attention and failed inhibitory processes in the disease. These olfactory data in schizophrenia are furthermore consistent with heterogeneity within the syndrome and between the sexes.
ID: 986706

THE INFLUENCE OF TARGET SALIENCE ON SPATIAL WORKING MEMORY ENCODING IN SCHIZOPHRENIC PATIENTS, UNAFFECTED RELATIVES, AND HEALTHY CONTROLS

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Background: Impairments in working memory (WM) are regarded as a core cognitive deficit in schizophrenia (SZ) and are linked to poor social functioning. WM deficits are already present during the prodromal phase, in spectrum disorders, and in unaffected relatives and therefore are discussed as a potential cognitive endophenotypic marker of the disorder. However, it is still unclear what causes these deficits and whether and how they can be ameliorated. Recent evidence indicates that WM is already compromised during the initial encoding of information. Selective attention plays a central role in the encoding of information into WM and SZ patients show deficits in top-down attention. Thus, encoding deficits in SZ may arise from reduced attentional processing. On the other hand, if this is the case, facilitating selective attention during encoding should improve WM performance in SZ patients. To test this hypothesis we developed a paradigm that manipulates orthogonally the degree of attentional selection (based on varying target salience) and spatial WM encoding (based on varying the number of locations to be memorized). Methods: Chronic SZ patients, unaffected first-degree relatives, and age-matched healthy controls participated in the salience WM task. In each trial, participants were presented with either 1 or 3 targets and asked to encode their locations into WM. The salience of the target items was manipulated by presenting either familiar (an A presented upright, low salient condition) or novel targets (an A presented upside-down, high salient condition). Thus, we manipulated the degree of top-down modulation of target selection by varying the degree of target novelty whilst keeping the basic stimulus properties physically identical. Clinical symptoms were also assessed. Results: SZ patients and the unaffected relatives performed significantly worse than healthy controls when they needed to encode either 1 or 3 locations into WM. Most interestingly, target salience as determined by target novelty improved WM performance in healthy participants. In contrast, increasing target salience had no impact on WM performance in both the SZ patients and the unaffected relatives. Conclusion: These findings seem to be consistent with the hypothesis that failures in the use of selective attention contribute to WM impairments in SZ and unaffected first-degree relatives and point to a potential remediation strategy.
This work was supported by NIH grant R01 MH073028.
ID: 977975

ABNORMAL "DEFAULT MODE" FUNCTIONAL CONNECTIVITY IN FIRST EPISODE SCHIZOPHRENIA

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Background: The exposure to pleasant and unpleasant stimuli has been shown to elicit positive or negative emotions and behaviors in healthy subjects. The abnormalities in these substrates and in the hedonic processing ability have been proposed as a marker of cerebral dysfunction in schizophrenia. Recent studies have shown that deficit associated with negative symptoms, such as anhedonia, are associated with disturb in emotions processing. The "default mode" has been defined as a baseline condition of brain function It was hypothesized that the default mode network would show abnormal activation and connectivity in patients with schizophrenia that is present not only in individuals suffering from chronic schizophrenia but from the first episode of illness. Methods: Fifteen (15) first episode (FE) schizophrenic subjects (age 15–34) participating to the study (DSM-IV-TR, APA, 2000). All subjects were outpatients of Psychiatric Department of L'Aquila, Italy. Fifteen (15) neurologically and psychiatrically healthy control subjects (matched for age and education) were included. Forty color pictures of scenes rated twenty as highly disgusting and twenty highly pleasant stimuli were obtained from the International Affective Picture System (IAPS). All subjects participated in a fMRI experiment and Images will be acquired using a General Electric 1,5T whole-body scanner at Department of Neuroradiology of L'Aquila, Italy. Independent component analysis was used to identify the default mode components. Differences in the spatial and temporal aspects of the default mode network were examined in first episode individuals vs. healthy controls Results: Healthy subjects and individuals with schizophrenia had significant spatial differences in the default mode network, most notably in the frontal, anterior cingulate, and parahippocampal gyri. In addition, in schizophrenia the medial frontal activity in patients correlated with severity of anhedonia and negatives symptoms Schizophrenics also showed significantly higher frequency fluctuations in the temporal evolution of the default mode. Conclusion: First episode schizophrenic individuals shown altered temporal frequency and spatial location of the default mode network. This network may be under- or overmodulated by key regions, including the anterior and posterior cingulate cortex. In addition, the altered temporal fluctuations in patients may result from a change in the connectivity of these regions with other brain networks.
ID: 978455

CULTURE, SOCIAL CONSTRAINT, AND SCHIZOPHRENIA IN INTERACTION: CULTURAL SIMILARITIES AND DIFFERENCES IN SOCIAL COGNITIVE JUDGMENTS OF AGENCY AND PERSON-DISPOSITION

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Background: Not much research has compared the social cognition of normal persons vs. those with schizophrenia across different Western cultures. The present study attempted to test this not only within a standard social cognition context, where making a proper behavioral judgment would depend on attending to relevant social constraint information, but within different Western culture contexts (North American, Netherlands, United Kingdom). We would hypothesize that differential social constraint effects found between schizophrenia and non-schizophrenic groups would be more apparent in the North American sample as opposed to the Netherlands and United Kingdom samples, given the greater emphasis on individualism in the former than in the latter 2 cultures. Methods: A total of 154 persons across North America, Netherlands, and United Kingdom gave informed consent to participate. There were 63 normal controls, 73 with schizophrenia, and 18 patient controls. Subjects read 3 health-related essays, allegedly written under conditions of either low or high social constraint. Subjects then answered questions relating to Agency (eg, how much control the writer had in writing the essay); Person-disposition (eg, how well one might be able to predict an essay-writer's future behavior); etc.. Additional information was gathered. Results: A series of 3 Way ANCOVAs (controlling for gender and age) examined main effects of constraint, diagnostic group, and culture, and any interaction effects on attributions of Agency and Person-disposition. While results showed that persons without schizophrenia were more likely to be affected by constraint information than persons with it, such a difference was not most pronounced in the North American sample. We did find 1 significant constraint, diagnostic group, and culture interaction relating to essay 2 Agency, but the culture that distinguished itself

was the United Kingdom, not North America. Two other relevant interactions were trends, 1 for essay 3 Agency, and 1 for essay 1, Person-disposition, but not quite in the predicted direction. Conclusion: While it appears that Culture exerts some effects in interaction with constraint and diagnostic group, such effects do not appear to conform to a pattern. While clearly the fact that all of the cultures are Western, and thus that fact alone may well explain the negligible effects of such a factor, the interaction effects that emerged are worthy of explanation.
ID: 980050

FUNCTIONAL DISABILITY IS PREDICTED BY DEGREE OF MOTIVATION AND THEORY OF MIND IN REMITTED SCHIZOPHRENIA PATIENTS

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Background: Enhancing functional ability in schizophrenia assumes prominence after the control of active symptoms. Factors determining functional disability in the remission phase of schizophrenia are poorly studied. We examined a comprehensive set of factors determining functional disability including social cognition, neurocognition, IQ, negative symptoms, motivation and insight. Methods: 172 schizophrenia patients meeting criteria for remission (Andreasen et al, 2005) were recruited. They were assessed using Social Cognition Rating Tool in Indian Setting [SOCRATIS- which included tests on theory of mind (ToM), emotion recognition, social perception & attributional styles], measures of neurocognition (speed of processing, verbal & visual learning and memory), Bhatia's battery of performance IQ, degree of motivation sub-scale of the Quality of Life Scale, Positive & Negative Syndrome Scale and insight (awareness) using the Scale to Assess Unawareness of Mental Disorder. A blind rater interviewed reliable caregivers using the Groningen Social Disabilities Schedule (GSDS) to assess patients' functionality in the past 1 month. Results: The table shows univariate comparison between disabled (mean GSDS $\geq$1) and non-disabled patients. Predictors significant at $P < .01$ were entered in logistic regression with disability status as the dependent variable. The model was significant at $P < .001$. A combination of degree of motivation and 2nd order ToM index could classify 73.3% (95% CI = 64.6–81.9) of subjects correctly with 70.2% sensitivity and 74.8% specificity. Conclusion: In the remitted phase of schizophrenia, motivation and ToM abilities are associated with functional disability. Assuming a causal relationship, these may be targets for interventions to improve functionality in schizophrenia.

Variable	Not disabled# (n = 103)	Disabled# (n = 69)	t	Effect Size
First Order ToM Index	0.9 (0.15)	0.81 (.24)	2.9**	**0.43**
Second Order ToM Index	0.53 (0.32)	0.32 (0.28)	4.3**	**0.70**
Faux Pas Composite Index	0.61 (0.21)	0.59 (0.21)	0.4	0.1
Social Perception Index	0.74 (0.12)	0.69 (0.12)	2.3*	0.42
Emotion Recognition Index	0.66 (0.13)	0.63 (0.13)	1.3	0.23
Externalizing Bias	2.73 (4.5)	2 (3.9)	1	0.17
Personalizing Bias	0.8 (0.29)	0.69 (0.35)	2.2*	0.34
Auditory Verbal Learning Test Total score	43 (11.06)	41.4 (9.7)	0.9	0.15
Complex Figure Test Delayed recall	15.5 (8.5)	12.8 (7.5)	2.1*	0.33
Motivation	4.36 (1.09)	3.33(1.12)	6**	**0.93**
PANSS Negative symptoms	10.51 (4.3)	12.52 (5.3)	−2.7**	**0.42**
Insight (awareness)	10.14 (2.3)	11.26 (2.6)	−2.9**	**0.45**
Intelligence Quotient	83.06 (14.1)	78.98 (11.1)	2.01*	0.32

Table. Continued

#Mean (SD), *$P < .05$, **$P < .01$
ID: 978233

HIPPOCAMPAL-DEPENDENT MEMORY IN TREATED AND UNTREATED SCHIZOPHRENIA

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Background: Though the relationship between cognitive dysfunction and reality distortion remains biologically unspecified in schizophrenia (SZ), in healthy persons it is widely acknowledged that hippocampus (hipp) is specialized for critically sorting percepts so that they can be related and called upon in novel contexts to support integrated knowledge of the world and self. Insofar as disruptions of medial temporal lobe (MTL) function may occur in SZ, giving rise to disintegrated knowledge, it is reasonable to hypothesize that in vivo assessment of hipp activity, as elicited by tasks that fractionate hipp-dependent cognition, will reveal focal alterations relevant to pathophysiology of either or both dimensions of the disease. Methods: Because anti-psychotic drugs (APDs) attenuate elevations in basal rCBF in MTL in SZ, we segregate data collected from volunteers who are treated (SV-ON) from those untreated (SV-OFF) with APDs, with an aim to delimit disease from medication effects. To this end, we engage SZ cohorts in tasks known to recruit hippocampal-based memory in healthy populations, specifically probing sensitivity to: (1) novel vs. familiar stimuli (Novelty Detection task); (2) associative vs. conjunctive memory formation (Acquired Equivalence and Conjunctive Memory tasks); and (3) identical vs. mismatched samples of temporally-constituted stimuli (Quartet task). Results: Novelty-Detection: Post-scan memory tests revealed that SV-OFF encoded significantly fewer images than both SV-ON and healthy volunteers (NV). NV (N = 18) correctly identified 47% of the scenes as "previously seen" with 20% false alarm rate (d' = 89%). SV-ON (N = 17) IDed 34% with false alarm rate of 18% (d' = 67%); SV-OFF (N = 7) IDed 27% with a 16% false alarm rate (d' = of 47%). Acquired Equivalence: 1-sample t tests showed that generalization accuracy, as opposed to memory accuracy for trained associations, was significantly above chance for both NV (N = 20) and SV-ON (N = 40) [NV, $t(19) = 10.47$, $P = .001$; SV-ON, $t(38) = 4.35$, $P = .001$] but not for SV-OFF (t = 1.0), despite SV-OFF having intact learning. Repeated measures ANOVA revealed a main effect of group [$F(1,71) = 5.53$, $P = .01$], a main effect of trial type ["generalized" vs. "trained" $F(1,71) = 36.15$, $P = .001$], and a group x trial type interaction [$F(2,710) = 4.676$, $P = .01$]. Conclusion: Results from fMRI-

BOLD paradigms with high spatial resolution are forthcoming. Behavioral analyses, summarized above by task, point to broad impairment in SZ, but selective memory deficits in SV-OFF.
ID: 988345

BRAIN FUNCTION IN SCHIZOPHRENIA: THE MIND'S EYE AND STRING THEORY

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Background: A central issue in the research on schizophrenia has been the role of brain abnormalities that appear to underlie processes leading to schizophrenic symptoms. This is central to the dominant neuro-scientific paradigm of localized hemispheric functioning. This study reviews the evolution of models of brain function in the study of schizophrenia including the lateralization models, a homeostatic model and the application of an adaption of string theory to describe functional and dysfunctional processes in the brain of people with schizophrenia. The special case of fMRI studies of covert imaging in creativity and schizophrenia is used to demonstrate the value of this approach to brain function. Methods: The primary method used is a literature review encompassing: 1. Studies of brain dysfunctions and functioning areas in people with schizophrenia 2. More recent fMRI studies of covert imaging in auditory and visual motor systems 3. Models of the ''Mind's eye'' in schizophrenia and creativity 4. Research exploring string theory to brain function and schizophrenia Results: The initial literature reviews have shown that modern fMRI technology does provide means to assess covert imaging both in creativity and in people with schizophrenia. These studies identify networks involving Frontal Temporal, Cerebellar and Limbic systems. The results of the studies are compared and contrasted. Conclusion: Conclusions: 1. There is considerable evidence from more sophisticated studies using fMRI that people with schizophrenia use the same covert imaging systems that are used by people in creative imaging and meditation. However, the nature of their brain function often leaves them in a closed loop state where voices, thoughts or images are recycled and cannot be terminated easily. 2. The localized brain model needs to be replaced by models which utilize plasticity and multiple networking concepts The applications of string theory and understanding the role of covert imaging ie the Mind's eye in schizophrenia research warrant future research and empirical validation
ID: 979750

PROBABILISTIC REINFORCEMENT LEARNING IN INDIVIDUALS AT RISK FOR PSYCHOSIS

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Background: At the group level, patients in the early stages of psychosis have subtle deficits in trial-and-error learning, though these deficits are sometimes only apparent in large sample sizes and are not present in all patients. We aimed to examine whether these deficits were apparent prior to the onset of psychotic illness. Methods: The study setting was the 1986 Northern Finland Birth Cohort (n = 9332), focusing on individuals at increased risk for psychosis due to a family history or clinical features. We identified a Family Risk group (n = 72) composed of cohort members with a family history of psychosis in a 1st degree relative and a Clinical Risk group composed of cohort members who met prodromal criteria on the Structured Interview for Prodromal Symptoms (n = 33). These subjects, along with a control group (n = 108), undertook a probabilistic reinforcement learning task with a financial reward. We hypothesized that there would be subtle learning deficits in both the at-risk groups. Results: All groups (Family Risk, Clinical Risk, and Controls) successfully learned to preferentially select the stimulus with the highest chance of reward and avoid the stimulus with the highest chance of punishment ($P < .05$). There were no differences between groups on choice behavior. Conclusion: Patients at risk for psychosis due to a history of mild psychotic symptoms or a parent with psychosis show good performance on probabilistic trial and error reward and punishment learning. Future follow-up of these individuals will examine whether probabilistic reinforcement learning is useful in predicting the conversion to psychosis in at-risk groups.
ID: 977517

IMPAIRED PREFRONTAL FUNCTIONING AS A MARKER OF PSYCHOSIS RISK STATE

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Background: Dorsolateral prefrontal cortex (DLPFC) structural abnormalities may pre-date and predict psychosis onset, yet it is unclear how functional deficits manifest and effect functioning prior to onset. A computerized cognitive control measure (AXCPT) was used in 3 samples including clinical-high-risk for psychosis (CHR), first-episode schizophrenia (SZ), early psychosis (EP), help-seeking psychiatric controls (PC), and healthy control (HC) participants. We hypothesized CHRs would show deficits on the AXCPT relative to HCs, in a manner that is similar to individuals in the early stages of psychosis (EP, SZ). Methods: Study 1: CHR (n = 119), EP (n = 21), and PC (n = 28) participants from 6 Early Detection Intervention for the Prevention of Psychosis Program (EDIPPP) sites completed the AXCPT. Study 2: Demographically-matched CHR (n = 25), SZ (n = 25) and HC (n = 25) individuals from the UC Davis Early Detection and Preventive Treatment (EDAPT) clinic performed the AXCPT during fMRI. Long-term clinical follow-up (26.78 ± 11.60 months) was completed on a subset of CHR (n = 23) individuals with AXCPT behavioral data to examine effects clinical outcome. Results: Study 1: EPs demonstrated a specific deficit in cognitive control compared with PCs and CHRs. CHRs showed an intermediate deficit between EP and PC participants. Study 2: When compared with HCs, CHRs demonstrated reduced cue-related DLPFC activation that was correlated with poorer performance and global functioning. Impaired cognitive control at baseline was not observed in individuals whose symptoms remitted over follow-up. Conversion to psychosis or persistent attenuated symptoms were associated with impaired cognitive control at baseline. Conclusion: Individuals experiencing less than 30 days of psychosis show cognitive control deficits similar to those seen in SZ, demonstrating that cognitive impairment appears early in the development of psychotic illness. CHR individuals show cognitive control impairment and reduced DLPFC activation, compared with controls, that is associated with poor global functioning. Impaired cognitive control at baseline is associated with worsening or persistence of symptoms, suggesting that this may be a specific marker for the psychosis risk state. Findings support early intervention strategies targeting cognition. Additional clinical and functional outcome data will be presented.
ID: 979739

MULTI-SITE FMRI STUDY OF COGNITIVE CONTROL-RELATED BRAIN ACTIVATION IN EARLY SCHIZOPHRENIA AND CLINICAL-HIGH-RISK YOUTH

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Background: Impairment in cognitive control has been consistently demonstrated in individuals with schizophrenia at all stages of the illness, and is associated with decreased activation of a prefrontally-mediated cognitive control network. However, it is unclear how such functional deficits emerge prior to illness onset. A modified AXCPT was used as part of a cross-site fMRI study of clinical-high-risk for psychosis (CHR), early psychosis (EP) and healthy control (HC) participants. We hypothesized that EPs and CHRs would show impaired cognitive control along with reductions in prefrontal activation relative to HCs. Methods: EP (n = 28), CHR (n = 21) and HC (n = 37) participants from the UC Davis Imaging Research Center, UCSF Brain Imaging and EEG Laboratory, University of Michigan Psychiatry Affective Neuroimaging Laboratory were identified using the Structured Interview for Prodromal Syndromes (SIPS) and Structured Clinical Interview for DSM-IV (SCID-I/P). Participants performed the modified AX-CPT, a computerized measure of cognitive control, during fMRI scanning. Results: Behavioral and imaging findings were consistent across sites. EP participants demonstrated a specific pattern of performance indicative of impaired cognitive control on the AXCPT and reduced cognitive control-related activation of the prefrontal cortex when compared with controls. Although their behavioral performance did not differ significantly from HCs, CHR individuals demonstrated a pattern of brain activation that was similar to EPs, with reduced activation in prefrontal and other areas of the cognitive control network. Conclusion: Convergence of findings across sites supports the feasibility of collaborative multisite fMRI studies, which are necessary to generate the large data sets needed to understand the cognitive and neural mechanisms underlying risk for psychosis and the transition from risk state to illness. Results provide robust evidence that prefrontal cognitive control mechanisms are disrupted in the early stages of psychosis and may serve as markers of risk. The greater sensitivity of fMRI vs. behavioral measures to CHR status also points to the value of obtaining imaging data in high risk studies. Additional analyses in an enlarged sample will examine the relationships between behavior, brain activity, and clinical and functional outcome in CHR and EP individuals.
ID: 979599

A RANDOMISED CLINICAL TRIAL OF COMPUTER-ASSISTED COGNITIVE TRAINING PLUS A PSYCHOSOCIAL TREATMENT PROGRAMME VS. A PSYCHOSOCIAL TREATMENT PROGRAMME FOR FIRST-EPISODE SCHIZOPHRENIA PATIENTS

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Background: A Randomised Clinical Trial of Computer-Assisted Cognitive Training plus a Psychosocial Treatment Programme vs. a Psychosocial Treatment Programme for First-Episode Schizophrenia Patients Methods: One-hundred and seventeen patients with first episode schizophrenia spectrum disorders were assessed on cognitive and daily functioning and randomly assigned to either 38 sessions of CT plus psychosocial treatments vs. 38 psychosocial treatments alone. The CT program was based on scaffolding and errorless learning and divided into modules of attention, memory, and executive functioning. Computerized exercises as well as daily tasks were conducted, and competence dialogues built a bridge to everyday life of patients. Examinations were carried to at baseline, post training (after 4 months) and at 10-month follow-up. Intention- to- treat analyses were carried out, and repeated measurements in mixed model with unstructured variance was applied. Outcomes were everyday skills capacity (UPSA-B), neuropsychological tests, self-esteem (Rosenberg SES), association with the labor market, and PANSS symptom severity. Results: CT significantly improved Rosenbergs Self Esteem 1.96 (0.6–3.3) and Panss general score −2.2 (−4.7 to −0.3)post training. At 10-month follow-up the-CT-group significantly differed from control group with regard to Panss positive scale −1.3 (−2.6 to 0.8), Compt 2.3 (0.0–4.6), WMT 3.6 (0.9–6.3) LNS 1.3 (0.3–2.4), HVLTR 2.1 (0.48–3.65) and Trail making B (−5.89 (−12 to 7–0)). Panss negative symptoms were not influenced Conclusion: CT did improve cognition in several areas and psychotic and general symptoms and self esteem in first episode schizophrenia
ID: 979216

VISUOSPATIAL WORKING MEMORY; THE INSIDE STORY

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Background: Working memory(WM) deficit is a core feature of schizophrenia but the origins of WM deficit are not yet clearly understood. It is commonly assumed that manipulation of mental representation plays a more important role than maintenance of information in WM deficit but very little empirical research has been conducted to examine these 2 components separately. Manipulation can be studied systematically by utilizing cognitive paradigms designed to parse visuospatial imagery. Although imagery and WM share common mechanisms and recruit overlapping neural circuits, visuospatial imagery has not been extensively studied in schizophrenia. We investigated the role of imagery processes in spatial WM in order to clarify the potential contributions of maintenance and manipulation of mental representation in WM. Methods: In a series of experiments, we tested visuospatial imagery generation, inspection and manipulation of shapes, objects, trajectories and social stimuli in schizophrenia patients and demographically matched healthy participants. Accuracy and response times were measured. A spatial delayed-response task was used to assess WM. Clinical symptoms and subjective ratings of the vividness of imagery were also assessed. Results: We found no evidence of impaired manipulation in schizophrenia. Although schizophrenic patients showed persistent spatial WM deficits, they had intact or enhanced visuospatial imagery compared with healthy participants. On a subset of imagery manipulation tasks, schizophrenia patients showed superior performance, as indicated by their faster response times and/or greater accuracy compared with healthy controls. Moreover, in healthy subjects, WM and imagery performances were positively correlated but in the patients, they were unrelated. The subjective ratings of vividness of imagery did not contribute to the imagery or WM task performances. Conclusion: The puzzling discrepancy between enhanced visuospatial imagery and impaired WM in schizophrenia needs to be further examined. Our data suggest that schizophrenia patients are able to manipulate internal representations in spite of their WM deficit. This pattern of behavior may indicate a functional disconnection between frontal and parietal areas. These results suggest that the mental landscape of persons with schizophrenia may be far from impoverished or limited, a finding at odds with the current view of reduced WM capacity in schizo-

phrenia, and hint at the possibility of utilizing imagery in cognitive remediation.
ID: 975361

ROLE OF NNOS IN HIPPOCAMPAL NEURITE OUTGROWTH AND SYNAPTOGENESIS FOLLOWING INHIBITION OF PDE9 BUT NOT PDE2

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Background: Activation of the calcium (Ca^{2+})/nitric-oxide (NO)/cyclic GMP (cGMP) pathway increases hippocampal synaptic plasticity which is involved in learning and memory. Hence, elevation of cyclic GMP (cGMP) levels by inhibiting the activity of the phosphodiesterases (PDEs) has been proposed as a novel strategy for the treatment of the cognitive deficits associated with schizophrenia and Alzheimer's disease (Reneerkens et al., Psychopharm, 2009). Particularly, selective inhibitors of the type 2 and 9 PDEs restore cognitive dysfunction in preclinical animal models (Boess et al., Neuropharm, 2004 and Van der Staay et al., Neuropharm, 2008). The aim of this study was to investigate the effect of selective inhibitors of PDE9 and PDE2 on neurite outgrowth and synaptogenesis and to determine the role of Ca^{2+}/NO/cGMP/cAMP-responsive element binding protein (CREB) pathway in rat hippocampal neurons. Methods: The study was carried out using a specific inhibitor of neuronal nitric-oxide synthase (nNOS), 7-nitro-indazole (7-NI) in combination with selective PDE9 and PDE2 inhibitors, PF-4447943 and Bayer 60–7550, respectively. Results: At 6 days in vitro, 55% and 80% of hippocampal neuronal cultures contained PDE9 and PDE2-labeled neurons respectively. Furthermore, 78% of PDE9 and 87% PDE2 neurons were also positive for nNOS. In this model, both the PDE9 and PDE2 inhibitors (100 nM and 10 nM, respectively) significantly increased cGMP levels, promoted neurite outgrowth (15% increase, P-value $< .01$) and synapsin-1 levels (15% increase, P-value $< .01$). In addition, the PDE9 and PDE2 inhibitors enhanced CREB phosphorylation at the same concentrations that increased neurite outhrowth and synapsin-1 levels. The combination with 7-NI completely blocked the effects of PDE9 inhibition in promoting neurite outgrowth, synaptogenesis, and CREB phosphorylation but did not affect the neurite outgrowth or synaptogenesis, produced by inhibition of PDE2. Conclusion: To summarize, this study revealed an essential role of nNOS in the promotion of hippocampal neurite outgrowth and synaptogenesis following inhibition of PDE9 but not PDE2.
ID: 975873

AFFECTIVE BIOLOGICAL MOTION RECOGNITION IN SCHIZOPHRENIA

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Background: Individuals with schizophrenia (SZ) consistently show impairment of facial emotion recognition, but underlying mechanisms that give rise to this difficulty have not been elucidated. Given the findings of abnormalities in the fusiform face area and deficits of visual information processing in SZ, it is possible that these patients may have a perceptual difficulty in extracting appropriate affective cues from visual stimuli. We thus investigated the potential perceptual underpinnings of this emotion recognition deficit. The human face and body are rich sources of social and emotional cues, but only the face stimuli have been used to examine emotion processing in SZ. Past studies have found that healthy individuals can accurately detect social information such as personality traits, gender, and affect from sparse, point-light displays that depict humans in motion (ie biological motion). Yet very little data exist on the role of biological motion perception in affect recognition in SZ. In the present study, we examined the ability to detect social cues from gait patterns presented by computer-generated volumetric walking figures. We hypothesized that SZ patients would show deficits in extracting affective cues from biological motion and that this difficulty might be associated with social deficits. Methods: Outpatients with SZ and demographically matched healthy controls (CO) viewed 1-second video clips of a "digital" walker in motion. In the Affect condition they were asked to decide whether the walker is angry or happy in a forced-choice task. In the Gender condition, they were asked to judge whether the walker is a male or a female. For each category (eg Happy, Female), there were 3 levels of intensity. A previous study validated the stimuli on their intended affect and traits. Overall accuracy, sensitivity (d') and bias were measured. Clinical symptoms (SAPS, SANS) and social functioning (SFS), mood (PANAS) and the Theory of Mind (Eyes Test) were also assessed. Results: SZ patients were less accurate and less sensitive than CO for both Affect and Gender conditions. Neither group differed in their response bias to the stimuli in either condition. Conclusion: These results suggest that SZ patients are impaired in extracting social information from biological stimuli and that this deficit may cascade into misinterpretation of social signals in the real world. Supported in part by NARSAD and R01 MH073028.
ID: 979451

FMRI OF GENETIC LIABILITY TO SCHIZOPHRENIA: REGIONAL ACTIVITY AND CONNECTIVITY DIFFERENCE PERSPECTIVES

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Background: Traditionally, fMRI analyses of patients' family members have employed the general linear model (GLM) to examine clusters of activation in the brain, which provides a region-by-region examination of brain activity. This study additionally examined a newer group independent component analysis (ICA) to test the hypothesis that the unexpressed genetic liability to schizophrenia is reflected in the functional connectivity between brain regions during a context processing task, the expectancy AX task. Methods: We compared 20 schizophrenia patients and 32 first-degree relatives to 22 controls and 28 control relatives. The subjects completed the expectancy AX task, a context processing measure, while being scanned in a 1.5T MR scanner. We then performed a group ICA on all participants' fMRI data using Group ICA of fMRI Toolbox (GIFT, see http://icatb.sourceforge.net) in order to examine the functional networks that are active during the AX task. Task-related components were identified and compared between groups based on how much functional activity they explained. Next, a GLM analysis was performed. Each trial type in the AX task was used as a regressor in this model. Groups' mean activations were contrasted with each other to obtain differential activation. Results: Both schizophrenia patients and their relatives performed worse than control subjects and their relatives on the expectancy AX task. The group ICA showed significantly different activations between patient probands and control probands in a network constituting dorsolateral prefrontal cortex and posterior parietal lobe. The relative groups differed in an anterior cingulate network. The GLM analysis showed differential functioning between patient and control relatives in the dorsolateral prefrontal cortex, but failed to show any differences between patient and control probands. Conclusion: The results of the ICA were areas that have been associated with cognitive control and conflict-monitoring. These findings suggest group ICA may be sensitive to deficits associated with the unexpressed genetic liability as well as the manifestation of schizophrenia. Additionally,

the GLM analysis found differential functioning in relatives but not in probands. These disparate findings suggest some potential advantages to functional connectivity relative to region-by-region approaches to understanding the neural basis of genetic liability to schizophrenia.
ID: 979883

PLANNING AND WORKING MEMORY IN PATIENTS WITH BIPOLAR DISORDER DURING EUTHYMIC PERIODS

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Background: Neurocognitive impairments have been identified in psychotic patients, including bipolar patients, but it is unclear whether impairment persists during euthymic periods. Several studies have reported that bipolar patients have alterations in executive functions during euthymia. The aim of this study was to identify neuropsychological deficits in planning and working memory in bipolar euthymic patients, comparing patients with Bipolar Disorder (BD) I and II, with or without previous history of psychosis. Patients will be compared with healthy controls. Methods: 145 patients with BD diagnosis in euthymia for at least the 3 previous months and 116 healthy controls between the ages of 18 and 65 were evaluated. Tests used were Tower of Hanoi and Digit Span from the WAIS-III, comparing also clinical and socio-demographical data. Results: Bipolar patients had significantly worse performance on both tasks in comparison to healthy controls. Results were also influenced by some clinical and demographical variables. There were no significant differences between BD I and II patients, or those with or without psychosis, with the exception of a high number of errors in the Tower of Hanoi performance in BD-I. Longer duration of bipolar illness correlated positively with neuropsychological impairment. Education, intellectual quotient, occupational situation, age and cigarrete smoking were the socio-demographical variables mainly influencing the performance of both tests, especially in BD I. Conclusion: Our results suggest that BD patients even in the euthymic phase show alterations in executive functions, particularly poorer planning and problem solving, and reduced performance in working memory. BD I is more impaired than BD II consistent with the literature. Neuropsychological deficits were associated with the length of bipolar illness and with socio-demographical variables. Thus, at least subtle neuropsychological impairments are a core feature of BD I.
ID: 986838

EARLY EMERGENCE OF REVERSAL LEARNING IMPAIRMENTS IN ISOLATION-REARED RATS

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Background: Understanding the trajectory of behavioral and anatomical abnormalities relevant to the schizophrenia prodrome and their sensitivity to interventions in animal models will be critical to identifying potentially prophylactic therapeutic strategies. Isolation rearing (IR) of rats is an environmental perturbation that deprives rodents of social contact from weaning through adulthood. IR produces behavioral and neuronal abnormalities that mirror some pathophysiology associated with schizophrenia, including abnormalities in the frontal cortex. In the current set of studies we examined the ontogeny of behavioral impairments in reversal learning in IR rats and whether these impairments relate to alterations in IL-6 mRNA expression in the frontal cortex. Methods: Separate groups of social and IR male Sprague Dawley rats were tested in a reversal learning digging task at 2 and 8 weeks post-weaning, then an additional group was tested at ~22 weeks post-weaning. The task consisted of 2 stimuli discrimination phases in which 1 stimulus identified the location of a food reward, followed by a reversal phase in which the stimuli prediction of food was reversed. Spontaneous exploration of the rats was measured in novel environment, and levels of IL-6 mRNA in the frontal cortex and hippocampus were measured using quantitative real time PCR. Results: IR rats displayed impaired reversal learning at the 2-, 8-week, and 22-week post weaning time points. These data suggest a deleterious and enduring effect of prolonged isolation rearing on reversal learning. Amount of locomotor activity was inversely correlated with trials to criterion during the reversal stage in social rats but not in isolation-reared rats, indicating that different factors contributed to the performance across the 2 groups. No differences in IL-6 mRNA levels were observed, however. Follow-up analyses are being conducted to determine markers that may contribute to impaired reversal learning as a consequence of social isolation. Conclusion: These data corroborate previous studies demonstrating reversal learning deficits in isolation-reared rats and suggest that these deficits a) emerge early in the course of isolation and b) remain consistent during prolonged periods of isolation. Hence, isolation rearing of rats may offer a unique model to examine the ontogeny of behavioral and neurobiological alterations which may be relevant to preclinical models of prodromal psychosis and cognitive deficiency associated with schizophrenia.
ID: 981119

MOCA: A SCREENING INSTRUMENT FOR THE ASSESSMENT OF COGNITION IN SCHIZOPHRENIA

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Background: Cognitive deficits are a distinct dimension of schizophrenia and have been shown to correlate with prognosis and functional disability. To date there are no validated brief screening instruments for the diagnosis and assessment of severity of schizophrenia cognitive deficits. In this study, we compared the Montreal Cognitive Assessment (MoCA), a clinician friendly, validated, brief instrument for the detection of mild cognitive impairment (MCI) with the Mini-Mental State Examination (MMSE) as a screening exam for cognitive deficits in schizophrenia. For a subsample of patients we have also conducted a study comparing the clinical utility and psychometric validity of the MOCA with a wide-ranging battery of commonly applied neurocognitive assessment instruments. Methods: All patients (N = 30) underwent the following assessments: MOCA, MMSE and PANSS. A subgroup (N = 13) also underwent a comprehensive neuropsychological assessment including attention, short term and working memory, as well as executive function testing. Results: The mean MoCA score was 20+/−4.7, consistent with moderate to severe cognitive impairment. In contrast, the mean MMSE score was 27.2+/−2, which is within the normal to mild MCI cognition score range. Twenty-one patients (84%) of those who scored >or = 26 (normal range) on the MMSE had a MoCA score <26 (MCI range). Twenty-three (85%) of those who scored >or = 24 on the MMSE (MCI range) had a MoCA score <24 (moderate to severe cognitive impairment). MOCA scores did not significantly correlate with PANSS total or general, positive and negative symptoms subscores. Preliminary analyses indicate that the MOCA shows a pattern of significant correlations with several measures of executive function (eg Reversed Verbal RT, Visuo-spatial Sequencing Test, Maze Solving, and Card Sorting Test) as well as with the Symbol-Digit Substitution (a test of speeded attention). Conclusion: The MoCA is an easy to administer, useful screening tool for the assessment of cognitive deficits associated with schizophrenia.

Our sample MOCA scores did not correlate with any of the PANSS scores, supporting the view that cognitive deficits might be an independent schizophrenia symptoms domain. Our preliminary results also suggest that the MOCA might be a sensitive test for the assessment of some of the core cognitive deficits in schizophrenia such as speeded attention and executive functioning. Further studies validating MoCA against standard neurocognitive testing batteries (eg, MATRICS) are recommended.
ID: 988160

EFFECTS OF CANNABIS DEPENDENCE ON COGNITIVE FUNCTIONING IN MALES WITH SCHIZOPHRENIA

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Background: A history of cannabis use/misuse is more common in schizophrenia than in the general population. Given that cognitive impairment is universally recognized as a core feature of schizophrenia, it is essential to understand cannabis' effects on neuropsychological functioning in this population. Methods: We examined cognition and symptomatology in schizophrenia as a function of cannabis use patterns by comparing neurocognition in patients with current cannabis dependence (CD), patients who were formally dependent (FD; no use in past 6 months) and those who have never met for a cannabis use disorder (ND; > 5 cannabis cigarettes used lifetime). Thirty (N = 30) stable male outpatients with diagnoses of schizophrenia with current cannabis dependence (n = 12), historical cannabis dependence (n = 14), and no history of cannabis use (n = 4) were recruited. All participants will complete a comprehensive neurocognitive battery which will include tests of attention (CPT and STROOP), verbal learning (CVLT-II), working memory (VSWM, DS), decision-making (Delay Discounting and IGT), speed of processing (TMT-A, pegboard) and executive functioning (WCST and TMT-B). The PANSS and BDI-II were also administered to assess psychiatric symptoms. Results: The sample consists of 16 Caucasians, 5 African Americans, 4 Asians and 5 men of other racial backgrounds. The mean age of the sample is 34.9 (10.1), having completed an average of 12.3 (2.5) years of education and an FSIQ of 95.1 (9.1). In our preliminary analysis, ND demonstrated the poorest performance in selective, sustained and divided attention, and executive functioning, while CD and FD performed similarly on these tasks. There were no group differences between CD, FD and ND groups on visuo- spatial memory, decision-making and impulsivity tasks, nor in psychotic or depressive symptoms scores. Conclusion: Our preliminary findings suggest enhanced cognition in specific domains with cannabis use in schizophrenia. Cannabis-users may represent a higher functioning sub-population of schizophrenia; possessing better cognitive function, pre-morbid adjustment, social skills and prognosis. Alternatively, exogenous cannabinoids may moderate the endocannabinoid system which serves to regulate neuronal circuits and pathways involved in neurocognition. We plan to recruit 20 subjects per group by study completion.
ID: 971075

REMEMBERING TO KNOW: DUAL PROCESS SIGNAL DETECTION (DPSD) ANALYSIS OF RECOLLECTION AND FAMILIARITY IN SCHIZOPHRENIA

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Background: Recognition memory can be supported by either assessments of the familiarity (F) of studied items, or by recollection (R) of contextual details associated with the study event. For example, when you see a person on the street you can have a sense that you met them before but be unable to retrieve the context or details of your meeting (a familiarity based memory), or you can vividly retrieve where you met them, who they are, and what you last talked about (a recollection based memory). It has yet to be established whether patients with schizophrenia have more prominent familiarity or recollection deficits. Answering this question may inform pathophysiology and treatment development as these 2 processes can be anatomically dissociated within the prefrontal and medial temporal lobe using fMRI. Methods: This quantitative review identified 20 studies that used remember/know (R/K) or source retrieval paradigms to address this question. A dual process signal detection (DPSD) analysis of reported study results was used to generate quantitative F and R parameter estimates. We also performed DPSD analysis of our own preliminary data from 3 memory studies. Results: Although many previous R/K studies concluded that patients had primary recollection deficits, the DPSD analysis revealed deficits in both R and F. Consistent R and F deficits were also observed in our own data. Conclusion: These results suggest that memory impairments in individuals with schizophrenia are secondary to difficulties retrieving contextual details of the encoding event and to problems using a subjective sense of familiarity to guide signal detection processes. Further, our findings imply that these memory deficits in patients with schizophrenia are not solely due to hippocampal dysfunction, and could also be explained by dysfunction in prefrontal or other cortical brain regions. Combined fMRI and DPSD modeling is clearly warranted to better establish these functional and anatomical correlates.
ID: 978102

MEMORY OF ITEMS AND THEIR RELATIONS: THE RISE TASK

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Background: Individuals with schizophrenia may be impaired remembering relationships amongst items (relational memory) even when memory for item features (item-specific memory) is intact. Item-specific and relational memory were defined by CNTRICS as episodic memory constructs most ready for translation, with the prediction that a differential relational memory deficit would refute a model of generalized memory impairment. The Relational and Item Specific Encoding (RISE) task was created to address this goal by: 1) developing item-specific and relational tasks equated for difficulty, and 2) developing parallel forms to allow repeated testing. Methods: The RISE employs visual objects. During encoding, participants make item (living/non-living?) or relational judgments (does 1 of 2 items fit inside the other?). This is followed by item recognition (is the item old or new) and relational recognition tasks (is the pair of items intact or re-arranged). In Study 1, 3 parallel forms were administered to patients and controls to establish construct validity, internal consistency, and equivalent forms. Study 2 assessed patients and controls on a revised task using word stimuli. Study 3 administered the task at 3 time points to investigate test-retest reliability. Results: Study 1 revealed equivalent difficulty of item and relational encoding conditions, high internal consistency, and equivalent forms. We also found predicted task by group interactions, with greater patient impairments in item recognition following relational vs. item encoding. However, difficulty of the associative recognition and item recognition tasks was not matched, and item recognition in controls was close to ceiling. Study 2 revealed that replacing visual objects with word stimuli did not improve psychometric characteristics and reduced task comprehension, encouraging use of visual object stimuli. Study 3 is in progress, and test-retest results will be complete by the time of presentation. Conclusion: Initial psychometric

data indicate that the RISE is a promising measure of item recognition that can reveal differential patient impairments in relational vs. item-specific encoding. The greater difficulty of the associative recognition task suggests caution when making claims about differential deficits in item vs. associative retrieval, but encourages use of the associative recognition task as a stand-alone measure.
ID: 963525

A NEW COGNITIVE MODEL OF DELUSIONS

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Background: This paper proposes a new cognitive model to explain the etiology of delusions irrespective of diagnosis and/or phenomenology. The model hypothesizes the influence of 2 processes in the formation and maintenance of delusions; (i) impaired perceptual abilities, particularly affect perception, which fosters the encoding of (ii) idiosyncratic semantic memories, especially those with an affective/self referential valence. Previous research has established that schizophrenia patients with delusions share both these impairments. In the current paper we sought to provide evidence for (i) and (ii) in persons with delusions with an alternative etiology. Methods: A group of individuals with high schizotypy, a group of bipolar patients with delusions and 4 cases with a significant delusion post a traumatic brain injury were all examined. All 3 groups performed a broad range of perception and semantic memory tests in comparison to age, sex and IQ matched healthy controls. Results: Overall perceptual and semantic processing was impaired in the 3 groups relative to a normative healthy control sample. Severity of delusions could be accounted for by these 2 impairments to a greater extent than other alternative theories of delusions (ie jumping to conclusions). Conclusion: We have shown atypical perceptual and semantic processing in deluded individuals who have sustained a traumatic brain injury, those with high schizotypy and those with bipolar disorder. Importantly, the pattern of perceptual and semantic performance recorded by these 3 groups is consistent with schizophrenia patients with delusions, although in some cases they did not show such global semantic processing impairments. Taken together, we consider this as preliminary evidence for consistent abnormal perceptual and semantic processing in persons with delusions, irrespective of diagnosis and phenomenology.
ID: 979193

PERCEPTUAL PRIMING: A STUDY OF CLOSURE PROCESSES IN SCHIZOPHRENIA

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Background: Perceptual closure refers to the neural processes responsible for "filling-in" missing information in the visual image under adverse viewing conditions such as fog. Here we used a closure task that required the identification of barely recognizable fragmented line-drawings of common objects. Closure has been shown to involve a distributed network of cortical regions, including the lateral occipital complex LOC, the prefrontal cortex and the hippocampal formation. Using event related electrophysiological recordings ERP we characterized a scalp negative potential NCL arising within LOC in a time-window of 230–400 ms indexing closure. Following priming, participants can complete the line-drawings at greater levels of fragmentation. By comparison of ERPs for the initial and the repeat image exposures we characterized a modulation of N1 (180–210 ms) arising within LOC indexing the "priming effect" and possibly access to a sensory trace that was laid down following the initial exposure by this region. This suggests that following priming closure could be achieved using this sensory trace. We have previously demonstrated the failure of closure processes in schizophrenia and shown that the dysregulation in the sensory information transmitted from the dorsal visual stream to the prefrontal cortex plays a critical role in this failure. Interestingly patients benefit from priming and are able to close images at greater levels of fragmentation. Methods: Here we compared the ERPs of 9 patients and 9 controls, for the initial and the repeat image exposures with multivariate analysis of variance MANOVA using within-subjects factors of condition (repeat, initial), region (LOC, frontal) and hemisphere (right, left) and the between-subjects factor of group (patients, controls). Results: The results revealed significant main effect of condition ($F(1,16) = 7.0$; $P = .01$), region ($F(1,16) = 7.6$; $P = .01$) and condition X region interaction ($F(1,16) = 5.2$; $P = .03$). Also, the NCL negativity in the initial exposure was found to be correlated with the modulation of the priming effect observed within the time-frame of N1 at LOC in controls ($r = .714$; $P = .03$) but not in patients. Conclusion: These preliminary results raise the possibility that the sensory trace from the initial exposure following perceptual priming aids in achieving closure by allowing patients to bypass the deficit in the dorso-frontal path. In addition they suggest a differential mechanism for the priming effect observed in the 2 groups.
ID: 978813

EFFECTS OF IMPAIRED PERCEPTUAL ORGANIZATION ON LATER COGNITIVE PROCESSES IN SCHIZOPHRENIA

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Background: Perceptual organization dysfunction is a well established phenomenon in schizophrenia, and its neural, illness subtype, and symptom correlates have been clarified in recent studies. However, the consequences of this disturbance, in terms of the burden it imposes on later cognitive processes, are not well understood. Methods: Data from 2 recently completed studies will be reviewed. In the first, schizophrenia patients and matched healthy controls viewed images of faces with high spatial frequency information removed (LSF), low spatial frequency removed (HSF) or all information present (broad spatial frequency, or BSF). In the second study, patients and controls completed a visual target detection task wherein degree of perceptual organization of the stimuli affected the demands on search processes. Behavioral and functional magnetic resonance imaging (fMRI) data were recorded for both tasks. Results: On the face processing task, patients demonstrated inferior performance compared with controls for LSF stimuli, consistent with past findings of impairments in processing global form information. However, consistent with past evidence of a superiority in rapidly processing individual features, patients outperformed controls in the HSF condition. Imaging data indicated increased activation in the fusiform gyrus in both degraded conditions for the schizophrenia group compared with controls. On the target detection task, patients demonstrated a smaller difference between conditions, indicating reduced sensitivity to grouping effects, and fMRI data indicated group differences in activity in regions subserving visual search, visual analysis, decision making and response generation. Conclusion: Effects of perceptual organization impairment include greater reliance on feature processing during face perception, excessive compensatory activity in the fusiform gyrus during face

processing, less efficient visual search and analysis, and poorer decision making about what is observed. These data suggest that further investigation into the consequences of perceptual organization impairments are warranted.
ID: 977215

OPTIMIZING MEASURES OF LOW- AND INTERMEDIATE-LEVEL VISUAL PROCESSING FOR USE IN BIOMARKER AND CLINICAL TRIALS RESEARCH

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Background: Visual processing disturbances in schizophrenia occur at various stages, and these impairments are associated with specific neurophysiological changes and clinical variables. For example, suppression effects during gain control are linked to activity within V1. Integration of features into wholes in the context of noisy backgrounds is associated with poorer premorbid functioning, disorganized symptoms, and activity in extrastriate occipital regions (eg, V2–V4) as part of a network including frontal and parietal areas involved in attentional control. However, standardized measures of visual processing measures that could be useful for clinical trials have not yet been developed. Methods: We examined, and made modifications to, a promising measure of gain control based on the Chubb illusion (Contrast-Contrast Effect Task, or CCE), and 2 measures of visual integration of Gabor elements into circular shapes (Spatial Offset Visual Integration task, or SOVI, and Jittered Orientation Visual Integration Task, or JOVI), to determine the versions with the greatest patient-control group separation and the greatest tolerability. An ongoing study is examining reliability of the optimized versions of each measure. Results: The CCE demonstrated a between-group difference indicating more veridical contrast sensitivity in response to the target patch among patients (ie, a smaller illusion effect caused by the contrast of the surrounding patch), but this effect was small, and considerably smaller than in an earlier published study. The SOVI data did not replicate the primary expected effect in control subjects and is being dropped from future study phases. The JOVI produced a moderate effect size for between-group discrimination, and replicated past studies. For both the CCE and JOVI, modifications were made including addition of practice trials to improve overall performance, the addition of catch trials to identify poorly motivated subjects, and elimination of conditions associated with floor and ceiling effects or that were seen as redundant. Test-retest reliability data on the CCE and JOVI will be will be complete by the time of presentation. Conclusion: Initial psychometric data suggest that the JOVI, a test of intermediate-level visual processing, is the most promising of the 3 measures developed, and this measure has already demonstrated validity in terms of known neurobiological correlates and clinical variables. Acknowledgments: Supported by NIMH grant 3R01MH084828-03S1.
ID: 975794

CAPACITY AND PROCESSING DEFICITS IN WORKING MEMORY IN SCHIZOPHRENIA

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Background: In research on working-memory (WM) deficits in patients with schizophrenia (SCZ), a major question has been whether such patients have a lower capacity than healthy controls (HCs). The results have been mixed, perhaps because the paradigms used have not provided a fine-grained variation in memory load. Another major question has been how to characterize the SCZ deficit in offsetting distraction. Methods: We present behavioral and imaging results from a new variant of the "Self-Ordering" paradigm (Petrides et al., 1993) that bear on both questions. In this paradigm, on each step of a trial participants are presented an array of novel geometric forms, have to select a form that has not been selected before; after each step the forms are scrambled in position, and represented to the participant who again has to select a form not chosen before. The number of steps that a participant can do without error is an estimate of their capacity in the face of perceptual distraction, and the estimate is based on a fine-grained variation in WM load within a single trial. Results: Our data indicate that patients with SCZ clearly have a lower capacity than HCs. Our fMRI data obtained while participants perform this task reveal step-by-step increases in activity in both the prefrontal cortex and the posterior parietal cortex, where the latter tracks memory load more precisely. Conclusion: Our results fit with other evidence (from normals) that the parietal area mediates WM capacity, while the prefrontal region mediates processes that deal with distraction.
ID: 976727

REDUCED AUDITORY LATERAL SUPPRESSION IN SCHIZOPHRENIA

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Background: Auditory processing deficits such as impaired frequency discrimination and reduced suppression of auditory brain responses have been documented in individuals with schizophrenia (SZ). These auditory processing deficits may contribute to abnormal social interactions by interfering with the accurate perception of vocal affect during conversation. Lateral suppression of non-stimulated neurons by stimulated neurons, which has not been previously assessed in SZ, likely plays an important role in precise encoding of sounds during frequency-based auditory tasks. Therefore, the purpose of this study is to determine whether lateral suppression of activity in auditory cortex is impaired in SZ patients. Methods: SZ patients and control participants watched a silent movie with subtitles while listening to trials composed of a 0.5 second control stimulus (CS), a 4 seconds comb-filtered masking noise (CFN), and a 0.5 second test stimulus (TS). The CS and TS were identical on each trial and had energy corresponding to the high energy (recurrent suppression) or low energy (lateral suppression) portions of the CFN. Event-related potentials were recorded during stimulus presentation, and suppression was measured as the change in amplitude between the CS and TS. Results: Mean amplitude of the auditory P2 component (160–230 ms) showed no group differences for recurrent suppression, but reduced lateral suppression in SZ patients. Conclusion: This reduced lateral suppression in SZ patients may lead to overlap of neuronal populations representing different auditory stimuli. Such imprecise neural representations may contribute to the difficulties SZ patients have in discriminating simple auditory stimuli in laboratory tasks and more complex stimuli such as vocal affect in everyday life.

Supported by a President's Research Award from the University of Nevada Las Vegas and NIH grant R21MH079987.
ID: 933118

COGNITIVE IMPAIRMENTS IN 26 CHILDREN AND ADOLESCENTS WITH PSYCHOTIC DISORDERS COMPARED WITH NORMAL CONTROLS

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Background: Cognitive impairment in psychotic disorders are linked to poor functional outcomes. Young people with child or early adolescent onset of psychosis tend to have poorer functional outcomes than adult onset, with higher rates of impairment, suggesting that they are more likely to have neurocognitive abnormalities at first presentation. This study describes the clinical and neurocognitive features of a pilot cohort with early onset psychosis and to identify differences in cognitive functioning in comparison with normal children of the same age. Methods: The subjects for this pilot study are 26 children with psychosis and 26 matched controls. Subjects and controls have data from IntegNeuro tasks, a computerized battery of cognitive testing. The IntegNeuro domains mirror the MATRICS battery, considered to be the gold standard for the assessment of cognitive functioning in psychosis. Results: The mean age at testing was 13.7, and 59% were female. A third had bipolar disorder with psychotic features, the others schizophrenia spectrum disorders or psychosis NOS. Subjects were significantly more likely to have impairment across a wide range of cognitive domains including working memory, processing speed, verbal learning, visual learning, reasoning and problem solving and attention/vigilance. Conclusion: This group of early and very early onset psychosis subjects have a wide range of cognitive impairments, including attention problems that would be consistent with the high rate of affective disturbance seen in this sample.
ID: 979030

TRAJECTORIES OF RESPONSE TO ATYPICAL ANTIPSYCHOTIC TREATMENT THERAPY IN PATIENTS WITH SCHIZOPHRENIA POOLED FROM 6 DOUBLE-BLIND, RANDOMIZED CLINICAL TRIALS

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Background: Distinct response patterns to antipsychotics have been identified in pts with chronic schizophrenia enrolled in trials of up to 12 weeks. We identified trajectories of response in pooled data from 6 randomized, 24-week clinical trials and assessed for associated baseline patient characteristics. Methods: We pooled data on 1990 pts with chronic schizophrenia from 6 randomized, double-blind, comparator trials of at least 24 weeks duration who were treated with olanzapine, ziprasidone, risperidone, quetiapine, or aripiprazole. Growth mixture modeling (GMM) was used to identify homogeneous subpopulations within the larger heterogeneous population. Baseline demographics were compared between the identified latent classes. Results: Five distinct response trajectories (classes) based on PANSS Total score over 24 weeks were identified. Class 1 pts (n = 47/1990, 2.4%) were severely ill at baseline (PANSS Total = 124), but responded with rapid (51% reduction in PANSS Total score by Week 3) and sustained improvement. Class 2 pts (n = 1802/1990, 90.6%) were moderately ill at baseline (PANSS Total = 90), with minimal improvement of 20% evident by Week 4. Class 3 pts (n = 32/1990, 1.6%) were moderately ill at baseline (PANSS Total = 95), showed minimal response initially followed by maximal improvement at Week 12, and gradual worsening thereafter. Class 4 pts (n = 28, 1.4%) were moderately ill at baseline (PANSS Total = 102), with limited early improvement, followed by rapid improvement between Weeks 8 and 12, with little change afterward. Class 5 pts (n = 81/1990, 4.1%) were characterized by marked to severe illness at baseline (PANSS Total = 113), an initial delay in response (11% improvement over 8 weeks), and noticeable improvement in the remaining 4 weeks (baseline-to-endpoint improvement = 28%). Significant differences between classes were noted for gender, age, race, baseline illness severity, specific symptom types, weight, extrapyramidal symptoms, and discontinuation rates (all $P < .05$). Conclusion: GMM analysis of antipsychotic response over 24 weeks in a large, pooled, heterogeneous population of pts with schizophrenia revealed 5 distinct trajectory classes. While most classes demonstrated minimal but sustained improvement, smaller subsets of patients showed rapid and dramatic improvement, delayed improvement, or improvement which was not sustained. Baseline differences associated with these trajectories may help identify pts more likely to follow specific response patterns.
ID: 978558

MOTIVATED ATTENTION AND AVOLITION IN INDIVIDUALS WITH SCHIZOPHRENIA

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Background: Emotional stimuli are thought to guide both top-down and bottom-up selective attentional control due to their inherent biological significance- a phenomenon that has been referred to as "motivated attention" to reflect the innate predisposition to have attention selectively guided by positive and negative stimuli. In the current study, we examined whether abnormalities in motivated attention are associated with negative symptoms of schizophrenia using 3 separate eye-tracking tasks. Methods: In these tasks, simultaneously presented emotional and neutral scenes are put in competition for selective attention while participants are asked to make emotional judgments regarding the stimuli. The probability of first fixation and of total fixations per scene region was used to index motivated attention. Participants included 25 controls (CN) and 32 individuals with schizophrenia who were divided into high (HI-NEG) and low (LOW-NEG) negative symptom groups using a median split on the SANS. Results: In the 1st Task, where participants were asked to determine whether emotional and neutral scenes were equally pleasant, results indicated that CN and LOW-NEG patients showed a greater proportion of first fixations for positive and negative over neutral scenes. HI-NEG patients failed to have a greater proportion of first fixations for positive over neutral scenes. The 3 groups did not differ in subsequent attentional engagement, as measured by the total proportion of fixations that were allocated to emotional vs. neutral scenes. Similar results emerged for Tasks 2 and 3, where participants were instructed to either avoid looking at the emotional stimulus pair (Task 2) or avoid looking at the neutral stimulus pair (Task 3). Specifically, CN and LOW-NEG patients showed a greater probability of first fixating on an emotional vs. neutral stimulus; however, HI-NEG patients failed to show a greater proportion of first fixations for positive relative to neutral stimuli, despite being able to perform the tasks and focus on only the emotional or neutral scene as instructed. Conclusion: Across the 3 tasks, results therefore suggest that emotional information has a bottom-up competitive advantage relative to neutral information in CN and LOW-NEG patients. HI-NEG patients fail to show this bottom-up advantage; however, with sufficient exposure, top-down attention is drawn toward emotional stimuli.

Thus, negative symptoms are associated with deficits in motivated attention and early emotion processing.
ID: 976898

CORTICAL PLASTICITY IN SCHIZOPHRENIA PATIENTS AFTER COGNITIVE TRAINING: BEHAVIORAL AND FMRI ASSESSMENTS OF WORKING MEMORY PERFORMANCE

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Background: Previous research has demonstrated that schizophrenia patients show impairments in attention, working-memory (WM) and cognitive control functions, associated with inefficiency in activation of dorsolateral prefrontal cortex (DLPFC), when compared with healthy controls (HCs). We investigated whether neuroplasticity-based cognitive training in schizophrenia patients would improve working memory performance, and whether behavioral improvement would be accompanied by changes in fMRI activation patterns suggestive of increased efficiency in the DLPFC region that mediates working-memory function. Methods: We used fMRI to assess cortical activation in 32 schizophrenia patients and 15 HCs while they performed 3 N-Back tasks, of increasing levels of WM load (0, 1, and 2-Back tasks). Sixteen patients were then randomly assigned to 16 weeks of computerized targeted cognitive training (TCT), which focused on training auditory and visual processing, affect recognition, and mentalizing (ie, the ability to recognize one's own and others' mental states). The remaining 16 patients were assigned to a control condition where they played computer games (CGs) for 16 weeks. All subjects repeated the fMRI N-back tasks after 16 weeks. BOLD fMRI activity was measured on a 3T-GE scanner. In order to isolate WM processes, we conducted whole-brain analyses to contrast activation throughout the brain on the 2-back with the 0-back task. Results: At baseline, HCs had greatest activation in the right DLPFC in the 2-0 back comparison, which correlated with their behavioral performance on the 2-Back task. Patients had bilateral activation in DLPFC, which did not correlate with 2-Back performance. However, after 16 weeks of training, the TCTs showed increased efficiency in the right DLPFC, which correlated with 2-back performance. The CGs did not show any change in DLPFC activation or any brain-behavior correlations after 16 weeks of playing computer-games as compared with baseline. Conclusion: These fMRI results indicate a possible ''restorative'' effect of cognitive training in schizophrenia subjects that was not observed in control patients. With training, behavioral working memory performance improved and was associated with increased efficiency in the right DLPFC. These findings suggest that targeted cognitive training of elemental processes can generalize to improve performance and neural activation patterns on an untrained working memory task in schizophrenia patients.
ID: 978978

COGNITIVE PHENOTYPES FOR SCHIZOPHRENIA AND PSYCHOTIC BIPOLAR DISORDER IN THE BSNIP STUDY

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Background: Multiple overlaps are evident in clinical, brain and genetic parameters from studies of schizophrenia and bipolar disorder with a history of psychosis. However, there has not been a large-scale head-to-head comparison to identify personal and familial phenotypic similarities between these disorders. Methods: As part of the dense phenotyping strategy of the BSNIP study, cognitive measures have been obtained in over 1500 participants to date, including schizophrenia probands and bipolar probands with a history of psychosis, 1st degree family members of both proband groups, and matched controls. The battery included the BACS, the WMS spatial span task, a facial emotion perception paradigm and the WCST-like test (PCET) from the Gur computerized battery, a manual stop signal task, a working memory test and the antisaccade test of voluntary executive control. Results: Results of preliminary analyses are as follows: On the BACS neuropsychological test, overall deficit in the bipolar group was approximately 75% of that of the schizophrenia group. Deficits in the schizophrenia family members were greater than those of the bipolar family members, which overall were marginal. Schizophrenia patients were significantly more impaired than other groups on the PCET. Deficits of bipolar patients more similar to those of schizophrenia patients on the spatial span and spatial working memory test. The greatest impairment of schizophrenia relatives was on the spatial span test. Schizophrenia patients were most impaired on the emotion identification test, while the bipolar patients and the 2 relative groups had similar, more modest impairment. On the antisaccade task, schizophrenia patients were most impaired, and the other 3 groups had a similar moderate impairment relative to controls. Only on the stop signal test of inhibitory control were bipolar patients the most impaired group. Conclusion: These data demonstrate robust cognitive deficits in bipolar patient with psychosis on the order of 75% of the severity seen in schizophrenia, but their relative deficits vary notably across cognitive domains in an informative way. The family member data may help define profiles of deficit related to illness risk, and suggest some areas where deficits in patients may be familial, while other deficits were not present in relatives and thus may not be familial - especially in bipolar disorder.
ID: 979308

DISTURBED SENSE OF BODY OWNERSHIP IN SCHIZOPHRENIA

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Background: A weakened sense of self-other distinction may contribute to, and even define, psychotic experiences. One paradigm to measure disturbances in sense of self, specifically body ownership, is the rubber hand task. In this task, the participant's own unseen hand and a visible fake hand are stroked simultaneously. Participants often experience the illusion that the rubber hand is their own (rubber hand illusion; RHI). They also report a proprioceptive drift towards the rubber hand, and a limb-specific drop in temperature has been reported in the stimulated hand. Patients with schizophrenia have been shown to experience a stronger RHI, indicated by self-report. The aim of the current study was to replicate this finding using more objective measures of RHI strength: proprioceptive drift and stimulation-dependent changes in hand temperature. Methods: Medicated schizophrenia patients and demographically matched controls participated in the rubber hand task. The participant's own hand and a rubber hand were placed adjacent to each other in a box, with only the fake hand being visible to the subject. The real and rubber hand were brushed for 3 minutes either synchronously or asynchronously. Perceived index finger location was measured before and after stimulation. Temperature at 3 locations on both hands was taken once before stimulation and 3 times during stimulation. A questionnaire assessing strength of the RHI was administered. This procedure was repeated for each hand and stimulation condition. Clinical symptom

ratings were also obtained. Results: Subjects reported a stronger RHI in the synchronous condition on questionnaires, and patients with schizophrenia reported that they experienced a stronger RHI than controls in both conditions. Patients indicated a larger drift towards the rubber hand, but only in the synchronous condition. Finally, hand temperature dropped significantly following tactile stimulation, but only in the stimulated right hand. Hand temperature of patients with schizophrenia dropped more than controls following stimulation. Conclusion: Results suggest that the RHI is experienced more strongly in schizophrenia. These findings suggest that patients have a more flexible body representation and a weakened sense of self, and potentially indicate abnormalities in parietal networks that have been implicated in body ownership. Acknowledgments: Supported in part by F31 MH085405, NARSAD, and R01 MH073028.
ID: 978853

HIGH-GAMMA BAND OSCILLATIONS AND VISUAL CLOSURE PROCESSING DURING FACE PERCEPTION IN SCHIZOPHRENIA

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Background: Recent evidence suggests that patients with schizophrenia are characterized by impaired perceptual organization that may underlie deficits in social cognition, such as face processing. In the current study, we employed magnetoencephalography (MEG) to examine the neural correlates of visual closure processes during face processing in a sample of chronic and never-medicated first-episode (FE) schizophrenia patients. Methods: Visual closure was investigated with Mooney faces which consist of degraded pictures of human faces where all shades of grey are removed, thereby leaving the shadows rendered in black and the highlights in white. During the presentation of Mooney faces, MEG signals were recorded and subsequently analysed for spectral changes in oscillatory activity in the frequency range of 25–150 Hz. A source localization with a beamforming approach enabled the identification of the generators of gamma-band oscillations. In addition, effective connectivity between source-signals was investigated with a novel transfer entropy measure to test the hypothesis that early visual areas are crucially involved in cognitive-perceptual deficits in the disorder. Results: Compared with healthy controls, both groups of schizophrenia patients were characterized by impaired behavioral performance during the detection of Mooney faces, suggesting an impaired ability to integrate stimulus elements into coherent object representations. Deficits in visual closure were accompanied by a highly significant reduction in high gamma-band activity (60–120 Hz) between 50–200 ms that was localized to early visual areas as well as to temporal and frontal regions. These deficits were present already in FE-patients and were more pronounced in chronic schizophrenia. Finally, the analysis of effective connectivity suggested that deficits in occipital cortex predicted impairments during later stages of ventral stream processing, suggesting a bottom-up driven dysfunction in the visual hierarchy. Conclusion: Thus, these findings highlight that deficits in high gamma-band activity in early visual areas are an important aspect of perceptual dysfunctions in schizophrenia that are related to impairments in face processing and are possibly progressive during the course of the disorder.
ID: 978511

RELATIONSHIP OF INSIGHT TO NEUROCOGNITIVE AND PSYCHIATRIC SYMPTOMS: A META-ANALYSIS

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Background: Previous studies of schizophrenia patients have shown that awareness of having a mental illness is related to various aspects of neurocognitive performance and to psychiatric symptoms. Knowing the relative magnitude of the relationships of awareness of illness to different domains of neurocognition and symptoms might suggest domains that are more critical determinants of awareness of having a mental disorder. Methods: A meta-analysis of 55 studies (combined $n = 6732$) was conducted to determine the magnitude of the relationships between awareness of illness and neurocognition defined according to the 7 domains identified by the MATRICS initiative. In contrast, we examined relationships of illness awareness and reality distortion (delusions and hallucinations), negative, and disorganization symptoms. We examined overall awareness of having a mental disorder as well as attributions for psychotic symptoms (ie, relabeling). Results: Regarding overall awareness of illness, of the 7 MATRICS neurocognitive domains, the 2 relationships with highest magnitude were with Attention ($r = .26$, $P < .001$) and Reasoning and Problem Solving ($r = .17$, $P < .001$). For the 3 symptom domains of interest, we found relationships with reality distortion ($r = .29$, $P < .001$), negative ($r = .22$, $P < .001$), and disorganization ($r = .32$, $P < .001$). Although fewer studies had examined relabeling of symptoms, the most strongly related neurocognitive domain was Reasoning and Problem Solving ($r = .16$, $P < .001$). For the 3 symptom domains of interest, there were relationships for reality distortion ($r = .15$, $P < .04$), negative ($r = .14$, $P < .001$), and disorganization ($r = .20$, $P < .001$). Conclusion: We found that overall awareness of illness and relabeling of symptoms was associated with both neurocognition and symptoms. Among neurocognitive domains, attention and problem solving appeared most critical to obtaining good awareness of having a mental disorder, and learning and memory ability appeared to be somewhat less critical. The magnitude of the relationships with insight was similar for neurocognition and symptoms. These meta-analyses do not support the common belief in the literature that neurocognitive deficits are the main underlying contributors to poor insight, and suggest that we need to look more broadly for additional determinants such as psychological factors.
ID: 977956

TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) INFLUENCES PROBABILISTIC ASSOCIATION LEARNING IN PEOPLE WITH SCHIZOPHRENIA

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Background: Probabilistic association learning, which involves the gradual acquisition of cue-outcome associations, is thought to rely on frontal-striatal activation in healthy individuals. Typically, people with schizophrenia demonstrate a deficit on this type of learning, which has been associated with fronto-striatal dysfunction in this population. Anodal transcranial Direct Current Stimulation (tDCS) of the dorsolateral prefrontal cortex has been shown to improve probabilistic association learning in healthy adults. The aim of the current study was to evaluate the potential of anodal tDCS

to the dorsolateral prefrontal cortex to reverse probabilistic association learning deficits in people with schizophrenia. Methods: In a single-blind, counterbalanced, cross-over design, anodal tDCS at an intensity of 2.0 mA or sham stimulation was administered continuously for 20 minutes to the left dorsolateral prefrontal cortex while participants performed 150 trials of the ''weather prediction'' probabilistic association learning test. Prior to tDCS, participants performed a baseline session of the weather prediction test without stimulation. Based on this baseline performance, each individual was classified as either a good or a poor learner. Results: Active tDCS compared with sham improved acquisition of the cue-outcome associations early in the task in those classified as good learners at baseline, whereas active tDCS impaired early acquisition in those classified as poor learners at baseline. Active tDCS did not affect the ultimate performance level achieved in either group. Conclusion: These results demonstrate that tDCS to the dorsolateral prefrontal cortex may facilitate access to existing neural reserves in the prefrontal cortex of some people with schizophrenia, to enhance early acquisition of probabilistic cue-outcome associations.
ID: 978198

SELECTIVE DEFICITS IN REWARD-DRIVEN PROBABILISTIC LEARNING IN SCHIZOPHRENIA POINT TO DOPAMINE D1 RECEPTOR DYSFUNCTION

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Background: Recent investigations have shown that some aspects of reinforcement learning (RL) are more affected by schizophrenia (SZ) than others, possibly due to differential disruption of basal ganglia (BG) circuits. Probabilistic contingency learning, for example, is an ability that has been shown to depend, in large part, on BG function, and for which there is some evidence of sparing in SZ. Evidence suggests that transmission at D1-type dopamine (DA) receptors most strongly influences the positive-feedback-driven ''Go'' learning of stimulus-response associations, whereas negative-feedback-driven ''NoGo'' learning relies on transmission at D2-type DA receptors. Methods: In a series of experiments, we administered clinically-stable outpatients with SZ, and matched controls, probabilistic learning paradigms, assessing the selective effects of rewards and punishments on learning 1) through response time changes across acquisition, and 2) through a transfer phase, involving novel pairings of training stimuli in the absence of feedback. Based on evidence of DA hyperactivity in the BG in SZ, leading to unreliable phasic bursts, we predicted that positive-feedback-driven "Go" learning would be more disrupted in SZ, whereas negative-feedback-driven "NoGo" learning might be spared. Results: This hypothesis is supported by multiple data sets from our group. Using a novel Go/NoGo paradigm, we found that SZ patients showed reduced reward-driven response-facilitation ("Go" learning), as evidenced by the lack of a reduction in "Go" response latency across the acquisition phase. In the transfer phase of multiple experiments, furthermore, SZ patients showed a normal tendency to avoid a frequently-punished stimulus, but a reduced rate of choosing a frequently-rewarded stimulus. In multiple paradigms, SZ patients also showed impaired rapid, early acquisition of probabilistic contingencies, which may reflect a contribution of prefrontal cortex (PFC) to RL deficits in SZ. Importantly, we found that rates of rapid, early acquisition of probabilistic contingencies correlated significantly with negative symptom scores, suggesting that the motivational deficits and rapid RL may share a neural substrate (eg, PFC) in SZ. Conclusion: These findings point to the differential disruption of various components of neural systems for RL in chronic SZ patients, with D1 and PFC mechanisms of RL being impaired, and D2-driven processes in the BG being relatively intact.
ID: 976232

INVESTIGATING THE NEURAL SUBSTRATES OF NEGATIVE SYMPTOMS: RESULTS FROM FMRI STUDIES OF OUTCOME PROCESSING IN SCHIZOPHRENIA

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Background: Negative symptoms, including deficits in motivation and emotional expression, are debilitating aspects of schizophrenic psychopathology, closely linked with functional outcome. Effective pharmacological treatments for negative symptoms remain elusive, due to the lack of a basic understanding of their underlying neural processes. An increased interest in neural mechanisms of reinforcement processing and motivation in the basic science literature, however, has given clinical neuroscientists new tools, which have been used to study these questions more systematically in mentally-ill populations. Methods: Our group has used multiple behavioral paradigms from the cognitive neuroscience literature, in conjunction with functional magnetic resonance imaging (fMRI), to determine whether patients with schizophrenia (SZ) exhibit aberrant patterns of neural activity associated with the processing of reinforcement, which might relate to the severity of negative symptoms. Results: In the context of a Monetary Incentive Delay (MID), requiring subjects to first anticipate monetary outcomes based on cues, and then integrate outcomes received, we observed abnormal responses to outcomes, in SZ patients, in medial and lateral prefrontal cortex (PFC), lateral temporal cortex, and the amygdalae, such that controls, but not patients, showed greater activation for gains, relative to losses. In the striatum, neural activity was modulated by outcome magnitude in both groups. Additionally, we found that ratings of negative symptoms in patients correlated with sensitivity to obtained losses in medial PFC, obtained gains in lateral PFC, and anticipated gains in left ventral striatum. More recent analyses, involving a probabilistic reversal learning paradigm, similar to that used by Cools et al. (2002), have produced consistent results, indicating that medial PFC activity in conjunction with negative feedback, in 22 SZ patients, correlates with those patients' global avolition ratings from the SANS. Conclusion: These 2 results suggest that motivational and emotional deficits that are rated as negative symptoms in schizophrenia may relate closely to patients' neural responses to feedback and outcomes, particularly in prefrontal cortex. A better understanding of the sources of motivational deficits in SZ patients could stand to improve our ability to develop pharmacological treatments for negative symptoms.
Reference: Cools, R., Clark, L., Owen, A.M., Robbins, T.W. (2002). J. Neurosci. 22, 4563–4567.
ID: 976224

AN ERP STUDY ON SEMANTIC PROCESSING IN INDIVIDUALS WITH TYPICAL SCHIZOTYPAL PERSONALITY FEATURES

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Background: Semantic processing impairment is one of the core features of schizophrenia. However, relatively few work has been done on at-risk individuals with schizotypal personality disorder (SPD) features who are supposed to share similar but attenuated impairments in neurocognitive and neurophysiological functions as well as neuroanatomical abnormalities. The current work attempted to investigate the semantic processing in individuals with typical schizotypal personality with an event-related potential (ERP) paradigm. Methods: Twenty participants (10 each in SPD and non-

SPD group) were recruited. The 2 groups did not differ from age, gender, education and IQ. A semantic relatedness judgment task with a long Stimulus Onset Asynchrony (700 ms) was administered to each participant independently. The experimental materials included 60 related word pairs and 60 unrelated word pairs. Continuous event-related potentials (ERPs) were recorded during the whole experimental session. Results: Large behavioral priming effects for both groups were observed ($P <$ .001). Neither group effect nor interaction between group and relatedness reached significant levels. The ERP data showed a widely distributed N400 for unrelated target words regarding to related target words in both groups. Critically, the mean amplitudes for the difference wave between unrelated and related target words in 300–400 ms time window tended to be larger in individuals with schizotypal personality features over frontal regions ($t(18) = 2.12$, $P < .05$). Conclusion: These results indicate that individuals with schizotypal personality features may need more effort to bring out similar behavioral semantic priming effects as controls, and may suggest a compensation for semantic processing in individuals with schizotypal personality features.
ID: 978172

WORKING MEMORY DYSFUNCTION IN DEFICIT SCHIZOPHRENIA COMPARED WITH NONDEFICIT SCHIZOPHRENIA AND HEALTHY CONTROLS -EVIDENCE FROM EVENT-RELATED POTENTIALS

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Background: Working memory (WM) dysfunction is a core component of schizophrenia. Although numerous neuroimaging studies supported the more WM impairment in schizophrenia on higher executive demands, studies have failed to get consistent conclusions. Heterogeneity maybe an important factor hindered to yield a consistent WM dysfunction model. The aim of the present study was to examine the aberrant neurophysiological response during the parametric N-back task in deficit and nondeficit schizophrenia. Methods: 20 deficit schizophrenia (DS), 20 nondeficit schizophrenia (NDS), and 20 matched healthy controls performed a parametric n-back task with increasing WM load (0-Back, 1-Back and 2-Back), while the EEG was recorded during they performed the task. Results: P3 was elicited in 300–700 ms after onset of stimuli in 3 group. In healthy controls, P3 peak amplitude decreased progressively as WM load increased (0-back>1-back>2-back). However, NDS patients showed no significant difference between the amplitude of P3 elicited in 1 and 2-back task, while DS patients didn't show any significant difference of P3 amplitude among 3 lever of WM load, which mainly existed in frontal area. Moreover, schizophrenia demonstrated an enhanced 1−0 N450 different waveform component in parietal region compared with controls, but a reduced 2−1 N450 in the same region. Significant difference was revealed in frontal area but not in parietal area when compared the amplitude of 1−0 and 2−1N450 between DS and NDS patients. In addition, the healthy controls showed a negative-positive difference waveform (NP) component occurred in 100–300 ms after stimulus onset, superimposed on the classical P200 and N200 components. N DS patients demonstrated a similar but more negative NP in 1−0 and 2−1 difference waveform. However, NP was not elicited in the 2−1 difference waveform in DS patients. Conclusion: Deficit schizophrenia showed more significant dysfunction than nondeficit patients in WM load condition, which mainly involved the updating and short-term storage process.
This research was supported by NSFC (30700236) and RFDP (20070533067).
ID: 980240

PROBABILISTIC ASSOCIATION LEARNING IMPAIRMENT PREDICTS DEGREE OF SCHIZOTYPAL PERSONALITY TRAITS

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Background: Although people with schizophrenia have been shown to display probabilistic association learning deficits, it is not clear whether these deficits are primarily an effect of the disease process or whether they are secondary to medication effects and/or chronic illness. Demonstration of probabilistic association learning deficits in healthy adults displaying schizotypal personality traits would provide evidence supporting a relationship between probabilistic association learning impairment and schizophrenia-like behavior. Methods: Sixty healthy participants completed a probabilistic association learning test and indices of general intelligence, personality, emotional state, quality of life, and daily function. Results: There were strong significant correlations between probabilistic association learning and schizotypal personality scores. Participants classified as poor learners during probabilistic association learning displayed significantly higher schizotypal personality scores relative to those classified as good learners. Conclusion: These results demonstrate that the degree of probabilistic association learning impairment can predict the degree of schizotypal personality traits. Because probabilistic association learning deficits have also been identified in people with schizophrenia, results from the present study suggest that there may be similar neural or cognitive underlying mechanisms responsible for abnormal probabilistic association learning in people displaying a high degree of schizotypal personality traits.
ID: 979868

PHOSPHODIESTERASE-1 INHIBITORS AS NOVEL THERAPEUTICS FOR ENHANCEMENT OF COGNITION IN SCHIZOPHRENIA

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Background: Cognitive dysfunction in schizophrenia is mediated in part by the hypo-functionality of the pre-frontal cortical dopamine D1 receptor system. Phosphodiesterase 1 (PDE1) is enriched in cortex and plays a major role in D1 receptor intra-cellular signaling. Inhibition of PDE1 amplifies D1 receptor signaling leading to enhancement of cognitive function. Methods: Novel object recognition (NOR) was performed after oral administration to rats with an inter-trial interval of 24h between training and testing trials. IC200214, a 58 nM inhibitor of PDE1 with over 2700-fold selectivity for PDE1 over PDE2-11, was administered orally before or after training and/or before testing in NOR. Motoric side effect liability was tested in mice using a haloperidol-induced catalepsy step-down latency model. Results: In the NOR assay IC200214 significantly improved performance over a broad range of doses from 0.1 to 3 mg/kg, p.o. Significant improvements by IC200214 were observed when administered 2 hour before training (acquisition), immediately after training (early consolidation), 3 hour after training (late consolidation) and 2 hour before testing (retrieval) in separate experiments. IC200214 reversed catalepsy induced by haloperidol over a similar dose range. Conclusion: A selective PDE1 inhibitor IC200214 was found to enhance cognition in a rodent model with a remarkably wide

span of efficacy across all 3 domains of memory: acquisition, consolidation and retrieval. Previously, PDE1 inhibitors have been shown to increase wakefulness in rodent models, but do not increase basal locomotor activity and do not show psychotomimetic-like effects. Furthermore, IC200214 reverses catalepsy induced by potent dopamine D2 receptor antagonists such as haloperidol, indicating the agent will prevent motoric side effects. With this profile, PDE1 inhibitors represent a novel target mechanism for development of therapeutics for the treatment of cognitive dysfunction in schizophrenia and for adjunctive use with antipsychotic agents. IC200214 is in preclinical development with a safety profile that supports continued development and advancement to clinical trials.
ID: 976687

EYE-MOVEMENT BEHAVIOR REVEALS RELATIONAL MEMORY IMPAIRMENT IN SCHIZOPHRENIA

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Background: Relational memory is impaired in schizophrenia. We used a novel experimental design to record both explicit recognition and early eye-movements during a relational memory task in healthy control and schizophrenia subjects. In addition, we used structural MRI to explore correlations between hippocampal volume and relational memory performance. Methods: 35 subjects with schizophrenia and 35 matched healthy control subjects were trained to associate a face with a background scene. During testing, scenes were presented as a cue and then overlaid with 3 previously studied faces. Participants were asked to recall the matching face, and both eye movements and forced-choice recognition were recorded. During Non-Match trials, no faces matched the scene. During Match trials, 1 of the 3 faces had previously been paired with the scene. Results: Healthy control subjects viewed all 3 faces evenly during Non-Match trials, but quickly (within 500 ms) and consistently exhibited preferential viewing of the matching face during Match trials. Subjects with schizophrenia viewed all 3 faces evenly during Non-Match trials, but they exhibited significantly less preferential viewing during Match trials (trial type by group interaction: Wald $\chi^2 = 82.8$, $P < .001$). An analysis of all correct Match trials revealed that preferential viewing was significantly reduced and delayed in subjects with schizophrenia ($F(7,51) = 2.8$, $P = .02$). Within the schizophrenia group, premorbid IQ scores were positively correlated with explicit ($r^2 = .38$, $P < .001$), but not eye movement relational memory measures. We found a modest hippocampal volume difference (control > schizophrenia, $F(1,57) = 3.8$, $P = .055$). However, hippocampal volume was not correlated with relational memory performance. Conclusion: We found novel evidence for a specific relational memory deficit in schizophrenia. Patients showed recognition deficits and abnormal eye movement patterns, indicating abnormal relational memory. We propose that eye movements are a promising new avenue for the study of relational memory in schizophrenia. Future studies using functional neuroimaging techniques, in conjunction with eye-movement data collection, are needed to elucidate the neural correlates of these preferential viewing effects.
ID: 978434

ATTENTION, LEARNING, AND MEMORY DEFICITS IN A RODENT VARIABLE PRENATAL STRESS MODEL OF NEUROPSYCHIATRIC ILLNESS

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Background: Recently published results of 3 large antipsychotic clinical trials clearly demonstrated the limitations of currently available treatment options for schizophrenia and further highlighted the critical need for novel drug discovery and development in the field, in particular for cognitive dysfunction. However, development of an appropriate animal model to test novel hypotheses at the basic science level has been a difficult challenge in schizophrenia-related drug discovery. It has been suggested that a rodent variable prenatal stress paradigm might be an etiologically appropriate neurodevelopmental animal model for some components of schizophrenia. Methods: The objective of this study was to perform a comprehensive study of the effects of variable prenatal stress on animal behavior to determine face validity of the model. The variable prenatal stress paradigm, beginning on day 14 gestation, included forced swim, cold exposure, social stress, fasting, restraint, and reversed light/dark cycle. Behavioral testing in the offspring (and controls) began on postnatal day 60. Results: Results indicate rats exposed to prenatal stress were found to have delay-dependent deficits in recognition memory (novel object recognition) and short-term spatial memory (radial arm maze), as well as alterations in hippocampus-dependent associative learning (contextual fear conditioning). Further, prenatally stressed rats showed significantly lower accuracy (% correct) and increased premature responses compared with controls during a 5-choice serial reaction time task (5C-SRTT), suggesting impairments in sustained attention and impulsive-like behavior. Conclusion: These results indicate that exposure to variable prenatal stress results in impairments of several domains of cognition often found in patients with schizophrenia and other neuropsychiatric disorders. The data supports this neurodevelopmental animal model as a useful platform for drug discovery, especially for deficits in cognition and attention.
ID: 978663

RELATIONSHIPS BETWEEN IMPULSIVITY, DECISION-MAKING AND EXECUTIVE FUNCTION IN SCHIZOPHRENIA AND CONTROLS: EFFECTS OF CO-MORBID CIGARETTE SMOKING

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Background: Cigarette smoking improves certain cognitive deficits in schizophrenia such as attention and working memory. The effect of comorbid tobacco dependence on impulsivity, decision-making and executive function, however, is less clear. Moreover, the relationships between these different aspects of cognitive function in patients with schizophrenia and the effects of cigarette smoking are unknown. Methods: 65 patients with schizophrenia (32 current, 12 former and 21 never smokers) and 61 non-psychiatric controls (23 current, 11 former and 27 never smokers) were assessed on the Kirby Delayed Discounting Task (KDDT), Iowa Gambling Task (IGT) and Wisconsin Card Sorting Task (WCST). Smokers were studied under satiated conditions. Results: Participants with schizophrenia performed significantly worse compared with controls on the IGT and WCST (P's $< .001$), measures of decision-making and executive function respectively, but performance was not modulated by smoking status in either group. Smoking status did modulate delay discounting, a form of impulsivity, in schizophrenia ($P = .03$) but not in controls. Performance in all the 3

tasks were significantly correlated in controls: IGT total money and WCST perseverative errors ($P = .02$) were positively correlated, whereas delay discounting was negatively correlated with both IGT ($P = .04$) and WCST ($P = .01$) performance. In contrast, no correlations between task performances were identified in the schizophrenia group. Conclusion: As expected decision-making and executive function were poorer in persons with schizophrenia but unlike other aspects of cognitive function these deficits were not remediated by cigarette smoking. In controls performance on decision-making and executive function tasks were correlated and performance on both these tasks was reduced in persons with higher impulsivity as assessed by the KDDT. The relationship between these measures appears to be more complex in schizophrenia which is likely due to the cognitive dysfunction and differential effects of smoking on impulsivity, decision-making and executive function found in this population.
ID: 979337

COGNITIVE CONTROL AND CORTICAL GAMMA SYNCHRONY DISTURBANCES IN SCHIZOPHRENIA

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Background: Schizophrenia patients have deficits in context processing, a component of cognitive control involving the maintenance of task-relevant information. Our EEG studies have found that, using the Preparing to Overcome Prepotency (POP) task, prefrontal cortical (PFC) gamma-band synchrony modulated with context load for healthy controls, but was disturbed in schizophrenia. Establishing gamma-band synchrony as a generic mechanism for the maintenance of task context information would advance our understanding of the neural basis for context processing deficits in schizophrenia. Methods: High-density EEG was recorded in 14 schizophrenia subjects and thirteen healthy controls performed a version of the Stroop task involving cued switches between color naming (high control demands) and word reading (low control demands). Induced gamma-band activity was calculated using wavelet transforms of EEG activity over the delay period of trials. Results: Behavioral analyses showed increased congruency effects in the color naming task for schizophrenia subjects compared with healthy controls, consistent with disturbed cognitive control. In the EEG analyses, healthy subjects exhibited modulation of frontal induced gamma activity by control demands whereas schizophrenia subjects modulated frontal gamma activity poorly. Conclusion: The consistent EEG findings across the POP and Switching Stroop tasks suggests that frontal gamma activity may be a generic mechanism for entraining cortical network activity in the service of task-relevant cognitive control representations. Disturbances in frontal gamma activity, then, may serve as a pathophysiologic mechanism for explaining cognitive control disturbances in schizophrenia.
ID: 979391

THE ROLE OF GLUTAMATE IN SCHIZOPHRENIA-RELATED COGNITIVE DYSFUNCTION: A META-ANALYTIC REVIEW

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Background: Cognitive dysfunction in schizophrenia (SZ) is a very common problem that strongly predicts future patient functioning. Studies suggest that glutamatergic (Glu) disruption may be an important factor in both SZ and its related cognitive dysfunction; however, the extent to which individual cognitive domains are impaired or enhanced by Glu manipulation is unknown. No previous review has synthesized the findings of studies of Glu function in both normal and SZ-related cognition across multiple neurocognitive domains, methodologies, and Glu receptor families. Methods: Fifty studies were identified through a literature search and included in this meta-analytic review. Studies had to include adults participants who were healthy or diagnosed with SZ, utilize a measurement or manipulation of an aspect of the Glu system (eg, magnetic resonance spectroscopy (MRS) or drug trials of Glu compounds), and include at least one objective test of cognition (eg, measures of general cognitive function; attention/working memory; executive function; memory; visual perception and construction; or psychomotor function). Results: Across all methodologies, domains, and groups, 93/218 (42.7%) cognitive tasks found significant effects related to Glu; however, these findings were not equally distributed across participant groups, methods, or cognitive domains. While MRS and post-mortem studies found more effects between Glu and cognition in SZ samples (38.9%) than normal participant groups (14.3%), the pattern was reversed in Glu drug trials (SZ: 17.4%; normal participant: 58.9%). Conclusion: These findings suggest that baseline Glu levels are more strongly related to cognitive function in patient than healthy samples, while NMDA receptor antagonism impairs cognition significantly more in healthy samples than in patients. Strategies of cognitive enhancement via multiple types of Glu receptor (NMDA, mGluR, and AMPA) agonists were generally non-significant in both groups. The effects of Glu appear to be strongest for verbal memory and executive function, which is generally consistent with the NMDA-dependent models of long-term potentiation and learning. These findings suggest that the relationship between Glu and cognition is different in SZ than healthy samples, differs across cognitive domains, and that there are important methodological factors to be considered in understanding this complex relationship.
ID: 978648

NEUROTROPIC VIRUSES AND COGNITIVE IMPAIRMENT

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Background: Neurotropic viruses can cause cognitive dysfunction. We have focused on neurotropic viruses that cause lifelong latent infections. A prototypic example is Herpes Simplex Virus type 1 (HSV-1), a human herpesvirus that generally causes self-limited localized oral mucosa lesions, followed by a latent infection within the central nervous system that is associated with reactivation and re-infection. Methods: We measured specific IgG antibodies to HSV-1 in 1251 individuals using immunoassays (schizophrenia, SZ, $n = 600$; bipolar disorder, BP, $n = 276$, control individuals without psychiatric disorder, $n = 375$). HSV-1 infection was defined by antibody levels greater than a pre-defined standard. Antibodies to other human herpesviruses were also measured. All participants were evaluated using the Repeatable battery for the Assessment of Neurolopsychological Status (RBANS), which estimates immediate memory, delayed memory, visual spatial constructional abilities, attention, and language. Standardized index scores for total RBANS scores and each RBANS domain were compared with level of HSV-1 infection using multinomial regression models incorporating age, gender, and race. Results: Serological exposure to HSV-1 was strongly associated with lower cognitive functioning in the entire sample (RBANS Total Scores, coefficient = −3.2, $P < .001$). The largest effect was seen for BP (coefficient = −4.5, $P = .015$). Strong associations were also found in SZ (coefficient = −3.6, $P < .001$) and controls (coefficient = −3.3, $P = .006$). There were no associations with antibodies to 5 other herpes viruses. Immediate Memory (coefficient = −3.7, $P < .001$) and Delayed Memory (coefficient = −3.8) were most strongly correlated with HSV-1 infection. SZ patients had the strongest association between HSV-1 and Immediate Memory (coefficient = −5.2; 95% CI −8.0, −2.4,

$P < .001$), while controls displayed the strongest association with Delayed Memory (coefficient = −4.4, 95% CI −6.6, −2.2). BP patients showed strong associations with Immediate and Delayed Memory. Conclusion: Infection with HSV-1 is associated with reduced cognitive functioning in all the groups. Memory is most strongly associated with HSV-1 infection. Better understanding of the pathogenic mechanisms may enable novel therapies.
ID: 979796

THE FUNCTIONAL CIRCUITRY OF PSYCHOSIS IN SCHIZOPHRENIA: SUBSTANTIA NIGRA/VTA HYPERACTIVITY, PREFRONTAL DYSFUNCTION AND THE SUBSTANTIA NIGRA/VTA-STRIATAL CIRCUIT

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Background: Psychosis is one of the defining features of schizophrenia. The hypothesis that prefrontal dysfunction leads to excess subcortical dopamine and psychosis has generated widespread interest and substantial empirical support. However, key aspects of the underlying neural mechanisms remain unclear. Methods: We used event-related fMRI of subjects with schizophrenia while they completed a face working memory task and applied univariate and functional connectivity analyses. We also studied a group of neuroleptic-naive, first-episode subjects with schizophrenia to address potential medication and illness chronicity confounds and to assess the reliability of our findings. Results: We observed task-evoked hyperactivity of the substantia nigra/ventral tegmental area (SN/VTA), diminished prefrontal activity and prefrontal-SN/VTA connectivity in subjects with schizophrenia. Additionally, disrupted SN/VTA-striatal connectivity predicted the level of psychosis. In neuroleptic-naive schizophrenia patients, we replicated these findings, together with the observation that SN/VTA hyperactivity itself predicted psychosis severity. Conclusion: These results suggest that impaired prefrontal function contributes to SN/VTA hyperactivity in schizophrenia and the SN/VTA-striatal circuit is a key mediator of psychosis. fMRI-based measurement of SN/VTA hyperactivity may be a broadly applicable indicator of excess dopaminergic activity in schizophrenia.
ID: 979817

IMPAIRED VIGILANCE BUT NOT ACCURACY OF PATIENTS WITH SCHIZOPHRENIA IN A HUMAN VERSION OF THE RODENT 5-CHOICE CONTINUOUS PERFORMANCE TEST

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Background: The discovery that cognitive function correlates with functional outcome in patients with schizophrenia has galvanized the search for pro-cognitive therapeutics for these patients. Tasks with cross-species translational validity are required to progress putative pro-cognitive compounds from preclinical to clinical testing. To assess attention/vigilance we recently developed a rodent 5-choice continuous performance task (5C-CPT) that requires the discrimination of target from non-target stimuli and the accurate identification of target stimulus locations from a given array. To evaluate the cross-species translational validity and utility of the 5C-CPT for assessing attention/vigilance in psychiatric populations, we created a human version and assessed the performance of patients with schizophrenia. Methods: Medicated patients with schizophrenia (n = 17) and healthy volunteers (n = 28) were required to move a joystick in the direction that 1 light appeared, but to inhibit responding when all 5 lights appeared, thus measuring hit and false alarm rates, vigilance, accuracy, bias, and reaction times (RT). Results: Patients with schizophrenia exhibited poorer vigilance ($F(1,43) = 8.4$, $P < .01$) due to a reduced hit rate ($F(1,43) = 4.9$, $P < .05$) and a trend toward increased false alarms ($F(1,43) = 4.0$, $P = .051$) when compared with gender and age-matched controls. No difference in bias ($F(1,43) = 2.6$, $P = .11$) or accuracy was observed ($F < 1.4$, ns). A trend toward slower RTs was observed ($F(1,43) = 3.4$, $P = .074$), with increased RT variability observed ($F(1,43) = 5.4$, $P < .05$). Conclusion: Patients with schizophrenia exhibit impaired vigilance in the human 5C-CPT as a result of missed trials during target stimuli and inappropriate responses to non-target stimuli. Patients exhibited comparable accuracy to controls suggesting a normal ability to respond to stimuli across an array of targets. Consistent with other CPTs, patients with schizophrenia exhibited more variable RTs than comparison subjects. These data support the sensitivity of the human 5C-CPT at detecting differences between patients with schizophrenia and healthy comparison subjects. Given that the rodent 5C-CPT is currently being used to dissect the mechanisms underlying these processes - utilizing both genetic and pharmacological techniques - the 5C-CPT has the potential to be a valuable addition to cross-species tests having translational relevance to identifying pro-cognitive therapies for treating schizophrenia.
ID: 979634

19. Clinical Neuropsychology

COGNITION IN SCHIZOPHRENIA: PRESERVED, DETERIORATED AND PREMORBIDLY IMPAIRED PATTERNS

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Background: Although impaired neurocognition is widely regarded as a core and enduring feature of schizophrenia, there are inconsistencies in the literature concerning issues of intellectual decline, premorbid cognitive functioning, and preserved abilities. The main purpose of this investigation was to identify patterns of cognitive performance in schizophrenia patients suggesting preserved, deteriorated, or premorbidly impaired intellect and to determine clinical, cognitive, and functional correlates of these patterns. Methods: We assessed 101 patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder and 80 non-psychiatric controls. The ''preserved'' performance pattern was defined by average estimated premorbid and current IQ with no evidence of IQ decline (premorbid- current IQ difference <10 points). The ''deteriorated'' pattern was defined by a difference between estimated premorbid and current IQ estimates of 10 points or more. The premorbidly ''impaired'' pattern was defined by below average estimated premorbid and current IQ and no evidence of cognitive decline greater than 10 points. Preserved and deteriorated patterns in healthy controls were also identified and studied in comparison to patient findings. The groups were compared on demographic, cognitive, clinical and functionality variables. Results: The groups were statistically similar in terms of age, sex, and parental socioeconomic status. There were no significant differences between patient groups on any of the clinical variables assessed. Patients with impaired intellect, as well as those who displayed a pattern of apparent intellectual decline exhibited deficits on the composite measure of cognitive ability and functional outcome measures when compared with healthy participants. Patients with the preserved pattern showed better performance on the composite measure of cognitive ability compared with patients in the deteriorated and premorbidly impaired subgroups. Nevertheless, the ''preserved'' patients still demonstrated impaired performance relative to healthy control participants. Interestingly, there were no significant differences between the ''preserved'' and ''deteriorated'' control groups. Conclusion: The existence of apparently ''deteriorated'' healthy controls raises questions about the validity of premorbid ability estimates as well as the possible role of individual differences and developmental course in cognitive performance.
ID: 978950

IMPACT OF CANNABIS USE ON NEUROCOGNITION AND SOCIAL FUNCTIONING IN ADOLESCENTS AT-RISK FOR PSYCHOSIS

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Background: Cannabis misuse is prevalent in persons with psychotic disorders and has been associated with increased symptoms and poorer outcome in some studies. The impact of cannabis use on neurocognition has also been examined in psychotic populations, but with counterintuitive results. Patients with schizophrenia who use cannabis often evidence better cognitive functioning than patients who do not use cannabis. The aim of the current investigation is to determine if this same relationship exists in clinical high-risk subjects, before the onset of psychosis. Methods: Participants were enrolled in the Recognition and Prevention (RAP) Program at Zucker Hillside Hospital in New York, a prospective longitudinal research program for adolescents at risk for psychosis. Forty-two clinical high-risk subjects with lifetime cannabis use (HR-C+) were compared with 69 clinical high-risk subjects without a history of cannabis use (HR-C−). High-risk status and cannabis use were determined by structured clinical interviews. Subjects also received a comprehensive battery that consisted of 18 neuropsychological tests assessing 8 domains of neurocognitive performance. Tests were *z* scored based upon the performance of 80 healthy controls. Social functioning was assessed with the Global Functioning: Social Scale. Results: HR-C+ subjects were more likely to be Caucasian ($P = .002$) and older in age (16.8 vs. 15.7, $P = .003$) at baseline than HR-C− subjects. There were no differences on gender, SES, or IQ at baseline. Both groups had comparable levels of attenuated positive symptoms, but the HR-C+ group had significantly lower attenuated negative symptoms ($P = .03$). In general, a number of cognitive deficits were noted in the high-risk group as a whole. However, in most cases, the HR-C+ group was less than −0.5 SD below normal, whereas the HR-C− group scores varied from −0.5 to almost −1.5 SD below normal. In terms of group comparisons, HR-C+ subjects had significantly better executive functioning ($P = .02$) and motor speed ($P < .001$) scores compared with non-cannabis using participants. The HR-C+ group also displayed higher social functioning scores ($P < .001$). Conclusion: Our results are consistent with the findings in first-episode and chronic schizophrenia populations in that cannabis using subjects evidenced better neurocognitive performance compared with those who had never used cannabis. Combined with better social functioning in the HR-C+ group, there is no evidence supporting the negative impact of cannabis use in this sample.
ID: 978650

HOW HYPOTHESIS-CONFIRMING AND HYPOTHESIS-DISCONFIRMING INFORMATION IS TREATED ACROSS THE PSYCHOSIS CONTINUUM

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Background: In recent years there has been increasing attention to how individuals with active delusions and those identified as ''delusion-prone'' treat hypothesis-confirming and -disconfirming information. Initial research suggested that individuals with delusions typically exhibit a jumping to conclusions (JTC) bias when administrated the probabilistic reasoning ''beads task'' (ie, decisions made on limited evidence and/or decisions are over-adjusted in light of disconfirming evidence). More recent research instead proposes that that the ''beads task'' in its traditional form may be confounded by non-comprehension of task instructions and the JTC effect may instead represent a hyper-salience to hypothesis-evidence matches. Moreover, other tasks have found that disconfirming evidence is actually ignored rather than being over-adjusted to. This study attempted to clarify this set of findings across a variety of cognitive-reasoning tasks. Methods: A total of 75 participants were recruited, consisting of 25 individuals diagnosed with schizophrenia (with a history of active delusions) and 50 controls (25 delusion-prone; 25 non-delusion prone as identified the Peters et al Delusions Inventory). Cognitive tasks employed included a modified version of the ''beads task (designed to promote task comprehension) and various other ''confirmation bias'' tasks, where participants evaluated pieces of information which are either con-

sistent or conflicting with the given hypothesis. Results: The results suggest that when non-comprehension of the "beads task" is significantly reduced, individuals with delusions will still make hasty decisions but no longer over-adjust their decisions in light of disconfirming evidence. Results on the other tasks suggested that people with delusions and delusion-prone individuals were hyper-salient to hypothesis-confirming evidence, whilst tending to downplay hypothesis disconfirming information. Conclusion: Taken together, these findings suggest individuals with delusions are more hyper-salient to hypothesis-evidence matches yet underemploy disconfirming evidence. This bias may influence delusion formation and/or maintenance.
ID: 1002797

PREDICTORS OF FUNCTIONAL DISABILITY IN PATIENTS WITH SCHIZOPHRENIA AND AFFECTIVE PSYCHOSIS: SYMPTOMS, COGNITION, AND GENES

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Background: Functional disability is common in both schizophrenia (SZ) and bipolar disorder (BPD) yet the severity of functional deficits varies within and across diagnoses. Functional disability has generally been studied from a psychosocial perspective; however, a biomarker approach may also be useful. In SZ, cognition and negative symptoms have been shown to directly influence functional outcome and have also been associated with genetic variation in candidate susceptibility genes. Fewer data are available in BPD but a similar pattern is emerging. Methods: Analyses included 185 stable SZ patients and 50 stable BPD patients with a history of psychosis. Subjects were characterized for current symptom severity and cognitive functioning, as measured by the MATRICS. We assayed functional capacity with an externally-valid test of everyday function, the UCSD Performance Skills Assessment (UPSA). Functional outcome measures included the Multidimensional Scale of Independent Function (MSIF) and the Social Adjustment Scale (SAS). We conducted regression analyses and correlations to clarify relationships among demographic, clinical, cognitive and functional measures in the full sample and in each diagnostic group independently. Results: In patients with SZ, we found significant relationships between key clinical and cognitive phenotypes and functional disability. Specifically, independent living status was associated with verbal memory performance (73% correct classification); work disability was associated with negative symptoms and working memory capacity (71% correct classification); and social functioning was related to negative symptoms, attention, and social cognition (73% correct classification). Preliminary data in the BPD patients indicate overlapping predictors of social functioning, with attention, social cognition and negative symptoms showing the strongest associations; while differing patterns emerged in the prediction of work and residential status. Data collection is ongoing; results will be updated prior to presentation. Conclusion: Several clinical and cognitive traits influence everyday function in both SZ and BPD, with some degree of overlap. These data are consistent with genetic evidence that these illnesses may not be distinct diagnostic entities. Results will be placed in the context of prior work in molecular genetics, using dysbindin (DTNBP1) as an example of a gene that may influence functional disability via its effects on negative symptoms and cognition.
ID: 979365

PERFORMANCE CHARACTERISTICS AND FACTOR ANALYSIS OF THE MATRICS CONSENSUS COGNITIVE BATTERY

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Background: The MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB) was developed for use in clinical trials of new treatments for schizophrenia. Although the MCCB was created for assessment in schizophrenia research, to date there is little information on how schizophrenia patients actually perform on the battery. This study aimed to characterize performance on the MCCB in patients with schizophrenia-spectrum disorders and to determine the pattern of relationships among subtests through factor analysis. Methods: 195 participants diagnosed with schizophrenia or schizoaffective disorder enrolled in a two-site study (Atlanta and San Diego) validating measures of functional outcome and examining functional correlates of cognitive performance. Participants completed a one-time battery including the MCCB, measures of functional capacity, and 6 questionnaires related to real-world outcomes. Uncorrected *t* scores for MCCB performance were generated from software available from MATRICS Assessment Inc. Factor analysis was conducted with principal components extraction of raw MCCB scores. Results: On average, participants were 44 years old and completed 13 years of education. The majority of the sample was male (69%), Caucasian (55%), and diagnosed with schizophrenia (58%). Participants' mean MCCB performance ranged from mildly-moderately impaired to low average (*t* scores ranged from 33.3 to 42.5; Table 1). They were most impaired on the symbol coding test of processing speed and least impaired on verbal fluency. Exploratory factor analysis yielded a one-factor solution, with all factor loadings $\geq$ .48. Conclusion: Consistent with the general literature on cognition in schizophrenia, participants in this sample performed one to one and a half standard deviations below the mean. The one-factor solution generated by the exploratory factor analysis appears to support a global neuropsychological construct measured by the MCCB.
Mean MCCB Performance (n = 195)

MCCB subtest	Mean *t* score	SD	Range
Symbol Coding	33.3	10.2	1–59
Trail Making Part A	36.8	12.4	0–74
Continuous Performance Test	34.2	10.4	10–60
Letter-Number Sequencing	37.4	10.1	15–70
Spatial Span	39.2	10.7	14–64
Verbal Learning	37.2	8.5	20–63
Visual Learning	40.0	13.0	10–66
Verbal Fluency	42.5	9.2	21–73
Mazes	41.4	10.0	28–65

ID: 949870

NEUROCOGNITIVE IMPAIRMENTS IN YOUTHS AT-RISK FOR PSYCHOSIS ARE STABLE OVER TIME

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Background: Accumulating evidence suggests that neurodevelopmental abnormalities preceding clinical manifestation of illness are present in youths at-risk for developing psychosis. Neurocognitive abilities, especially exec-

utive, attention and memory dysfunction, are implicated as candidate endophenotypes of schizophrenia, including through evidence of impairment in adult first-degree relatives. Impaired endophenotype performance in youths deemed at-risk for schizophrenia bears directly on the endophenotype's ability to serve as a marker for early identification and treatment, but the developmental profile of impairments is unclear. We therefore evaluated 6-month test-retest stability of neurocognitive performance in young people. Methods: Young people (age 10–25) completed a comprehensive diagnostic assessment and the University of Pennsylvania Computerized Neurocognitive Battery (CNB) in the context of the Neurodevelopment in Adolescence and Young Adulthood (NAYA) program and other NIMH funded multi-site collaborations. Groups included Clinical Risk (CR; prodromal status based on Structured Interview for Prodromal Syndromes, $n = 12$; mean age = 20.2); Genetic Risk (GR; first-degree relative with schizophrenia, $n = 44$; mean age = 21.5); Psychotic Disorder (PSY, $n = 97$; mean age = 21.9); and Low Risk (LR, $n = 97$, mean age = 21.8)]. Fifty-4 participants (CR $n = 5$; GR $n = 9$; PSY $n = 15$; LR $n = 25$) completed a 6-month follow-up assessment. Results: At baseline, CR showed significant (all P's $< .05$) impairments in accuracy of attention and spatial memory, with trends in both CR and GR for impairments in other aspects of memory (verbal and facial), and abstraction. PSY were impaired across all assessed domains. Repeated measures ANOVA revealed no significant time by group effects, indicating that observed group differences remained stable at 6-month follow-up. Conclusion: Candidate neurocognitive endophenotypes reported in adult patients with schizophrenia and their relatives, especially attention and memory, are also observable and temporally stable (over 6 months) in young people at-risk for psychosis. They thus may reflect pathophysiological abnormalities involved in schizophrenia development, and may ultimately facilitate early identification of at-risk youths.
ID: 978787

THE ROLES OF IQ AND CLINICAL PROFILE ON WORKING MEMORY AND SUSTAINED ATTENTION PERFORMANCE IN PATIENTS WITH SCHIZOPHRENIA: A NEUROPSYCHOLOGICAL APPROACH

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Background: The resources of working memory (WM) deficit in schizophrenia remains unclear. We aimed to examine the specific roles of IQ and clinical profile upon different working memory (WM) components and sustained attention dysfunction in patients with schizophrenia. Methods: We compared 60 patients with schizophrenia to 41 healthy controls matched on age, educational level, and pre-IQ in 4 WM tasks, namely the Digit Span Backward Test (in WAIS-RC), the Chinese version Letter-Number (L-N) Span Test, and the N-back Tasks (both semantic and spatial versions). A test of the Sustained Attention to Response Task (SART) was also administered to participants for assessing sustained attention performance. Results: The results of the MANCOVA controlling for IQ, age and years of education showed that patients with schizophrenia performed significantly worse than healthy controls in L-N span test, N -back Tasks (both semantic and spatial versions), and SART ($F(1,96) = 7.107, 6.227, 6.884$, and 15.354; $P = .009, .014, .004$, and $P < .001$, respectively), with a medium to large effect (partial η square ranged from 0.084 to 0.13). IQ had significant main effects on accuracy in all WM tasks but no significant main effects on reaction time in 2-backs and SART performances. On the other hand, attention also had significant main effects on accuracy in all WM tasks. WM (especially spatial WM) deficit in patients with schizophrenia were significantly associated with the clinical characteristics of the patients [$r = (-.321)–(-.352)$, $P = .006–.012$]. None of the relationships between attentional function and IQ, age, and clinical variables was significant (r ranged from .003 to .271, P ranged from .036 to .975). A stepwise linear regression analysis with the accuracy of spatial 2-back as the dependent variables suggested that, in the final model, significant predictors was the accuracy in SART, IQ and group (ill/healthy). The model was significant (ANOVA $F(3,97) = 8.338$, $P < .001$), and explained 20.5% of the variance ($R^2 = .205$). In the model, the accuracy in SART explained 10.4% (R square change=.104, $F(1,99) = 11.465$, $P = .001$), IQ 5.50% (R square change = .055, $F(1,98) = 6.37$, $P = .013$) and group (ill/healthy) 4.7% (R square change = .047, $F(1,97) = 5.675$, $P = .019$) of the variance. Conclusion: These findings suggest a general impairment of WM across modalities in schizophrenia, with IQ, attentional function and clinical features played significant roles in WM, especially semantic WM deficits in schizophrenia.
ID: 978288

IMPACT OF NEUROCOGNITION ON FUNCTIONAL OUTCOME IN THE PRODROMAL PHASE OF SCHIZOPHRENIA

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Background: A major public health concern associated with schizophrenia is the long-term disability that involves impaired cognition, lack of social support, and an inability to function independently in the community. A critical goal of research concerned with early intervention is therefore to understand the factors lead to this often profound impairment. The current study focuses on the development and interrelationships of the major early components of later disability in adolescents at risk for psychosis. The question of primary interest is the extent to which early cognitive deficits are associated with emerging social and role problems prior to the onset of psychosis and whether there is a common underlying decline. Methods: 127 patients at clinical high-risk (CHR) for psychosis were identified and recruited for research to the Recognition and Prevention (RAP) Program. At baseline, patients were administered a comprehensive neurocognitive battery, as well as measures of social and role functioning (Global Functioning: Social and Role scales). Functioning was also assessed during routine follow-ups over a 3 to 5 year time period. Of the 127 assessed at baseline, 79 subjects had follow-up ratings available and were selected for this study. Functional outcome was based on the last follow-up rating available ($M = 3.5$ years). Results: Of the 79 CHR patients, 46.8% and 49.4% had a poor outcome (defined as having a GF score of <7) in social and role functioning, respectively. We found significant relationships between neurocognitive domain scores and functional outcome in CHR patients. Specifically, we found that social functioning was predicted by verbal memory performance, while role functioning was predicted by negative symptoms and verbal memory scores. We also found that positive symptoms and demographic variables were not related to functional outcome. Conclusion: Consistent with the findings of FE and ME schizophrenia studies, neurocognitive impairments were associated with functional outcome in patients at clinical high-risk for psychosis. In addition, a large proportion of the CHR subjects displayed social and role impairments at last follow-up, highlighting the importance of characterizing non-psychotic outcomes. These findings strongly support the increasing emphasis on functional decline as a critically important outcome that parallels conversion to psychosis, and suggest that both psychosis and long term functional disability are equally important targets for prevention.
ID: 980021

DIFFERENTIAL NEUROCOGNITIVE PROFILE BETWEEN PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDERS: EXAMPLE FROM PROSPECTIVE MEMORY

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Background: Categorization of psychotic illnesses into schizophrenia and affective psychoses remains a going controversy. Most recent evidence also suggests schizophrenia and bipolar disorders present a clinical continuum with partially overlapping in genetics, symptom dimensions, and neurocognitive deficits. This study attempted to examine the potential differential deficits of a specific memory ability to remember for the future, namely prospective memory (PM), between patients with schizophrenia and bipolar disorders. Methods: This study recruited 58 participants (19 schizophrenia, 19 bipolar disorders, and 20 healthy controls) through a well-established early intervention program for psychosis in Hong Kong Special Administrative Region. Participants were matched in gender and age. A computer test specifically capturing the time-based, event-based, activity-based PM components were administered to all participants on an individual basis. Each participant also received a full set of neurocognitive functioning test assessing IQ, memory and executive functioning. Results: A MANCOVA analysis controlling for education and IQ indicated that there was no significant difference among groups in time-, event-, activity-based PM or PM composite score. However, there were subtle impairments of PM in patients with bipolar disorders compared with healthy controls (perceptual event-based PM, $P = .094$), and schizophrenia compared with controls (semantic time-based PM, $P = .061$). An examination of other neurocognitive functions also indicated that there were significant differences among the 3 groups in visual reproduction immediate recall ($P = .047$), letter-number span longest passed ($P = .026$), and Wisconsin Card Sorting Test perseverative error ($P = .017$). Conclusion: These current findings are consistent with the previous findings that patients with bipolar disorder and schizophrenia both share neurocognitive deficits. However, these 2 clinical groups also demonstrate a qualitatively different neurocognitive profile. Specifically, there is also a continuum of dysfunction along which patients with schizophrenia consistently manifest the most severe impairments, and bipolar disorders, on average, showing a similar but attenuated pattern of dysfunction.
ID: 977196

NEGATIVE SYMPTOMS AND NEUROCOGNITIVE DEFICITS IN FIRST-EPISODE SCHIZOPHRENIA SPECTRUM DISORDER

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Background: Negative symptoms and neurocognitive deficits in schizophrenia are found to be correlated cross-sectionally but their longitudinal relationship remains unclear. Most studies focused on chronic illness and negative symptoms were examined as single construct instead of its subdomains. We aimed to investigate relationship between diminished expression and neurocognition in patients presenting with first-episode schizophrenia utilizing a prospective design. Methods: Ninety-three subjects (42 males, 51 females, mean age: 31.2) with first-episode schizophrenia, schizoaffective disorder or schizophreniform disorder were followed up for 3 years during which regular assessment in neurocognition and symptoms were conducted. Neurocognitive assessments included Wisconsin Card Sorting Test (WCST), digit span, verbal fluency, visual reproduction and logical memory. Cambridge Neurological Inventory (CNI)and PANSS were administered to evaluate neurological soft signs and clinical symptoms respectively. Severity of Diminished Expression (DE) was sum of item scores in Affect, Behaviour and Speech subscales of High Royds Evaluation of Negativity Scale (Mortimer et al. 1989). Results: Neurocognitive deficits were correlated with severity of DE on a cross-sectional basis. When sex, educational level, DUP, chlorpromazine equivalent, positive symptoms, drug-induced Parkinsonism and depression were controlled, regression analysis showed that at year 1, DE was significantly associated with verbal fluency (R square = .12, $P < .01$); at year 2, DE was predictive of WCST perseverative error (R square = .12, $P < .001$), WCST categories completed (R square = .10, $P < .001$), visual reproduction (R square = .16, $P = .01$) and CNI-motor coordination (R square = .18, $P < .05$); at year 3, DE was significantly associated with verbal fluency (R square = .09, $P < .05$) and forward digit span (R square = .05, $P < .05$). Longitudinally, change of DE rating (and PANSS negative symptoms score) was uncorrelated with neurocognitive change over 3 years. Baseline DE was not associated with neuropsychological performance at year 3. Conclusion: Neurocognitive deficits and DE were correlated in successive assessments but longitudinal association between changes of these 2 domains in first-episode schizophrenia could not be demonstrated. Our findings indicated that negative symptoms and cognitive deficits are separable illness domains with potentially related underlying neurobiological abnormalities.
ID: 979369

RELATIONSHIP BETWEEN SENSORY DEFICITS AND LANGUAGE PROCESSING IMPAIRMENTS IN CHINESE SCHIZOPHRENIA PATIENTS

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Background: Occidental schizophrenia (Sz) patients show impairments in tone matching ability related to impairments in emotional prosodic processing. Deficits in syllable detection, however, are mild. In contrast, in Mandarin, syllables are voiced in 1 of 4 tones with the same syllable having different meaning depending upon tone. We hypothesized therefore that the Mandarin-speaking Sz patients would have auditory word recognition deficits related to impairments in underlying basic auditory processing. Methods: 20 Mandarin-speaking Sz patients and 24 matched healthy participants were recruited from a Chinese-bilingual psychiatric inpatient unit and a Chinese church in New York City, respectively. The main auditory tasks administered to all participants were (1) tone matching, (2) Chinese word discrimination, and (3) Chinese word identification. Demographic and employment measures were used to examine potential effects of tonal deficit on social-occupational function. Results: As a group, Sz showed significant deficits in tone matching ($P < .0005$),

word discrimination ($P < .005$) and word identification ($P < .05$). Sz made significantly more errors vs. controls to words that were phonologically similar ($P < .01$), but not to words that were phonologically unrelated. Both word identification ($\rho = .45$, $P < .005$) and discrimination ($\rho = .35$, $P < .05$) correlated significantly with underlying impairments in tone matching across groups. To assess relationship to social-occupational function, employment status was dichotomized into menial (long hours/low wages) vs. skilled (high pay/student). All patients with impaired auditory processing were found to be holding menial jobs (10/10) vs. only 2/10 patients with intact auditory function and 6/24 controls (chi-square(2, $N = 44$) = 22.5, $P < .0005$). Sz in the good vs. poor outcome groups did not differ in age, gender, or parental education level. Conclusion: This is the first study to evaluate auditory processing in tonal-language Sz. Consistent with the priori prediction, Sz were impaired in both basic tone processing and auditory word processing, with significant correlation between the 2 measures. Sz with auditory sensory impairments showed significantly worse social-occupational function than those with intact word recognition, suggesting a link between sensory impairment and overall functional outcome. Thus, while neurophysiological deficits associated with Sz are likely the same across cultures, consequences of such deficits may be language and culture dependent.
ID: 975115

EFFECTS OF AMISULPRIDE, ARIPIPRAZOLE, RISPERIDONE AND HALOPERIDOL ON COGNITIVE FUNCTION IN HEALTHY VOLUNTEER

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Background: Cognitive impairment is a core feature of schizophrenia and a major impediment to social and vocational rehabilitation. Recent evidence suggest that atypical antipsychotics may impair cognitive function. The aim of the present study was to assess the effects of single doses of antipsychotics or placebo on cognitive function in healthy volunteers. Methods: This study was a randomized, double-blind, placebo-controlled trial. Seventy-eight subjects (mean age, 28.28 ± 2.57) were randomized to 5 group: haloperidol(HPT) 3 mg, risperidone(RIS) 2 mg, amisulpride(AMS) 400 mg, aripiprazole(ARP) 10 mg, and placebo(PL). For the evaluation of cognitive function, computerized neuropsychological tests including digit span test(DST), auditory continuous performance test(Auditory CPT), Stroop test(ST), verbal learning test(VLT), Trail marking test(TMT), Wisconsin card sorting test(WCST), and word fluency test(WFT), were performed. All assessments were conducted at 1 week before the ingestion of the drugs and 4 hour after the administration by blind rater. Results: All antipsychotics except placebo produced significant impairment of auditory CPT. However, all drugs including placebo induced significant improvement of verbal learning test and differential improvements of tests were observed in different drugs: AMS produced significant improvement of WFT and TMT, ARP significant improvement of DST and TMT, and PL significant improvement of WFT, ST, and TMT. Analysis of change scores from baseline to end point revealed that AMS induced greater improvement of WFT compared with ARP, HPT, RIS and PL. Conclusion: Single administration of atypical antipsychotic drugs impeded sustained attention. However, significant improvements of memory and other cognitive domains were observed which may be related to practice effects. These findings should be considered in choosing optimal antipsychotics for patients with psychosis.
ID: 976105

NEUROPLASTICITY-BASED COGNITIVE TRAINING IN SCHIZOPHRENIA IN A "REAL WORLD" SETTING

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Background: Recent neuroplasticity-based cognitive training programs have shown positive effects in improving cognition in schizophrenia. While most prior studies have provided cognitive training in a laboratory setting, few studies have assessed whether such training programs are feasible in a "real world" setting. Here we examine the differences in applying cognitive training in a laboratory setting vs. in a community mental health setting. Methods: To date, 27 participants have enrolled in 2 on-going studies of cognitive training: 1) cognitive training combined with social cognition training in a laboratory setting, 2) cognitive training combined with supported employment in a community mental health setting. MATRICS-recommended measures were used to assess cognition. Symptom severity and global functioning were assessed with the Positive and Negative Symptom Scale and the GAF. The characteristics of subjects at each site and attrition rates were compared via Independent Samples t tests and Chi-Square. Results: Subjects in training in the community mental health setting show significantly lower baseline cognitive functioning on measures of Global Cognition ($P = .01$), Speed of Processing ($P < .009$), and Working Memory ($P = .004$), relative to subjects in the laboratory setting. Community setting subjects also show significantly lower GAF scores ($P = .04$) and higher symptom severity across all PANSS subscales, approaching trend level significance. To date, there are no significant differences in attrition rates between the 2 sites: 14 subjects have enrolled in the laboratory study and 21% have discontinued, while 13 subjects have enrolled in the community setting study and 8% have discontinued. Conclusion: Subjects in a "real world" setting show greater cognitive impairment, symptom severity, and lower global functioning compared with subjects in a laboratory setting, yet the groups do not differ in attrition rate. These results suggest that it is indeed feasible to run a complex, cognitive training treatment study with participants in a community mental health setting. The results also suggest that subjects in a laboratory setting are less representative of individuals with schizophrenia in the "real world," and that caution should be taken when interpreting laboratory-based results.
ID: 979743

AUDITORY VERBAL HALLUCINATIONS AND COGNITIVE FUNCTIONING IN HEALTHY INDIVIDUALS

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Background: Cognitive deficits in psychotic patients with auditory verbal hallucinations (AVH) have often been described. When investigating psychotic patients it is unclear whether the decline on cognitive domains stems from specific symptoms such as AVH, or from an overall diminished functioning due to associated symptoms, decreased general functioning or medication. Examining the cognitive profile of healthy individuals experiencing auditory verbal hallucinations may reveal a more direct association be-

tween AVH and cognitive deficit in a specific domain. Moreover, performance on cognitive tasks of such a healthy hallucinating group might give more insight into the underlying pathophysiology of AVH. Methods: A group of one-hundred healthy individuals frequently experiencing AVH was carefully screened to rule out psychopathology. Performance on several cognitive domains was compared between these 100 healthy individuals with AVH and 101 healthy control subjects, successfully matched for sex, age, handedness and education. The measured domains are executive functioning, memory (both short- and long-term), lexical access and abstract reasoning, verbal fluency and intelligence correlates. Results: Significant differences between the groups were found within the verbal domain only: healthy individuals with AVH scored lower on the vocabulary test, similarities test as well as the NART, a measure of verbal IQ. Performance on other cognitive domains was not significantly different between the groups. Conclusion: Experiencing AVH is associated with cognitive deficits in the verbal domain. Possibly, a central abnormality in the language system, reflected in decreased test results, underlies the tendency to experience AVH.
ID: 976176

ESTIMATES OF PREMORBID AND CURRENT IQ IN FIRST EPISODE PSYCHOSIS: WHAT DO THEY MEAN?

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Background: Estimates of pre-morbid IQ have been used to infer cognitive deterioration ("IQ decline") in schizophrenia as a substitute for prospective measures. This pattern of cognitive functioning is established at the first episode. Interpreting apparent decline is complicated by psychometric and other methodological considerations and its implications are unclear. Methods: Two clinical cohorts underwent a comprehensive neuropsychological battery. Cohort 1 comprised 53 patients with first episode psychosis, and 71 geographically matched controls from South East London. Cohort 2 comprised 153 patients with psychosis (including non affective and affective disorders) and 177 healthy controls from the UK AESOP study. Results: Cohort 1: Current IQ was estimated using the WAIS III. The National Adult Reading Test (NART) and the Wechsler Test of Adult Reading (WTAR) were used to estimate pre-morbid IQ. On pre-morbid and current IQ estimates, patients underperformed compared with controls. NART significantly underestimated controls' IQ while apparently overestimating patients' IQ. The WTAR showed a similar pattern. In a comparison of NART vs. current IQ, 16% of patients showed IQ deterioration of least 10 points compared with 5% of controls. Patients with stable-low and deteriorating IQ showed impairments on memory tasks, although processing speed further differentiated the sub-groups. Cohort 2: A degree of apparent IQ decline was seen in all diagnostic groups in various cognitive domains although there were interactions between gender and diagnosis. Conclusion: Discrepancies between estimates of IQ derived from reading tests in relation to standardized measures of IQ are a reliable finding in schizophrenia and other psychotic disorders. However this may reflect differential deficits in fluid vs. crystallized intelligence, or performance vs. verbal IQ. Results from Cohort 1 highlight differences between apparently similar reading tests and also, contrasting patterns of under- and over-estimation of IQ with patient and control groups respectively. Results from the larger Cohort 2 enabled us to explore "IQ decline" in relation to diagnosis and other important moderating variables such as gender. We conclude that discrepancies between reading-based and other cognitive measures may not reflect simple IQ decline but nevertheless account for important aspects of the cognitive profile of psychosis.
ID: 976595

NOISE POWER DURING AUDITORY PROCESSING AND NEUROCOGNITIVE OUTCOME IN SCHIZOPHRENIC PATIENTS AND FIRST DEGREE RELATIVES. A PROSPECTIVE STUDY OF CORTICAL NOISE AS A POSSIBLE ENDOPHENOTYPIC MARKER

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Background: In recent years, the increase of stimulus-uncorrelated cortical activity or Cortical Noise during information processing has emerged with some consistency in schizophrenia, and it may be an important feature underlying certain clinical and/or cognitive symptoms. The objective of this investigation is to carry out a prospect of Cortical Noise as a biological marker of the disease. Methods: A sample of 22 schizophrenic patients (mean 45.4; 15 male) was assessed with an extensive neurophysiological (P3ab Auditory-ERP 3-stimulus paradigm) and neuropsychological (BACS, MATRICS and WCST) battery. In the same way, a group of 7 unaffected first degree relatives (mean age 51.0; 2 male) and a group of 8 control subjects with no family history of the illness (mean age 39.1; 5 male) took part in the study. Results: Patients showed a significant increase in Noise Power, compared with relatives and control groups, mainly in central (C3, C4 and Cz) and temporal (T5) electrodes for theta, alpha and beta-1 frequency bands. However, the relatives group evidenced a significant increase in Noise Power only for the theta band at C3 electrode ($F = 2.52$; sig. < 0.10). Patients obtained a significantly worst outcome practically on every cognitive area compared with control and relatives groups. On the other hand, relatives showed a significant deficit in attention (CPT: $F = 32.06$; sig. < 0.01), working memory (Digit Sequencing Task: $F = 17.59$; sig. < 0.01) and speed of information processing (Symbol Coding: $F = 25.56$; sig. < 0.01). A negative correlation between theta band noise and neurocognitive outcome (CPT: rho = 0.67; sig. < 0.05; Digit Sequencing Task: rho = 0.58; sig. < 0.10) was found. Conclusion: Neuropsychological models for P3ab ERP support that P300 potential for target stimulus (P3b) obtains its maximum at central-parietal areas and is related to mnesic store and information recovery during attentional working. Our findings show that a theta cortical noise increase is located specifically in central areas, and are not only present in schizophrenic patients but in unaffected first degree relatives as well. Moreover, an equivalent and correlated deficit has been found in neurocognitive attentional and mnesic tasks. In this sense, the increase of theta Cortical Noise in central areas may underlie attentional and mnesic deficits. Although this is a preliminary study, our results point out positively to a valuable research target in the search for biological markers of the schizophrenic illness.
ID: 979279

VIRTUAL REALITY MEASUREMENT OF DAILY LIVING FUNCTIONING IN SCHIZOPHRENIA: A VIABLE ALTERNATIVE TO DIRECT ASSESSMENT?

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Background: Real-world functioning is markedly impaired in schizophrenia, is predicted by cognition and is an important target for psychological and pharmacological interventions. Direct assessment of day-to-day function is problematic. Virtual reality (VR) provides an opportunity to assess

this functioning in an immersive virtual environment akin to real life (RL), allowing greater experimental control, greater reliability of measurement, and a more timely assessment. Taking supermarket shopping as the target function, it is hypothesized that performance in VR will associate with that in RL. It is hypothesized that both shared and distinct cognitive processes will underlie performance due to inherent differences in the real and virtual environments. Methods: People with schizophrenia ($n = 43$, 53% male) completed a single assessment comprising both RL and VR supermarket shopping tasks and cognitive measures, selected for their hypothesized relationship to the shopping tasks or to the environment (RL or VR). Participants were required to shop for 10 items from a list in a self-directed search, once in RL and once in VR. In each task, measures were derived for i) accuracy (number of correct items selected) and ii) efficiency (time taken and number of aisles entered). Assessments of IQ, executive function, working memory, spatial memory and social cognition were also administered. Results: Significant inter-correlations were identified between all RL and VR shopping efficiency measures. Inter-correlations with accuracy measures were more limited. RL accuracy correlated exclusively with VR accuracy. In terms of underlying cognitive factors, a novel link was identified between RL shopping accuracy and social cognition. Emerging trends were found, consistent with previous research, between RL efficiency and the use of spatial search strategies and working memory. A link between VR efficiency and long-term visual reproduction memory was also suggested. Conclusion: RL and VR shopping performance are correlated, but may involve distinct cognitive processes which are themselves independently impaired in schizophrenia. Social cognition may have a particular role in the ability to shop for oneself in real life (but not virtual reality), where the search is self-directed but the task requirements are provided by others in the social environment. These findings have important implications for the assessment of real world function, the use of virtual reality and the approach to interventions.
ID: 979511

COMPARISON OF SELF-REPORT AND CLINICIAN EVALUATION OF NEUROCOGNITIVE DEFICITS IN SCHIZOPHRENIA

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Background: Patients with schizophrenia have been shown to have poor insight into neurocognitive symptoms but the stability of their insight into neurocognitive symptoms has not been well delineated. Methods: METHOD: 52 outpatients with schizophrenia or schizoaffective disorder were identified as evidencing cognitive impairment, defined as performance 1 or more SD below the normative mean on any one of the WAIS-III working memory or matrix reasoning subtests. Two measures of insight were administered, the Measure of Insight into Cognition - Clinician Rated (MIC-CR) and the Measure of Insight into Cognition - Self-Report (MIC-SR). Correlational analyses examined the relationships between the 2 subjective measures and objective measures of illness symptomatology. Test retest reliability of the MIC-CR and MIC-SR was calculated in the experimental control group ($n = 35$) from ratings completed 1 week apart. Results: Among those with objective cognitive impairment, there was significant ($r = -.53$; $P < .001$) but moderate agreement between patient (MIC-SR) and clinician (MIC-CR) subjective reports of cognitive ability. While clinician-rated insight was significantly related to objective performance measures (LNS: $r = -.32$, $P = .02$; matrix reasoning: $r = -.31$, $P = .03$), patient ratings of cognitive ability were not significantly ($P > .05$) related to actual performance. Test retest reliability was high for the MIC-SR (0.94, $P < .001$) and adequate (P values $< .001$) for MIC-CR assessment of awareness ($r = .81$) and (mis)attribution of cognitive deficit ($r = .64$). Conclusion: In outpatients with cognitive performance deficits, the MIC-CR and MIC-SR are reliable measures of awareness of dysfunction, but capture different aspects of insight. Importantly, patient perception of cognitive functioning is highly stable but inaccurate.
ID: 971453

THEORY OF MIND, SCHIZOPHRENIA AND VIOLENCE

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Background: There is a well recognized association between schizophrenia and violence. While substance misuse, especially in community settings, is important, there is relatively little known about other illness specific factors that might drive this link. One factor to consider is social functioning deficits. Methods: We conducted a literature database search and manual cross referencing, using combinations of the following terms: schizophrenia, psychosis, antisocial, violence, aggression, forensic, theory of mind, emotion recognition and facial affect. All identified studies were subsequently included in our review. Results: It is widely accepted that theory of mind (ToM) deficits are found in individuals with schizophrenia; however few have attempted to examine this in relation to violence in the disorder. Despite a modest number of studies ($n = 3$) and methodological inconsistency, there is increasing evidence that patients with schizophrenia who are violent exhibit greater/better ToM abilities than those with schizophrenia who are not. When compared with violent individuals with personality disorder, only more complex 2nd order ToM is compromised in schizophrenia. However, violent patients with schizophrenia exhibit impaired ability to recognize facial emotions in others, in particular fear and anger, compared with their non violent counterparts. This is consistent with findings in non psychotic conduct disorder patients who also manifest marked impairments in facial recognition and non psychopathic antisocial personality disorder subjects. Conclusion: This data suggest that a proportion of violent schizophrenia patients, possibly those with premorbid conduct disorder or antisocial personality traits, are likely to be characterized by a combination of good mentalizing and poor empathetic inferencing abilities as well as impaired inferencing of mental states. Although many of these studies are compromised by methodological inconsistencies, there is increasing evidence that social functioning deficits such as ToM, emotion recognition and empathy may play a significant role in informing our understanding of violence and aggression in schizophrenia. Future research should concentrate on more detailed investigation of violence in schizophrenia, examining comorbid disorders in order to identify illness specific aspects of social functioning focused on schizophrenia itself.
ID: 978508

COGNITION AND DISABILITY IN SCHIZOPHRENIA AND BIPOLAR ILLNESS

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Background: Recent research has revealed that patients with bipolar disorder manifest qualitatively similar patterns of disability and cognitive impairment compared with patients with schizophrenia. In schizophrenia that poor performance on measures of functional capacity is predictive of underachievement of functional milestones. In this presentation, performance on cognitive tests and measures of functional capacity and their relationships with real-world disability will be compared across these patient groups. Methods: A large sample of people with schizophrenia ($n = 164$) and bipolar illness ($n = 142$) was examined. They were tested with a com-

prehensive assessment of cognitive functioning, rated for clinical symptoms, tested on measures of social skills and the ability to perform everyday living skills, rated for their everyday functioning by an examiner who consulted an informant, and examined for the achievement of social and functional milestones such as employment, independence in residence, and history of long-term stable social relationships. Results: Patients with schizophrenia had greater impairment on cognitive tests and functional capacity compared with bipolar patients ($P < .001$). However, bipolar patients performed more than 0.5 SD more poorly than normative standards. In addition, schizophrenia patients were less likely than bipolar patients to have had stable social relationships, to be responsible for their residence, and to be employed. However, more than 1/3 of the bipolar patients were chronically unemployed, not financially responsible for their residence, and receiving disability or retirement compensation. Hierarchical linear modeling found that the diagnosis of schizophrenia vs. bipolar disorder did not account for any significant variance in the prediction of community activities or social functioning when performance on functional capacity measures were used to predict these outcomes. When predictor models were compared across diagnoses with a multiple-group modeling strategy, there was no significant difference in the overall goodness of fit for models predicting residential, social, or vocational outcomes (all $P > .50$). Conclusion: Cognitive functioning and functional capacity are impaired in people with bipolar disorder. The influence of these impairments on real world outcomes was indistinguishable across these 2 diagnostic groups, suggesting that differences in the prevalence of disability in these 2 populations are due to modest differences in functional abilities.
ID: 977017

WHICH TEST MEASURES BEST EXECUTIVE FUNCTIONS IN EARLY-ONSET SCHIZOPHRENIA?

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Background: The literature on adult-onset schizophrenia (AOS) shows that one of the most severe neuropsychological impairments are apparent in executive functioning, evident on a background of a generalized cognitive deficit. Accordingly, executive functioning deficits have been found prevalent in early-onset schizophrenia (EOS), but are investigated to a much lesser extent. Because the EOS group seems to exhibit poorer cognitive functions and is clinically more compromised than the AOS group, it is of great importance to choose the right assessment measures in this group. We wanted to examine whether the MATRICS' choice of Mazes (Neuropsychological Assessment Battery [NAB]) to measure executive functioning is suited for use in this patient group, compared with 2 commonly used tests; D-KEFS Color Word Interference Test (Stroop) and the Wisconsin Card Sorting Test (WCST). Methods: 31 adolescents (12–18 years) with schizophrenia spectrum disorders were included at the time of their first contact with a psychiatric department. Diagnoses are based on DSM-IV criteria. Symptom level was assessed using the PANSS and the Global Assessment Scale. Executive functioning was assessed with the Mazes Test, WCST and Stroop. 66 healthy adolescent controls have also been included in the study. Results: Significant discriminating power was found for all 3 measures. Stroop proved to be the most sensitive measure among the 3, while WCST was the least sensitive. Conclusion: The Mazes test proved sensitive enough to separate the EOS patient and control group and appears as a sensible choice in clinical settings. If a more elaborated evaluation of the executive functioning domain is needed, Stroop should be considered as a complementary test.
ID: 975569

DEAF SUBJECTS ARE MORE SENSITIVE TO THE EBBINGHAUS ILLUSION THAN THEIR HEARING PEERS: EVIDENCE FOR ENHANCED VISUAL-CONTEXT PROCESSING IN SCHIZOPHRENIA

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Background: Schizophrenia has been consistently characterized by impairments in perceptual organization, or the integration of separate elements into coherent wholes and object representations. The purpose of this investigation was to: 1) replicate past findings regarding context integration using a psychometrically sound version of the Ebbinghaus illusion task; 2) to characterize the nature of the effect (if any) in deaf patients with schizophrenia, which had not been done before, and 3) to address the issue of plasticity of the perceptual organization deficit in schizophrenia. Methods: Based on the Ebbinghaus illusion, a 2-alternative forced choice paradigm required subjects to compare 2 separate arrays, and decide whether the target stimulus in the left- or right-hand array was larger. The illusion was created by surrounding the target circles with additional circles of particular sizes. A process-oriented approach was employed that exploits the use of tasks producing both enhanced and reduced performance indicators. The result pattern predicted is thus distinguishable from patterns associated with generalized deficits. Results: Deaf subjects with low levels of disorganization and shorter illness durations were the most context sensitive subjects in the study as indicated by more accurate size perception when the context was helpful (control condition) and less accurate size perception when the context was misleading (test condition). All differences between deaf and hearing subjects were significant across both conditions. Although the hearing subjects were significantly less context sensitive than their deaf peers, the pattern of performance observed suggests that dysfunctional perceptual integration mechanisms were the result of a specific deficit in integrating stimulus elements for all subjects. Conclusion: We interpret these data as further support for the hypothesis that the disorganization syndrome in schizophrenia reflects a widespread deficit in the cognitive coordination of contextually related stimuli and may lead to dysfunctional grouping of stimulus features in vision, thought and language. Given deaf people's unique experience with visuospatial processing, and in the context of data indicating that the susceptibility to the Ebbinghaus illusion develops on the basis of visual experience, our data suggest that perceptual organization dysfunction in schizophrenia is plastic and may be amenable to remediation.
ID: 980145

PREVALENCE OF PERSISTENT NEGATIVE SYMPTOMS IN FIRST EPISODE PSYCHOSIS: A COMPARISON OF 3 DEFINITIONS AND THEIR RELATION TO COGNITION AND FUNCTIONAL OUTCOME

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Background: What constitutes persistent negative symptoms (PNS) remains highly debated due to the lack of a consensus definition, which may contribute to the uncertainty of the prevalence of such symptoms. Hence, the aim of this study was to apply different PNS definitions and

to explore their associations with functional outcome, which may help provide a heuristic value to our PNS definition. Associations with cognition were also assessed. Methods: Our cohort consisted of 148 first episode psychoses (FEP) patients recruited from the Prevention and Early Intervention Program for Psychoses (PEPP) of the Douglas Institute. As part of the regular PEPP protocol, negative symptoms (NS) were assessed at baseline, month 1, 2, 3, 6, 9, and 12 using the Scale for the Assessment of Negative Symptoms (SANS). Only patients with primary NS were included, thus as suggested by Buchanan (2007) those with positive, depression or extrapyramidal symptoms were excluded. Three PNS definitions were examined: 1) having moderate NS on at least 1 global item of the SANS (PNS-1); 2) at least 2 global items of the SANS (PNS-2); 3) a hybrid of global items (PNS-h) as outlined by Foussias et al. (2010). Each group was compared with patients without PNS to determine whether one definition was better associated with functional outcome at 1-year follow-up (FUP). The Social and Occupational Functioning Assessment Scale (SOFAS) was administered at baseline and 1-year. The following domains of cognition were assessed at the same frequency as the SANS: verbal and visual memory, working memory, speed of processing, reasoning and problem solving and attention. Results: Of the 148 patients with FEP, 29% fell into the PNS-1 group, 16% were in the PNS-2 group and 14% were in the PNS-h group. When compared with non-PNS, only PNS-1 was significantly associated with functional outcome with the PNS group exhibiting poorer functional outcome after 1 year. However, all 3 definitions were equally associated with cognitive function suggesting that although PNS-1 may help identify a larger sample of FEP patients with PNS, all 3 definitions may be comparable at correctly identifying PNS in an FEP population. Conclusion: This exploratory study suggests that PNS can have a prevalence of 14%–29% in FEP depending on the definition used. Our preliminary data suggests that examining the persistence of a single NS may be helpful in identifying early on cases at risk for a poor functional outcome.
ID: 979746

LIKELIHOOD OF SIGNIFICANT DIFFERENCES BETWEEN GROUPS WHEN SIMULTANEOUSLY ASSESSING SEVERAL COMPONENTS OF MULTIPLE NEUROPSYCHOLOGICAL DOMAINS

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Background: Schizophrenia research increasingly relies on the use of multiple neuropsychological measures addressing a range of domains. Interpretation of differences among and between groups is influenced by the numbers of measures used and the criteria used for impairment or clinical significance. Several approaches have been proposed to address this challenge, each with potential confounds. Methods: We have developed a relatively simple approach to determine criteria for significant differences when using highly multivariate measures based on the binomial probability distribution. An approach to evaluating the effects of multicollinearity is suggested. The problem of the observation of correlated deficits observed in multiple domains in clinical samples that are not highly correlated in control subjects is also addressed. Results: When applied to samples of multivariate clinical data, the method provides a reasonable estimate of the probability of observed differences. Potential error due to multicollinearity is estimable, and differences in intercorrelation matrices between clinical and control samples do not necessarily adversely affect the interpretation of results. Conclusion: The current application of the binomial probability distribution to multivariate clinical data provides a straightforward approach to the assessment of the significance of observed differences.
ID: 979649

THE IMPACT OF COGNITIVE RESERVE ON SCHIZOPHRENIA: NEURAL UNDERPINNINGS AND CLINICAL OUTCOMES

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Background: The cognitive reserve hypothesis proposes that those with higher intellectual function are more able to cope with the impact of neural insult because of higher brain structural reserve or better functional capacity to use compensatory neural processing (1). In schizophrenia, better cognitive reserve may result in fewer symptoms and better functional outcome (2). Methods: Two separate cohorts from the West London study of first episode schizophrenia were assessed for symptoms, social function, premorbid and current IQ, memory and executive function at psychosis onset and on 2 subsequent occasions over 3–4 years. A structural MRI was performed in a subset. Results: Premorbid IQ correlated with age of psychosis onset. Premorbid IQ and IQ at onset were both more sensitive and reliable predictors of 4-year social function than memory and executive functions(3). IQ was the most consistent predictor of the negative syndrome. Compatible with chronic schizophrenia findings (4), 40% showed a decline of 10 IQ points or more; the remainder showed either preserved average/high IQ or low premorbid IQ that had not changed (5). These IQ subtypes were also present in a different cohort (6); when these and healthy controls were assessed at 1 and 3 years following onset, all forms of cognitive function were stable, with any improvement explained by practice effects. Both low and deteriorated IQ groups had longer index admissions, more core negative symptoms and worse occupational outcomes at 3 years than the preserved average/high IQ group. Cortical area was reduced in patients and fronto-temporal area correlated with IQ which was stronger for IQ at illness onset than premorbid IQ(7). Conclusion: IQ reflects an abnormal process affecting cortical morphology in schizophrenia which critically determines illness severity with respect to cognitive function and clinical outcome. Because a large subgroup of patient undergo a change in IQ over the transition to psychosis, it is cognitive reserve at onset of psychosis that determines outcome. Early cognitive remediation may be particularly successful in this subgroup.
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ID: 978282

EMOTION PROCESSING IMPAIRMENT IN YOUNG PERSONS AT-RISK FOR PSYCHOSIS

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Background: Neurodevelopmental abnormalities affecting behavior are present in young persons at-risk of developing psychosis before the onset of illness. Cognitive abilities, including neurocognition and social cognition, are extensively implicated in schizophrenia and may represent candidate endophenotypes. Impaired performance in those deemed at-risk for schizophrenia is a characteristic reflecting the endophenotype's ability to serve as a marker for early identification and treatment. Methods: Young persons (ages 14–25) completed a comprehensive diagnostic assessment and

the University of Pennsylvania Computerized Neurocognitive Battery, which includes tests of emotion identification (ER40) and emotion differentiation (EmoDiff), and other measures. Groups included individuals deemed at-risk for psychosis [Genetic risk (GR): family history of schizophrenia, n = 52; Clinical Risk (CR): prodromal symptoms but no family history, n = 16]; schizophrenia (SZP): n = 100; and healthy controls (CNT), n = 101. Kruskal-Wallis analyses of variance were performed with Bonferroni adjusted P-values for multiple comparisons. Results: On ER40, persons with SZP and those with CR compared with CNT showed impairments in overall (SZP:P < 001, CR:P < .001), happy (SZP:P = .002, CR:P = ns), sad (SZP:P = .04, CR:P = ns), anger (SZP:P = .002, CR:P = .05), fear (SZP:P < .001, CR:P = .03) but not neutral identification. On EmoDiff, SZP compared with CNT showed impairments in happy (P < .001) and sad (P = .003) differentiation, while performance of CR was intermediate between SZP and CNT. Performance in GR was did not differ from CNT or SZP for most measures, except for overall (<.001) and anger (P = .032) identification, and happy differentiation (P = .025) which were better than in SZP. Effect sizes underscored the stepwise performance decrement between groups correlating with at-risk state. Conclusion: Tests of emotion processing revealed that young persons with CR showed decreased performance similar to young persons with SZP. Processing of facial affect may represent an endophenotypic marker related to relative risk of illness and reflect pathophysiological abnormalities involved in the development of schizophrenia.
ID: 978675

COGNITIVE DEFICITS IN FIRST-EPISODE ANTI-PSYCHOTIC NAIVE SCHIZOPHRENIC PATIENTS - A VALIDATION OF THE DANISH VERSION OF BACS (BRIEF ASSESSMENT OF COGNITION IN SCHIZOPHRENIA)

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Background: Schizophrenia is associated with deficits in cognitive functions, with prevalence estimates ranging from ca. 70%–85%. As part of the PECANS project (Pan European Collaboration on Antipsychotic Naïve Schizophrenia) the overall objectives of the present study are to establish the profile of cognitive deficits in first-episode, anti-psychotic naïve schizophrenia patients and relate these findings to measures of psychopathology, and examine effects of medication. The aim of the current presentation is to examine the prevalence and profile of cognitive deficits on the Danish version of the BACS. Methods: The overall design of the PECANS project is a 2-year longitudinal study with assessment at baseline and follow-ups after 6 weeks, 6 months, 1 and 2 years. First-episode, antipsychotic-naïve schizophrenia patients are included, as well as healthy controls. Data collection began in the fall of 2008, and so far includes 30 patients and 20 HC. The goal is to include 60 patients and 60 HC subjects and monitor and assess their clinical, functional, and cognitive status continuously. The study uses several instruments, including BACS and CANTAB (Cambridge Neuropsychological Test Automated Battery). Premorbid intelligence is estimated using DART (Danish Adult Reading Test) and current intelligence from 4 subtests from WAIS-III (Wechsler's Adult Intelligence Scale, 3rd ed.). Psychopathology ratings are obtained using PANSS (Positive and Negative Symptom Scale). Results: Significant deficits were present in all cognitive domains assessed on the BACS, with effect sizes ranging from 0.8 to 2 SD below the level of the healthy controls. Comprehensive deficits across several cognitive domains were detected in the antipsychotic-naïve, first-episode patients. Compared with the healthy control group, 65 % of patients (N = 19) were impaired below 1 SD in at least 3 cognitive domains in BACS; while this was the case for only 2 healthy controls. In fact, most of these patients (N = 17) were impaired in more than 3 cognitive domains, while this was not the case for any of the healthy controls. Conclusion: Comprehensive cognitive deficits across several cognitive domains are prevalent in schizophrenia patients from the time of their first episode, before initiation of treatment of antipsychotic medication. Effect sizes were similar to previous reports using the BACS, thereby validating the Danish version of this battery as a sensitive measure of cognitive deficits in first-episode anti-psychotic naïve schizophrenia.
ID: 979184

NEUROCOGNITIVE MARKERS OF TRANSITION TO PSYCHOSIS AND CHANGE IN PERFORMANCE OVER TIME - A MEDIUM TO LONG-TERM FOLLOW-UP OF THE ULTRA-HIGH RISK (UHR) COHORT AT PACE

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Background: Mechanisms that contribute to the progression from UHR to frank psychosis remain unclear. Neurocognitive impairment may be a valuable predictor of transition. Longer-term follow-up studies are necessary to validate the utility of neurocognition as a predictor. Additionally, few studies have investigated changes in neurocognition over time from UHR to frank psychosis. The current follow-up study investigated baseline predictors of transition to psychosis and change in neurocognition in a group of individuals identified as UHR between 2 and 15 years prior. Methods: Follow-up assessment occurred from 2007 to 2009. Transition status was established for 416 participants identified as UHR between 1995 and 2005. Baseline IQ data was available for 336 of these participants, 91 of whom had comprehensive neurocognitive data at baseline. 214 participants had both baseline and follow-up IQ data, while 68 had comprehensive data at both time points. Change in performance was investigated in relation to transition to psychosis and poor functional outcome (defined as low SOFAS and poor quality of life, regardless of psychotic status). Results: Transition to psychosis was associated with poorer performance at baseline on tasks of memory, psychomotor speed, PIQ and FSIQ. When modeled using survival analysis, only lower visual memory scores at baseline predicted transition (OR = 0.94, P = .002). Repeat measures ANOVAs (controlled for length of follow-up period) were conducted to investigate change in neurocognitive performance over time. In general, there were significant improvements in cognition over time. However, there was no significant interaction between transition and change in performance, indicating no differential neurocognitive change between those who transitioned and those who did not. Conversely, there were significant interactions between functional outcome and change (VIQ, FSIQ and Trails A), indicating that those with good outcome improved in cognitive performance over time, while those with poor functional outcome worsened over time. Conclusion: Poorer visual memory predicts transition to psychosis in this UHR sample, but transition was not associated with a worsening of neurocognition. However, participants with poor functional outcome showed worsening cognition from baseline to follow-up. This is the longest follow-up study of a UHR sample to date, providing valuable information on neurocognition over the phase of transition to frank psychosis.
ID: 979158

DEFICIT IN SHIFTS OF ATTENTION TO DIFFERENT LEVELS OF GLOBAL-LOCAL STIMULI IN SCHIZOPHRENIA

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Background: Aberrant attention and visual perception have long been considered core deficits of schizophrenia. The global-local task is a measure of attention and perceptual organization that utilizes visual stimuli comprised of large letters (global level) made up of smaller letters (local level). The purpose of this study was to investigate the persistence of global advantage effect and global/local level repetition and switching effects in schizophrenia using the global-local paradigm. Methods: Participants were twenty patients with schizophrenia and 20 age- and gender-matched healthy controls. They were administered the global-local tasks including repetitions and switching of global/local level. There were 6 patterns of repeated-level trials: the repetition in target level was the global-level and the local-level, and the number of repetitions in same target level was 2, 4, and 5, respectively. These trials between repeated-level trials defined as a switching trial. Thus, the switching trial indicated that the target level of the preceding level (N−1) mismatched the target level of the current level (N) after each repeated-level trial. Results: Schizophrenic patients showed higher rate of errors than controls in both repeated-level trials and switching trials. Healthy controls showed reaction time of global level was consistently shorter than that of local level in any repeated-level trials, while patients did not show such a pattern. In addition, healthy controls showed reaction time of the local-to-global level switch was shorter than that of the global-to-local levels switch. On the other hand, there was no difference between both switches in patients. Furthermore, healthy controls showed higher switching cost from global to local levels than the opposite switching cost. Patients showed higher switching cost from local to global levels than the opposite switching cost. Conclusion: This study using level-repetition procedure demonstrated that schizophrenic patients were difficult for voluntary switching of attention from local target to global target compared with healthy controls. The attention processing bias (local or global bias) was directly shown by switching cost and healthy control showed higher switching cost from global to local levels, while patients showed the reverse. These findings suggest an impaired ability to shift the visual attention from local to global processing in patients with schizophrenia.
ID: 979961

DIFFERENCES IN THE TRAJECTORIES OF IQ AND EPISODIC MEMORY IMPAIRMENTS IN YOUNG OFFSPRING AT HIGH GENETIC RISK FOR MAJOR PSYCHOSIS: STABILITY OF IMPAIRMENT VS. RECUPERATION FROM AGE 7 TO 22

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Background: Neurocognitive dysfunctions in episodic memory are well described in schizophrenic (SZ) or bipolar (BP) patients. Such dysfunctions have been detected in children at risk of SZ and BP, suggesting that memory impairments emerge a long time before the prodrome [1, 2]. However few studies have investigated the longitudinal mechanisms of cognitive dysfunctions in children at risk, which contrasts with the increasing number of studies addressing risk evaluation in the few years preceding the illness prodrome or onset. Our objective was to investigate the evolution in time of IQ and of verbal and visual memory impairments in young high-risk offspring. To what extent do the different dysfunctions persist, leading to different developmental courses from age 7 to 22? Methods: In a high risk sample, we used a step by step sampling approach to narrow-down the early disease mechanisms. Upstream, we started with a 20-year follow-up of 48 densely affected multigenerational kindreds, including 1500 clinically characterized adult members. We then identified 400 members affected by a DSM-IV schizophrenia or bipolar disorder. Downstream, we finally focused on 65 offspring aged 7–22, who were administered a neuropsychological battery. We then constructed cross-sectional trajectories that were compared with those of controls. Results: Our results suggested different developmental courses for IQ and memory. The childhood IQ deficit remained stable until young adulthood. In contrast, the delay in visual memory (*RCFT*) presented a non-linear 2-stage trajectory: a **lag** during childhood followed by a **recuperation** from adolescence until adulthood, as supported by a significant *group x age periods* interaction. No data suggested deterioration between 7 and 22 years of age. Conclusion: In children at risk of major psychosis, different cognitive dysfunctions would mark different developmental courses and the developmental trajectory of IQ impairment would differ from the one of specific domains of cognition such as memory. The potential recuperation process observed in visual episodic memory may indicate a corresponding capacity for neural plasticity. This raises the issue as to which should be the best cognitive target for prevention research. Our data also highlight the importance of focusing future prevention research on the right cognitive function at the right time in the child's life.
[1] Maziade, et al., Schizophr Bull, 2009. 35: 919–930
[2] Maziade, et al., Schizophr Bull, 2010. In press, online
ID: 978532

SYMPTOMS AND THEIR RELATION TO SOCIAL PERCEPTION IN SCHIZOPHRENIA: EXAMINATION OF A NEW INSTRUMENT

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Background: Impairments in social perception are prevalent among individuals with schizophrenia and are associated with social skill deficits (Meyer & Kurtz, 2009) and functional outcome (Mathews & Barch, 2010). A new measure, developed as part of the Wechsler Adult Intelligence Scale (4th edition; WAIS-IV) Advanced Clinical Solutions (ACS) Battery, shows particular promise in identifying these impairments among those with the illness. Although several measures have been examined over the years, this new instrument presents social cues in both visual and auditory modalities, conferring greater complexity to the tasks. Hence, this study sought 1) to assess the sensitivity of the Social Perception subtests of the WAIS-IV ACS battery to impairments in schizophrenia relative to healthy controls; and 2) to examine the relationship between positive, negative, and general symptoms and the ACS-based social perception measures. Methods: Outpatients with schizophrenia or schizoaffective disorder (n = 37) were recruited from a community based psychiatric care facility in Hamilton, Canada. Demographic information was gathered through chart reviews and brief clinical interviews. All participants were given the Positive

and Negative Syndrome Scale (PANSS), and the WAIS-IV ACS battery's Social Perception subtests. Results: One-tailed independent samples *t* tests revealed significant differences ($P < .05$) between the schizophrenia and healthy control groups (obtained from the WAIS-IV standardization sample and matched for age, gender and education level) on all measures of social perception. In the schizophrenia group, negative symptoms correlated significantly with all measures of social perception, and general symptoms correlated with all but the affect naming composite measure. In contrast, positive symptoms did not correlate with any of the social perception measures. Conclusion: Findings suggest that the Social Perception subtests of the WAIS-IV ACS are sensitive to schizophrenia impairments and vary with negative and general symptoms. These results demonstrate the potential utility of this new instrument and have implications for research examining the nature of social perception relative to symptoms in schizophrenia. This study is supported by the Canadian Institutes of Health Research, the Ontario Mental Health Foundation, and the CSVR foundation. We also thank Pearson Clinical Assessments for unrestricted prepublication use of WAIS-IV materials and standardization sample data.
ID: 976703

COMORBID ANXIETY AND SHORT-TERM CLINICAL OUTCOME IN FIRST EPISODE PSYCHOSIS

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Background: In psychotic disorders, a limited number of studies have looked at the effect of comorbid anxiety, especially in first-episode psychosis. Currently, there is growing interest in comorbidity, which is driven primarily by concerns on how these symptoms might affect severity and outcome. However, psychiatric literature provides very few references to the nature of the link between symptoms for anxiety and schizophrenia. Our goals for the current study was first to see whether the PANSS single item subscale "anxiety" item would be significantly correlated to the total score value of the HARS. Secondly, we were interested to see if among the FEP patients, fewer patients with comorbid anxiety (CA), as measured by the PANSS "anxiety" item, would have attained remission when compared with patients that did not obtain a significant rating of anxiety on the same scale. Methods: Data were collected in 175 FEP patients. The patients were divided into good and poor outcome groups. Comorbid anxiety was compared among 103 poor outcome, 72 good outcome. Regression analyses were performed to measure the correlation between HARS overall rating and the PANSS single item "G2" anxiety score. ANCOVA was used to compare overall anxiety ratings between groups separately for both HARS total score and the PANSS G2 item "Anxiety." Post-hoc Fisher's LSD was used to identify any group differences. Age of entry was used as a covariate in all analyses. Results: There was a strong correlation between HARS ratings and PANSS G2 item scores. At study baseline there were no significant differences between the poor outcome and good outcome groups on anxiety scores. However, at 6-months the groups significantly differed as improvements were seen in the good outcome group. HARS total rating score ($F = 8.3$, $P = .005$) was similar to the single item (G2) PANSS rating ($F = 10.1$, $P = .002$) when comparing clinical outcome in both groups. When comparing the PANSS score at 6-month, the groups also significantly differed in the measure of anxiety ($F = 5.8$, $P = .017$). Conclusion: When CA is marked or significant in FEP, it appears to be linked to poor short-term clinical outcome when comparing course of illness from baseline to 6 months. The PANSS single item "anxiety" item (G2) seems to be a good indicator of anxiety in being comparable to the total HARS score rating. The current findings highlight that from the onset of illness clinicians should consider potential comorbidity in order to improve patient clinical outcome.
ID: 979775

CBD VS. THC: HOW DO EFFECTS DIFFER IN USERS PRONE TO PSYCHOSIS, ACUTELY AND CHRONICALLY, AND NATURALISTICALLY AND IN THE LABORATORY?

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Background: Cannabis contains a myriad of different chemicals, more than 60 of which are unique to the plant and called cannabinoids. The main psychoactive ingredient is delta9-tetrahydrocannabinol (THC) and this produces the effects that users seek. When given intravenously to healthy humans, THC produces psychotic-like symptoms. In contrast, cannabidiol (CBD), another major constituent of most strains of cannabis, appears to have antipsychotic properties. The relative THC/CBD ratio of "street" cannabis varies greatly. Although it is documented that high THC cannabis has become increasingly available on the street in recent years, little is known about changes in levels of other cannabinoids as these are seldom measured. We previously found that users with high levels of THC in hair but no CBD demonstrated greater levels of schizophrenia like symptoms than users with higher levels of CBD (Morgan & Curran, 2008) and recently replicated this finding. Methods: In a recent, large scale naturalistic study, we collected samples of cannabis smoked, analysed these for levels of CBD and THC and related these to the acute effects of the drug. We have also recruited, from this large sample, cannabis users high and low in psychosis proneness. We administered synthetic THC and CBD to these individuals, both alone and in combination, in the laboratory. Results: We found that individuals smoking high CBD strains of cannabis showed different patterns of effects than those smoking low CBD strains. Smokers of high CBD strains showed an attenuation of the acute THC induced memory impairment and reduced "attentional bias" to cannabis and food stimuli. There were no differences between the groups in the acute psychotomimetic effects of THC. We noted markedly different profiles of cognitive and psychotic-like effects in those high and low in psychosis proneness in response to synthetic CBD and THC in the lab. Conclusion: CBD can act as a protective compound in street cannabis against psychosis, cognitive impairment and dependence; with its protective capacities in each domain related to dose and chronicity. In terms of harm reduction, individuals intent on smoking cannabis should be made aware of the greater risks associated with smoking low CBD strains of cannabis.
ID: 979317

TIME PERCEPTION AND ITS RELATION TO WORKING MEMORY IN SCHIZOPHRENIA

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Background: In everyday life, working memory (WM) helps us integrate external and internal experiences over time. Schizophrenia (SZ) is associated with enduring deficits in WM. Past research suggests that time perception may also be abnormal in these patients but the relationship between WM and time perception has not been carefully examined in SZ. The goal of the present study was to elucidate the potential link between time perception and WM deficit. Methods: Outpatients with SZ and demographically matched healthy controls (HC) participated in 2 time perception tasks. The goal of the temporal duration estimation task was to examine

the accuracy of the judgment of temporal duration. Participants were asked to estimate 1, 3, and 5 seconds by indicating the beginning and the end of these time periods by key presses. A second task was conducted to examine the consistency of the duration judgment. In the temporal interval task, participants were asked to press a key every second for a period of 30 and 45 seconds, while saying the word "one" aloud to prevent counting. In both tasks, the accuracy of the estimated duration and the variability of their responses were measured. In addition, all subjects were given verbal and spatial WM tasks. Clinical symptoms were assessed with SAPS, SANS and BPRS. Delusions were assessed with the PDI. Results: Time estimation was altered in SZ compared with HC. Variance is consistently larger in SZ for all temporal estimations. Delusional ideation was associated with time estimation performance in HC. Conclusion: Altered sense of time may contribute to the formation and maintenance of delusions. This may also contribute to impaired working memory. Further research is needed to better understand the cognitive basis for time perception.
ID: 987707

CAUSAL EXPLANATORY MODELS DEMONSTRATE THE IMPACT OF NEUROCOGNITION ON LATER WORK/SCHOOL FUNCTIONING IN FIRST-EPISODE SCHIZOPHRENIA

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Background: The influence of cognitive deficits on functional outcome in schizophrenia is now widely accepted, but almost all of the supporting evidence has been simple correlations between these 2 domains. Methods: We employed causal explanatory models in the form of cross-lagged panel analyses with 12-month longitudinal data from 53 first-episode schizophrenia patients to test whether cognitive deficits do influence later work/school functioning. The MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein & Green, 2006) and the Role Functioning Scale (Goodman, Sewell, & Cowley, 1993) were administered at a baseline outpatient point, typically 3 months after study entry, and 12 months later, both times while patients were treated at the UCLA Aftercare Research Program. Cross-sectional and cross-temporal correlations were computed between baseline measures in 1 domain and 12-month measures in the other. Results: Better baseline overall cognitive performance (MCCB composite score) was significantly associated with better 12-month work/school productivity (r = .46, $P < .001$). However, baseline work/school functioning did not significantly predict 12-month MCCB composite scores (r = .17). Statistical comparison of these cross-lagged correlations indicated that the predictive relationship between baseline MCCB composite scores and 12-month work/school functioning was significantly larger than the reciprocal cross-lagged correlation (12-month work/school functioning to baseline cognition) (Z = 2.01, P = .03 (one-tailed), N = 53). This pattern indicates that higher levels of baseline cognitive performance not only predict, but may also cause, better work/school functional outcome over the 1 year follow-through period. Similar analysis of the MCCB visual learning domain suggests that higher levels of baseline visual learning causally contribute to better work/school functional outcome over the 12-month follow-through period (Z = 2.57, P = .007 (one-tailed), N = 53). Conclusion: These cross-lagged panel analyses provide additional evidence to support the view that the severity of cognitive deficits in schizophrenia is indeed a rate-limiting factor in recovery of work and school functioning. Furthermore, they highlight this influence in the initial period of schizophrenia, when the possibility of recovery of work/school functioning may be the greatest. The results emphasize the importance of the search for interventions that can meaningfully improve cognitive functioning in schizophrenia.
ID: 979037

INSIGHT IN SCHIZOPHRENIA: THE ROLE OF AFFECTIVE PERSPECTIVE TAKING AND EMPATHY

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Background: Many people with schizophrenia (50%–80%) demonstrate impaired insight, which has been associated with a poorer outcome of the disease. Impaired insight has been linked to both cognitive impairments and denial, due to sensitivity for the stigma of the diagnosis. However, a substantial amount of variance remains unexplained. We were interested in whether social cognition and empathy with others would contribute to the prediction of insight in schizophrenia. Methods: Forty-seven patients with a diagnosis of schizophrenia and 53 healthy controls were assessed with a test battery consisting of tests of social cognition (cognitive and affective ToM and emotion perception), intelligence and a self-rating scale for empathy. Insight was assessed with item G12 of the PANSS. Results: We found a significant relationship between emotion perception, cognitive and affective ToM and empathy at one hand and insight on the other. A regression equation demonstrated that affective ToM and empathy were the best predictors of insight in schizophrenia. Conclusion: Our results show a hierarchical ordering in the way social cognitive processes are associated with insight. The most basic perceptual processes are only weakly correlated with insight in our sample. Hearing, and to a smaller extent seeing, the emotional reaction of others may give patients a hint of what others think of them. Second, being able to take the perspective of others and infer their mental states, will help patients to see themselves as others see them and leads to better insight than affect perception alone. Finally, feeling empathy, or being able to feel what others feel (about their mental state), shows the strongest association with insight. In sum, the better a patient is able to place himself in the mental shoes of others, the better the insight.
ID: 979407

NEGATIVE SYMPTOMS AND SOCIAL COGNITION IN SCHIZOPHRENIA

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Background: Social cognitive impairments and negative symptoms are implicated as contributing factors to poor functional outcome in schizophrenia. It is possible that social cognition and negative symptoms may also be associated. Reports on the nature of this relationship vary and remain unclear. In addition, a majority of previous reports investigated this relationship as a secondary outcome using a global score of negative symptoms. It may be that primary negative symptoms, which constitute more social-type behaviors and functions (eg social withdrawal, apathy) and which affect social functioning, also have an effect on performance on test that tax socially relevant abilities. In this study therefore, the aim was to focus on individual negative symptoms and their individual contribution to performance on multiple measures of social cognition. Methods: The subjects were 103 patients with schizophrenia. Social cognition was assessed using 2 facial affect tasks and 3 social perception/knowledge tasks. Negative symptoms were assessed with the Positive and Negative Syndrome Scale for Schizophrenia (PANSS), comprising all symptoms from the negative syndrome subscale and 2 from the general psychopathology subscale. Results: Multiple regression analyses were conducted to explore the association between criterion variables (social cognition) and predictor variables (negative symptoms). The current sample had a relatively low severity of negative symptoms. There was an inverse moderate correlation between a number of

individual negative symptoms including abstract and stereotyped thinking and social perception/knowledge tests (ranging from $r = -.350$ to $-.437$). Conversely, only stereotyped thinking correlated weakly with facial affect tests ($r = -.261$ and $-.221$). The amount of variance in social cognition explained by individual negative symptoms however, was small to moderate ranging from 10% to 31%. Conclusion: Difficulty in abstract thinking and stereotyped thinking appeared to be the strongest indicator of poor social cognition. However, these symptoms are more cognitive in nature and less like the negative symptoms that reflect diminution of normal behaviors and functions (ie primary negative symptoms). That is, cognitive impairment rather than blunted affect, emotional or social withdrawal and apathy, seem to contribute to poor social cognition in the current sample. The contribution of these primary negative symptoms however, may only be contingent on their severity.
ID: 977130

SEARCHING FOR SCHIZOPHRENIA RISK GENES: BIVARIATE GENOME-WIDE LINKAGE SCAN OF SCHIZOPHRENIA AND EXECUTIVE COGNITIVE PROCESSES IN MULTIPLEX FAMILIES

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Background: Despite having a high overall heritability (h2 = .80), to date no common gene variants of large or moderate effect have been identified for the diagnosis of schizophrenia. In such a situation, detection of gene variants with small main effects require either extremely large sample sizes or improved measurement of phenotypes that are more sensitive to the effects of schizophrenia risk gene variants than is the diagnosis of schizophrenia itself. The current study employed the latter ''endophenotype'' strategy in an attempt to identify novel risk loci for schizophrenia. Methods: Based on previous findings, we focus here on a genome-wide linkage analysis of a neuropsychological measure of speed of executive processing, the Trails Making Test A & B (TMT), in the context of a multiplex, large pedigree sample of schizophrenia families. Forty-3 probands with schizophrenia who had at least one first degree relative with schizophrenia or schizoaffective depressed disorder and a minimum of 10 willing relatives were identified. All participants were assessed for DSM IV diagnoses, neuropsychological performance, and pedigree members for 386 microsatellite genetic markers spaced 10 cM apart. 574 pedigree members (1st to 4th degree) and 137 unrelated controls had complete data for these analyses. Results: Heritabilities for TMT scores ranged from .35 to.49 and their genetic correlations with schizophrenia diagnosis were .54–.71. Univariate linkage results for the schizophrenia diagnosis itself identified only 1 significant locus on chromosome 19 (LOD 3.60). In contrast, univariate linkage analyses of TMT scores found significant linkage on chromosome 22 (LOD 3.24) and suggestive linkages on chromosomes 1 (LOD 2.22) and 5 (LOD 1.52). Bivariate linkage analyses indicated that these loci on chromosomes 1 and 5 were not only linked to TMT deficits but also had significant pleiotropic effects on the diagnosis of schizophrenia itself. Conclusion: These results imply that the TMT may be a useful endophenotype that can detect novel genetic risk loci for schizophrenia on chromosomes 1 and 5 that were not apparent using the diagnosis alone.
ID: 979926

PARSING THE HETEROGENEITY OF COGNITIVE TASK PERFORMANCE IN SCHIZOPHRENIA

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Background: Many studies show that schizophrenia patients perform in the range of impairments at tasks measuring cognition. However, large heterogeneity in performance exists within this population, and it is not clear whether this represents a continuum of severity or a limited number of distinct and qualitatively meaningful subtypes. The current study investigated both possibilities. Methods: As a part of the GROUP-project, cognitive and clinical data were obtained from 1051 patients with a non-affective psychotic disorder and 650 healthy controls. The cognitive battery encompassed several domains. Using the z scores of patients with the controls as a reference group, a K means cluster analysis was performed. Next, analyses of covariance were performed to investigate differences between subgroups of patients on clinical symptoms and functional outcome, with age and gender as potential covariates. Results: Six subgroups of distinct profiles were identified, consisting of at least 100 patients each. Overall, 3 subgroups were characterized by performance within the normal range ($z = -0.5$, $N = 180$; $z = 0.2$, $N = 100$; $z = 0.2$, $N = 145$); 2 by low average performance ($z = -0.8$, $N = 106$; $z = -0.8$, $N = 152$), and 1 by borderline performance ($z = -1.6$, $N = 129$). Processing speed, problem solving, working memory, and verbal learning/memory differentiated between the low average performing groups, with the former 2 factors only differentiating between the average subgroups. The subgroup with borderline performance experienced significantly more negative symptoms, disorganization and poorer functional outcome, when compared with the average subgroups. One average performing subgroup experienced less disorganization and better functional outcome, as compared with the low average and borderline performing subgroups. This subgroup had processing speed as a relative strength and attention and problem solving as relative weaknesses. Conclusion: Our findings indicate that different cognitive profiles in schizophrenia may exist, and that these profiles have clinical relevance. Cognitive profiles may be of importance for (non-)pharmacological treatments of cognitive deficits, as well as studies that focus on genetic variations in schizophrenia.
ID: 980051

A 1-YEAR FOLLOW-UP STUDY OF COGNITION IN SUBJECTS AT ULTRA-HIGH RISK FOR PSYCHOSIS

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Background: In the last 2 decades, research on subjects in putative prodromal phases of psychosis has intensified. It is possible that the damaging clinical and functional consequences of psychotic disorders and their prodromal phases may be ameliorated, delayed or even prevented by facilitat-

ing pre-psychotic detection and intervention. One of the promising candidates for identifying subjects at ultra-high risk (UHR) for psychosis is cognition. Several studies indicate that the neurocognitive performances of UHR subjects are intermediate between healthy control (HC) and first-episode of psychosis subjects. However, the possible role of cognition as a predictor of clinical and functional outcomes is inadequately understood. Furthermore, the profile of cognitive deficits, and cognition in everyday life and social cognition have not been well characterized in this population. Therefore, the purpose of the study is to identify both the basic features of various cognitive domains and the cognitive predictors of clinical and functional outcomes in a UHR sample. Methods: The design constitutes a 1-year longitudinal study with predefined intervals, and data collection has begun in summer, 2010. The study is carried out in close collaboration with the NEURAPRO-E study. We will include a minimum of 40 UHR and 40 HC subjects. We will monitor and assess their clinical, functional, and cognitive status continuously. Seeking to delineate the various cognitive domains and their associations with outcomes, the study utilizes multiple instruments, including CANTAB (Cambridge Neuropsychological Test Automated Battery) and BACS (Brief Assessment of Cognition in Schizophrenia). It also utilizes an interview-based measure, SCoRS (The Schizophrenia Cognition Rating Scale), and a questionnaire, BRIEF (Behavior Rating Inventory of Executive Function), both being sensitive to cognition in everyday life. Concerning the assessment of social cognition, we will use (amongst others) TASIT (The Awareness of Social Inference Test). Finally, we will use multiple clinical and psychosocial rating scales, including CAARMS (Comprehensive Assessment of At-Risk Mental States) and PSP (Personal and Social Performance Scale). Results: Data collection will end in 2012. Conclusion: We will delineate the cognitive profile of UHR subjects and identify possible predictors of clinical and functional outcomes.
ID: 978847

ARE INDICES OF INTELLECTUAL DECLINE IN SCHIZOPHRENIA RELIABLE? EVIDENCE FROM A LONGITUDINAL STUDY

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Background: Numerous studies have used premorbid and current IQ estimates in people with schizophrenia to represents a trajectory over time and to imply IQ decline. However, the usefulness and validity of this approach has been challenged. The purpose of this historical prospective study was to follow the cognitive impairment in schizophrenia from the premorbid period until after the establishment of the schizophrenic illness, and to evaluate the validity of retrospective measures of intellectual change for use in research and clinical settings. Methods: 100 schizophrenia patients and 100 controls were enrolled in the study. Their cognitive performance was assessed as part of the Israeli Draft Board aptitude assessments at ages 16–17, when all were found to be in good mental health (first assessment) and again, in adulthood (second assessment). The second assessment included the WAIS-III and WRAT Reading. Results: Schizophrenia cases were significantly impaired on IQ compared with controls at age 16–17 (Effect size = 0.49). In adulthood, schizophrenia cases demonstrated significant impairment and deterioration on IQ compared with controls (Effect size = 1.04). Using Draft-Board - WAIS discrepancy scores as a ''gold standard,'' WRAT-WAIS discrepancy scores reliably classified schizophrenia cases. Conclusion: A decline in intellectual functioning occurs in schizophrenia. This can be modeled reliably using available assessment instruments.
ID: 978788

LEARNING POTENTIAL IN PEOPLE WITH SCHIZOPHRENIA

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Background: In recent years, there has been growing interest in utilizing the concept of learning potential to explore individual variation in cognition/learning among people with schizophrenia. Learning potential refers to the ability to benefit from instruction and is measured by assessing test performance before and after training. Much of this research has examined executive functioning on the Wisconsin Card Sorting Test (WCST) and recently has focused on individual variability in learning potential (eg, Wiedl, 1999; Wiedl et al., 2001). Learning potential is based on dynamic assessment and evaluates performance improvement following training (test-train-test). In schizophrenia research, learning potential has been associated with attention and memory, as well as functional outcomes such as work skills and treatment outcome. This study utilized a novel measure of learning potential, the Rey-Osterrieth Complex Figure Test (ROCFT) to categorize participants as high-scorers, learners or non-learners. A primary aim of this study was to examine the cognitive characteristics associated with learner status. Methods: Eighty individuals with schizophrenia or schizoaffective disorder completed a modified version of the ROCFT that provided enhanced instruction and feedback. Participants were categorized as high-scorers, learners, or non-learners, based on their performance across 3 consecutive administrations of the ROCFT (test-train-test paradigm). Learner status was based on an algorithm taking into account the standard error of prediction based on established reliabilities of the measure. Participants also completed a battery of standard cognitive measures, including tests of executive functioning (WCST, trail making test), verbal memory (California Verbal Learning Test), working memory (letter number sequencing test and a months-ordering task), and sustained attention (D2 Test of Attention). Results: Analyses of variance (ANOVA) indicated several significant differences between learner groups on the cognitive measures. Most notably, individuals identified as good learners on the ROCFT differed from non-learners on measures of working memory. Conclusion: The findings provide preliminary support for the use of the ROCFT in assessing learning potential in persons with schizophrenia, and indicate that the ability to learn on the ROCFT may be specifically related to working memory abilities.
ID: 979712

SEX-SPECIFIC ASSOCIATIONS BETWEEN PERIPHERAL OXYTOCIN AND POSITIVE EMOTION PERCEPTION IN SCHIZOPHRENIA

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Background: We previously reported that high levels of peripheral oxytocin are associated with better positive, general, and overall symptoms in women but not in men with schizophrenia. Oxytocin has widespread effects beyond its characteristic roles in pregnancy and lactation, including effects on behaviors that are impaired in schizophrenia such as emotional processing and social cognition. In the present study, we investigated sex differences and the effects of menstrual cycle phase and related fluctuations in peripheral hormone levels on social cognition in schizophrenia. Methods: Twenty-two women with schizophrenia completed the Penn Emotion Acuity Test

(PEAT), a measure of facial emotion recognition and perception, at 2 menstrual cycle phases: 1) early follicular (Days 2–4; low estrogen/progesterone) and 2) midluteal (Days 20–22; high estrogen/progesterone). Twenty-six males with schizophrenia and 57 controls (31 female) completed testing at comparable intervals. We obtained plasma hormone assays of estrogen, progesterone, testosterone, and oxytocin. Results: No sex differences were noted on the PEAT. Women with and without schizophrenia more accurately identified facial emotions during the early follicular vs. midluteal phase ($P < .05$). Performance on the PEAT did not differ significantly across sessions in men. Although oxytocin did not fluctuate across phases, higher oxytocin levels related to perceiving faces as happier ($P < .05$) in both groups of women but not in men. Conclusion: Contrary to predictions, there were no sex differences in social cognition in schizophrenia. Consistent with previous work in healthy women, our results suggest that the ability to recognize emotional faces varies across the menstrual cycle in schizophrenia. Notably, even in women with persistent social deficits due to schizophrenia, oxytocin was associated with emotion perception. Unexpectedly, this same relationship was not found in men. Future trials of oxytocin in patients with schizophrenia should include measures of social cognition to evaluate whether exogenous oxytocin also makes patients view faces as "happier" and explore the functional correlates of this benefit. Additionally, it may be important to consider sex when evaluating oxytocin in the management of schizophrenia.
ID: 980004

COGNITIVE AND PERCEIVED ABILITIES AFFECT UTILIZATION OF COGNITIVE REMEDIATION SERVICES FOR PEOPLE WITH SCHIZOPHRENIA IN A COMMUNITY PSYCHIATRIC REHABILITATION SETTING

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Background: Cognitive remediation (CR) is a behavioral training intervention that targets cognitive abilities in order to alleviate functional disability. Identifying factors affecting treatment engagement in vivo is needed to inform development and implementation research. Methods: This study examined the significance of cognition and perceived abilities in predicting CR utilization for outpatients with schizophrenia ($N = 39$) in a community clinic. Standardized neuropsychological evaluation and validated self-report questionnaire data were analyzed from 39 clients enrolled in twice weekly sessions of CR at 2 community mental health sites in New York City. Results: Mean treatment utilization, defined as the percentage of scheduled sessions attended, was 65.1% during a 3 month period following baseline evaluation. Multiple regression analysis, controlling for estimated premorbid IQ, revealed that those who reported greater impairments in attention, memory, and executive functions attended sessions less frequently. In a subsample of clients ($N = 22$) who scored 1.3 SD below the normative mean on a global neuropsychological index, treatment utilization was low (58.7%); less frequent attendance was significantly correlated ($P < .05$) with poorer performance on objective measures of working memory ($r = .57$) and processing speed ($r = .48$) and subjective report of more impaired cognitive ability ($r = -.46$). Greater awareness of impairment was associated with lower ratings of autonomy, interest/enjoyment in training tasks, and perceived competence. Conclusion: Results reflect the impact of actual and perceived cognitive ability on motivation for cognitive treatment and indicate the need for additional supports to optimally engage those who might most benefit from cognitive treatment.
ID: 962532

PREDICTORS OF PERFORMANCE ON SPECIFIC EXECUTIVE SKILLS IN SCHIZOPHRENIA

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Background: The goal of the current study was to examine potential predictors of profiles of executive functions in schizophrenia. Methods: We examined data from a cross-sectional sample of 145 community-dwelling individuals with schizophrenia (SCs), who were administered 10 tasks of the Delis-Kaplan Executive Function System (D-KEFS). Results: Latent Profile Analysis yielded 3 distinct patterns of D-KEFS performance that largely varied in terms of level of impairment, including a non-impaired profile (12.4% of SCs) in which the mean scores for all D-KEFS tasks were in the average to high average range. The modal group (53.1%) had D-KEFS scores in the mildly impaired range. The third group (34.5%) had scores that were mostly in the moderately impaired range. SCs with the non-impaired profiles had better premorbid verbal functioning (as estimated with the ANART), as well as better processing speed (Digit Symbol) and functional capacity (UPSA total) than those with mildly or moderately impaired profiles. Severity of psychopathology (measured with the PANSS and HAM-D) did not show a consistent linear relationship to severity of D-KEFS impairment. Conclusion: Results suggest that schizophrenia is commonly, but not universally associated with impaired range executive function across a variety of more specific executive tasks. That the highest functioning group also had higher premorbid function as well as better processing speed raises the question of whether executive impairment may reflect a broader (non-specific) cognitive impairment in schizophrenia.
This work was supported by the National Institutes of Health/National Institute of Mental Health (grant numbers MH19934, MH064722, and MH080002) and a grant from the National Alliance for Research on Schizophrenia and Depression.
ID: 979045

COGNITIVE FUNCTION OF CHRONIC SCHIZOPHRENIC PATIENTS IN LATE LIFE

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Background: A number of cross-sectional and longitudinal studies in patients with schizophrenia suggest a moderate to large decline in a variety of neuropsychological domains. While evidence indicates that there is a neurodevelopmental process affecting intellectual function during childhood and adolescence prior to the onset of the clinical syndrome, there is an ongoing debate about the existence of a neurodegenerative aspect later in life. Because most of the studies examining the neurocognitive function in schizophrenia focused on young and middle aged populations, nature and course in late life schizophrenia is not very clear. Methods: In our study we evaluated cross-sectionally the cognitive functioning of 42 older schizophrenic patients (age $M = 59$, 88 years; SD = 8, 20) with a chronic lifelong course of illness and contrast their performance with

41 younger chronic schizophrenics (age M = 30, 39 years; SD = 5, 93). We compared these patient samples with healthy age-matched comparison subjects as well. Cognition was estimated using the Consortium to Establish a Registry for Alzheimer's Disease, the Trail Making Test as well as the Logical Memory and the Digit Span from the Wechsler Memory Scale. Results: In general, both patient groups demonstrate moderate to large impairments across a variety of neuropsychological domains, but the older chronic schizophrenic sample show significant more cognitive deficits on global and specific neuropsychological domains. They demonstrate a greater extend of psychopathology with broad negative symptoms as well. Conclusion: We assume that those old schizophrenics with poor overall outcome experience an interactive effect of aging on neurocognition. There is a suggestion of a possible neurodegenerative process in this patient group.
ID: 979358

PREMORBID TO POSTMORBID IQ IN SCHIZOPHRENIA: IMPLICATIONS FROM META-ANALYSIS AND A 35 YEAR FOLLOW-UP STUDY

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Background: The search to understand neurocognitive functioning in schizophrenia across the lifespan includes a broadening focus from premorbid to prodromal (high risk) periods, to the first episode and to later phases of the illness. IQ has been of major interest, at least in part, because IQ measurement is relatively standardized compared with most other measures used to evaluate neurocognition in schizophrenia. In this presentation, I will summarize my work from a number of meta-analyses of IQ at different phases of schizophrenia, studies on the prodrome to psychosis, as well as the results from a 35-year follow-up study from premorbid to postmorbid period demonstrating a decline in functioning in schizophrenia (Seidman et al., 2006). Methods: A systematic literature search yielded 18 studies meeting criteria for meta-analysis with premorbid IQ (Woodberry, Giuliano & Seidman, 2008). A second larger meta-analysis on neurocognitive measures in first episode (FE) or very early phase schizophrenia (Mesholam-Gately et al 2009) uses 43 separate samples of 2204 FE patients with a mean age of 25.5 and 2775 largely age- and gender-matched control subjects. Results: Overall, schizophrenia samples demonstrated a reliable medium-sized impairment in premorbid IQ ($d = -0.54$). Schizophrenia samples consistently demonstrate IQ impairments of roughly one-half standard deviation below healthy controls years before the onset of psychotic symptoms. Heterogeneity of effect sizes was minimal and methodological differences, such as diagnostic criteria, type of IQ measure, sample ascertainment strategy, and age at premorbid testing contributed minimally to effect size variance. Importantly, studies with pre- and post-onset testing within the same sample all suggest that a significant decline in IQ relative to controls is associated with the onset of frank psychosis. In fact, FE samples demonstrated effect size impairments for IQ close to a Cohens *d* of 1.0, roughly twice the size of the premorbid deficit, and quite similar to those identified by Heinrichs and Zakzanis (1998) in older, chronic samples. Larger IQ impairments in the first episode compared with the premorbid period, but comparable to later phases, suggests deterioration between premorbid and FE phases followed by deficit stability at the group level. Conclusion: Additional research focusing in on the prodromal and first episode periods will be presented to clarify the nature and timing of decline in IQ (Seidman et al, 2010).
ID: 978654

THE INFLUENCE OF SEMANTIC PROCESSING ON ODOR IDENTIFICATION ABILITY IN SCHIZOPHRENIA

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Background: Individuals with schizophrenia have shown reduced semantic and olfactory processing in comparison to healthy controls. However, the contribution of semantic dysfunction to odor identification deficits has not yet been elucidated. The aim of the current study was to systematically examine the relationship between olfactory and semantic impairment in schizophrenia patients and healthy controls in order to determine any possible moderating effects of the semantic system on the observed chemosensory dysfunction in patients. Methods: Sixteen patients with schizophrenia (12 males) and 16 healthy control subjects (13 males) matched for age and gender were tested for odor identification and semantic abilities. All subjects completed 2 versions of the University of Pennsylvania Smell Identification Test (UPSIT): an uncued free-response version followed by the standard multiple-choice paradigm. Subjects were also given 3 standard tasks thought to measure semantic abilities: the Boston Naming Test (BNT), the Animal Naming Test, and the Pyramids and Palm Tree Test. Results: Consistent with previous research, patients yielded significantly lower scores than controls on the standard UPSIT and all 3 semantic tests. Notably, the 2 groups did not differ on the free-response version of the UPSIT, with both patients and controls demonstrating impaired ability to label the target odorants. However, error analysis revealed that patients made significantly more far-miss errors than controls, as controls provided more semantically-related labels for target odors even when responding inaccurately (near-misses). No relationship was observed between the standard and free-recall olfactory tasks and semantic task performance in patients, but a correlation between performance on the standard UPSIT and the Pyramids and Palm Tree Test was found in the control group. Conclusion: Collectively, these data suggest that odor identification deficits are independent of semantic processing deficits in schizophrenia. The correlation between the standard UPSIT and the Pyramids and Palm Tree Test in controls, as well as the "near-miss" nature of their errors on the free-response UPSIT suggest some semantic contribution to odor identification abilities in healthy individuals. However, the absence of any correlation between odor identification and semantic performance in patients implies that olfactory deficits are largely independent of semantic difficulties in schizophrenia.
ID: 977251

THE ROLE OF CHILDHOOD TRAUMA AND COGNITIVE DEFICIT IN MODERATING THE RISK FOR PSYCHOTIC DISORDERS: A COMPARISON BETWEEN PALERMO AND SOUTH-EAST LONDON FIRST EPISODE PSYCHOSIS (FEP) SAMPLES

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Background: Research suggests that childhood trauma and cognitive deficits are both associated with psychosis but the relationship between the 2 risk factors is still unclear. Methods: Childhood trauma data and WAIS III measures from a sample of 34 cases and 16 controls from the Palermo first

episode psychosis case control genetic study, S-GAP, were compared with 67 cases and 86 controls from the similar Genetic and Psychosis study, GAP, from South East London. Results: In both samples the FEPs had lower IQ and lower level of education compared with controls (P = .014). The prevalence of childhood severe abuse (either physical or sexual) observed in South East London was higher than in the Palermo sample and significantly higher than the reference control (P = .042). Furthermore, in the South East London sample FEPs who reported both physical and sexual abuse, performed significantly worse in working memory tasks (P = .05) and with a trend of significance in abstract reasoning (P = .07) compared with those who reported only 1 type of abuse and to those who did not suffered any abuse. Conclusion: In both samples psychosis is associated with high prevalence of childhood trauma. Multiple types of abuse (both physical and sexual) are more prevalent in FEPs than in controls and are significantly associated with poor working memory performance.
ID: 978550

SUCCESSFUL COMPUTER-BASED VISUAL OR AUDITORY TRAINING SPECIFICALLY ENHANCES VISUAL, NOT AUDITORY, LEARNING IN SCHIZOPHRENIA

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Background: Computer-based cognitive remediation (CCR) that is designed to refine sensory processing improves global cognition in schizophrenia, but it is unclear whether cognitive gains are specific to the modality trained. To examine whether successful visual training selectively improves visuospatial memory over auditory memory, and if auditory training does the opposite, we performed a post-hoc analysis of Difficulty Levels Achieved on Visual Training software (DLVT), Performance on Auditory Exercises (PAE) and neuropsychological assessments from a larger, on-going randomized controlled trial of CCR in schizophrenia patients. We hypothesized greater advancement though visual training exercises would correlate with improved visual memory but not auditory memory, and the reverse outcome with high performance on auditory exercises. Methods: We analyzed data from 15 subjects who received vocational rehabilitation; a computer-based cognitive training package of visual, auditory and cognitive control exercises developed by Posit Science; and neuropsychological testing before and after cognitive training. Changes in subtests from the WAIS-III and MATRICS batteries were correlated with DLVTs. Significant correlations were further explored to investigate the contribution of DLVTs on the neuropsychological improvement in visual compared with auditory memory tests and to explore similar relationships with PAE. Results: Improvement on a visual learning test, the Brief Visuospatial Memory Test (BVMT), was significantly correlated with DLVTs. Maximum DLVTs achieved explained 73% of the variance in improvement in BVMT, but did not significantly account for changes in an auditory test, the Hopkins Verbal Leaning Task (HVLT). PAE strongly correlated with improvement in one visual task, Spatial Span, but not with that of 2 auditory memory tests, Letter Number Sequencing and HVLT. Conclusion: Both visual and auditory training measures predict improvement in visual, but not auditory, learning tests. Visuospatial learning may be more easily improved by computer-based visual or auditory training, as CCR in either domain depends upon interacting with visual information, through a computer screen. Similar analyses can help unravel the mechanism of cognitive gains with cognitive remediation in schizophrenia and guide the design of interventions that specifically target known cognitive deficits. Acknowledgements: Funding: NIMH T32 MH-19961-14.
ID: 979454

NEUROCOGNITION AND OCCUPATIONAL FUNCTIONING IN PATIENTS WITH FIRST EPISODE PSYCHOSIS: A 2- YEAR FOLLOW-UP STUDY

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Background: Neurocognitive deficits are considered a core feature of schizophrenia and an important factor associated with poor functional outcome. Numerous studies have shown a relationship between neurocognition and occupational functioning in patients with schizophrenia. Corresponding studies investigating patients with early-onset psychosis are scarce, and the results are inconsistent. The aims of this study are (i) to investigate differences in clinical and neurocognitive characteristics in patients with first-episode psychosis based on their occupational status at baseline, (ii) to describe change in occupational status during a 2-year follow-up period, and (iii) examine whether neurocognitive functioning at baseline can predict occupational status at 2-year follow-up. Methods: One-hundred and fifty 6 patients coming to their first treatment for a DSM-IV broad schizophrenia spectrum psychotic disorder were assessed with clinical and neurocognitive measures at baseline. Occupational status was assessed at baseline and 2-year follow-up. Results: There were no significant differences between the employed and unemployed group with regard to neurocognitive or clinical characteristics at baseline. The total employment rate was relatively stable over time with 37 % employed at baseline and 33 % at the 2 year follow-up. Despite this apparent stability, further investigation showed substantial individual changes in occupational status resulting in 4 different employment paths. During the 2 year period 50 % of those employed at baseline remained employed at follow-up, while 50 % were no longer employed. Of those unemployed at baseline, 22 % were employed at follow-up, while 78 % remained unemployed throughout the follow-up period. None of the neurocognitive measures predicted occupational status at the 2 year follow-up. Conclusion: Neurocognitive functioning does not appear to be associated with or predict occupational status in patients with first episode psychosis. Only one third of these patients are employed at the start of treatment and the total employment rate remains relatively stable over a follow-up period of 2 years. However, there seems to be substantial instability in occupational status at the individual level over the same time period.
ID: 977516

SEX DIFFERENCES IN NEUROCOGNITIVE PERFORMANCE ACROSS PSYCHOTIC DISORDERS

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Background: Neurocognitive dysfunction is a characteristic of both schizophrenia and bipolar disorder. Sex differences in neurocognition are well-known in healthy samples. In general, women outperform men for verbal abilities whilst men show superior performance for visuospatial skills. Neurocognitive sex differences have also been reported for schizophrenia, but to our knowledge there are no studies on neurocognitive sex differences in bipolar disorder. The aim of this study was to investigate sex differences in neurocognition across psychotic disorders, for both schizophrenia and bipolar disorder. Methods: One hundred and fifty-four participants with schizophrenia (60 women/94 men) and 106 with bipolar I disorder (55 women/51 men) verified by SCID interview were included in the study along with 344 healthy control persons (158 women/182 men). All participants were assessed with a neuropsychological test battery covering the following domains: verbal memory, speed of processing, attention, working memory and executive function. Participants from the clinical groups were assessed for current psychopathology (psychotic symptoms, depression and mania). Results: We found a significant overall main effect of sex for neuropsychological tests ($P < .001$): males were outperformed by females across groups for all neuropsychological tests (except attention and working memory). The overall main effect of diagnostic group was also significant ($P < .001$): both clinical groups performed below healthy controls for all neuropsychological tests (except attention). Post-hoc 2-group comparisons yielded significant interaction effects of group and sex for persons with schizophrenia compared with healthy controls, but not for persons with bipolar I disorder compared with healthy controls. The significant interaction effects ($P < .05$) were found for 3 neuropsychological tests measuring verbal memory (CVLT-II long delay free recall) and executive function (Color-Word Interference and Interference/Switching). Males with schizophrenia were disproportionally disadvantaged for these 3 tests. Conclusion: We found neurocognitive sex differences across psychotic disorders with females showing superior performance compared with males for both schizophrenia and bipolar I disorder.
ID: 978287

THE MATRICS CONSENSUS COGNITIVE BATTERY: RELATIONSHIPS WITH PERFORMANCE-BASED MEASURES OF FUNCTIONAL CAPACITY

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Background: Performance-based measures of everyday tasks in domains such as communication and finance are important predictors of everyday functioning in individuals with schizophrenia. In previous studies cognitive performance was less strongly correlated with social competence and social outcomes than with functional capacity in the community. We examined the factor structure of a battery including 3 separate performance-based measures: the UCSD Performance-based Skills Assessment-Brief (UPSA-B), Advanced Finances subtest of the Everyday Functioning Battery (EFB), and the Social Skills Performance Assessment (SSPA). We also examined how these factor structures were related to measures of cognitive ability, using the MATRICS Consensus Cognitive Battery (MCCB), developed specifically for use in clinical trials of new treatments for schizophrenia. Methods: In a multi-site study devised to validate measures of functional outcome in individuals with schizophrenia, 195 participants completed a battery including the MCCB, a measure of premorbid IQ (WRAT-III Reading), and the 3 performance based measures. Factor analysis of the total score on the SSPA and the subscale scores on the UPSA-B and EFB was conducted with principal components extraction; correlations between the resulting factors, premorbid IQ, and the MCCB raw scores were examined. Site effects will be examined prior to presentation. Results: Exploratory factor analysis of the performance-based measures yielded a 2-factor solution, with factors representing Finance and Communication/Social domains. The Finance factor was significantly correlated with all of the MCCB raw scores (rs ranged from .18 to .55; P's $\leq .029$); however, the Communication/Social factor was significantly correlated only with BACS Symbol Coding ($r = .17$; $P = .039$) and Letter-Number Span ($r = .21$, $P = .010$). Premorbid IQ was correlated with the Finance factor ($r = .35$; $P < .001$), but not the Communication/Social factor ($P = .907$). Conclusion: Exploratory factor analysis revealed 2 distinct factors across 3 separate performance-based measures representing Finance and Communication/Social domains. Although performance-based measures of the ability to apply financial skills are correlated with multiple cognitive abilities, the associations between communication/social skill and cognitive performance were more modest. These results support the need for including measures of both cognition and functional capacity in evaluations of functioning in people with schizophrenia.
ID: 979958

SUSTAINED ATTENTION IN FAMILIAL BIPOLAR I DISORDER PATIENTS AND THEIR UNAFFECTED RELATIVES

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Background: A recent meta-analysis by Bora et al (2010) reported deficits in sustained attention in bipolar patients with psychotic features comparable to impairments found in schizophrenia, a connection between both disorders that will interest researchers whose findings point to shared genetic risk for the 2 disorders/overlap in the candidate genes for the 2 disorders. However, examining these neurocognitive indices in unaffected relatives of both patient groups can further elucidate whether they might be trait rather than state markers of psychosis. in the current study we compared sustained attention in patients with familial bipolar I disorder (BD1) to their unaffected first degree relatives and normal controls. Methods: The Rapid Visual Information Processing (RVIP) task from the Cambridge Neuropsychological Test Automated Battery (CANTAB) was assessed in 43 familial patients with a lifetime diagnosis of BD1 who had experienced psychotic symptoms, 46 of their unaffected non-psychotic, non-bipolar first-degree relatives and 48 controls. Five indices of sustained attention were administered to all participants: A' sensitivity; total hits; total misses; total false alarms; and mean latency. Results: There was some weak evidence that BD1 patients but not their unaffected relatives showed worse performance on aspects of sustained attention than healthy controls. Conclusion: We do not find genetic liability for bipolar disorder with psychotic features to be associated with impairments in sustained attention, suggesting such deficits are a poor candidate endophenotype marker for the disorder. Attention impairments in patients may be due to medication effects or illness progression.
ID: 979257

DIFFERENTIAL IMPAIRMENTS OF SELF-REFERENCE IN SCHIZOPHRENIA

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Background: Studies suggest that schizophrenia is associated with disturbances of self. However, very little is known about the basic cognitive processing of self in terms of self-referential processing. This study attempted to examine the disturbances of self-reference in schizophrenia. Methods: 25 in-patients with schizophrenia and 25 well-matched healthy controls were recruited in the study. Each of them was administered with a computerized test assessing the self-reference. The self-reference test is comprised of 2 parts, an unconscious coding phase followed by a sudden recognition test as well as a R/K (Remember/Know) judgment. Since Know judgment does not need self-referential process, Remember judgment performance is a more appreciate parameter to reflect self-related processing. Results: The results indicated that self-related coding led to better remember performance than a celebrity-related coding, ie, Sun Yat-sen (a famous Chinese) related coding, in both groups (for recognition performance $P = .012$, $P < .001$; and for remember judgment performance $P = .005$, $P < .001$, corresponding to schizophrenia patients and healthy control respectively). However, there was no significant difference in Sun Yat-sen related remember performance between the 2 groups, while significant difference in self-related remember performance was observed (schizophrenia < control, recognition: $F(1,48) = 5.53$, $P = .023$; remember: $F(1,48) = 4.13$, $P = .048$). Conclusion: These preliminary findings suggest there is a differential self-reference impairment observed in patients with schizophrenia.
ID: 977499

SCHIZOPHRENIA AND ACCELERATED AGING: FURTHER EVIDENCE FROM PROSPECTIVE MEMORY PERFORMANCE

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Background: Schizophrenia and normal aging have both been associated with impairments in prefrontal cortex and prospective memory (PM). This study compared PM performance in schizophrenia patients and healthy younger and older individuals, and tested the accelerated aging hypothesis of schizophrenia. Methods: Computerized tasks capturing event- and time-based PM were administered to 30 schizophrenic patients, 30 healthy older adults, and 30 healthy younger adults, several tests on memory (Logical Memory, Visual Reproduction, and Chinese Letter-Number Span) and executive function (Wisconsin Card Sorting Test) were also conducted. Results: The findings showed that the healthy older adults and schizophrenia patients demonstrated deficits in time-based PM as compared with the healthy younger adults. Moreover, schizophrenia patients did not differ significantly from the healthy older adults in time-based PM (even after controlling for recall of task requirements), Logical memory immediate recall, Chinese Letter-Number Span and Wisconsin Card Sorting Test. Unlike healthy older adults, schizophrenia patients were not found to be impaired in event-based PM as compared with the healthy younger adults. Conclusion: Taken together, these findings suggest that, in terms of nature and extent of neurocognitive functions, schizophrenia may be a developmental stage analogous to a "mild" grade of aging and support the accelerated aging hypothesis of schizophrenia.
ID: 977301

ASSESSMENT OF TOBACCO CRAVING IN SMOKERS WITH SCHIZOPHRENIA USING VIRTUAL REALITY

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Background: The prevalence of tobacco use is 2–3 times greater in people with schizophrenia than the general population. Tobacco craving is an important reason why people relapse; cessation efforts in this population have been modest. Tobacco craving paradigms in people with schizophrenia should be developed to better understand craving and to test novel anticraving treatments in this population. A virtual reality paradigm using social and environment cues along with scent was used in this study to elicit craving in smokers with schizophrenia. Methods: Five people with a DSM-IV diagnosis of schizophrenia were enrolled in this pilot project. Participants underwent a baseline assessment and acclimation period and then participated in an experimental condition of 4 virtual reality cues (Virtually Better™). These included 2 smoking cues (a paraphernalia room and a social interaction/gathering room) and 2 neutral rooms. A follow up session for craving and symptom assessments occurred 1 week after the experimental session. Participants rated their tobacco craving using a visual analog scale (VAS) and the Tobacco Craving Questionnaire-Short Form (TCQ-SF) at the conclusion of each 3 minute virtual environment. Results: The 5 completers reported average use of 16.4 (SD 7.6) cigarettes daily. Mean VAS craving increased from 63 (SD 29.9) to 69.2 (31.9) in the social interaction room and to 70.9 (20.9) in the paraphernalia room (all P = NS). Participants experienced a nonsignificant increase in craving as measured by TCQ-SF total score over baseline in the social interaction room (increase of 8.2 points SD 5.0), and a decrease (3 points) in the paraphernalia room. Participants experienced a significant increase in TCQ-SF compulsivity subfactor after the social interaction environment (5.2, $P = .02$). On a scale of 1 = not consistent to 7 = very consistent, participants indicated that the virtual experiences seemed moderately consistent with real world experience (mean = 5.4, SD = 1.95). Reported side effects included dizziness, headache, and mild anxiety. Conclusion: Pilot data from this ongoing study

suggest that virtual reality provides a mechanism to investigate tobacco craving and that the social interaction room may be a trigger for increased craving.
ID: 977889

NEUROPSYCHOLOGICAL CHANGE OVER 2 YEARS IN YOUTH AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Evidence from both cross-sectional and longitudinal studies suggests that a progression of neuropsychological (NP) impairment may precede and/or accompany the onset of psychosis. However, minimal data are available during the putative prodromal stage of illness to clarify the timing and specific nature of such a progression. Methods: We report on NP data across 8 cognitive domains at baseline, 1 and 2 years for a sample of clinical high risk (CHR) youth compared with baseline and 1-year data for demographically similar healthy comparison (HC) participants. 1-year scores were predicted based on linear regression of HC 1-year scores on baseline scores and relevant demographic variables. We used raw scores and MANOVAs of the standardized residuals to test for progressive impairment over time and possible illness progression. Results: At 1 year, overall NP functioning of CHR fell significantly below predicted levels. Effects were largest and most reliable for a failure of normative growth in executive functions. The discrepancy between observed and predicted 1 year performance was greatest in the subset of CHR who developed frank psychotic symptoms after baseline assessment. Data analyses from 2-year NP assessments in the CHR sample are ongoing and will be presented. Conclusion: Findings support the presence of progressive NP impairment during the prodrome to psychosis that appears to be greatest for those at highest risk or presumably closest to illness onset. We discuss the implications of these findings for the timing and nature of NP impairments in relationship to psychosis risk and onset.
ID: 978962

VERBAL INFORMATION MANIPULATION AND SOCIAL SKILLS IN PSYCHOSIS: A PILOT STUDY

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Background: Social deficit is generally regarded as a hallmark feature of schizophrenia (APA, 1994). Social efficiency is related to the ability to understand other's intentions and beliefs with the aim to manipulate information to achieve relevant objectives (Clutton-Brock & Harvey, 1976). One applicable strategy is to tactically use ambiguous terms to distract the listeners. This study intends to investigate the ability of patients with early psychosis to manipulate verbal information. Methods: Patients with schizophrenia ($n = 11$) and healthy controls ($n = 11$) were recruited. The Ambiguity Questionnaire (AQ) was used to assess subjects' ability to adopt ambiguous answers in daily social scenarios. To assess their ability to manipulate verbal information, the Conversation Analysis Paradigm (CAP) was developed to elicit a conversation between individual participants and the experimenter under competitive or cooperative conditions. The amount of information (rated as high, middle, or low value) communicated in each unit of discourse and the number and the type of distractive terms (DT) used, defined as pieces of information that could mislead the listener, were recorded. Results: A significant interaction ($F = 16.18$, $P < .001$) between experimental groups and conditions was found in the CAP for high-value information. Controls used significantly different percentages of high-value information ($t = -6.44$, $P < .0001$), low-value information ($t = 5.93$, $P < .0001$), and DT ($t = 2.99$, $P = .014$) between test conditions, as well as the DT types used ($t = 4.22$, $P = .002$). In patients, only the percentages of low-value information used ($t = 3.89$, $P = .03$) and DT adopted ($t = 2.65$, $P = .02$) differed between conditions. On the other hand, patients used less ambiguous terms in the AQ compared with controls ($t = 2.66$, $P = .018$). Among patients, a significant correlation ($r = .656$, $P = .028$) was found between the number of ambiguous terms used in the AQ and the DT types under the competitive conditions in the CAP. Conclusion: Patients with schizophrenia perform worse in tactically controlling the amount of verbal information to communicate with the interlocutors. They also tend to use less ambiguous terms in daily life contexts. Performance in these 2 areas were significantly correlated in patients. These converging findings highlighted patients' poorer capacity in tactically manipulating verbale information, which may contribute to the social deficits observed in schizophrenia.
ID: 978261

PATTERNS OF ASSOCIATION BETWEEN PERFORMANCE IN A NATURAL ENVIRONMENT AND MEASURES OF EXECUTIVE FUNCTION IN PEOPLE WITH SCHIZOPHRENIA

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Background: This study examined the relationships between a set of real-world performance measures and a set of executive function measures with a sample of community based individuals with schizophrenia ($N = 80$). Methods: Participants were given a battery of cognitive tests and were evaluated with a real-world performance measure, the Test of Grocery Shopping Skills (TOGSS). Using canonical correlation analysis, executive functions of planning, problem-solving, working memory, and task persistence were significantly related to grocery shopping efficiency and accuracy. Results: Two canonical variates with moderate correlations (.547 and .519) explain that 30% of the variance in the executive function and grocery shopping measures was shared. Conclusion: These results identify patterns of association between executive function performance and the independent living skill of grocery shopping indicating the Test of Grocery Shopping Skills may be considered a sensitive measure of executive function performance in a real-world setting.
ID: 979985

20. Functional and Psychosocial Outcome

PREDICTORS OF FUNCTIONAL OUTCOME FOLLOWING CBT IN FIRST-EPISODE PSYCHOSIS

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Background: Cognitive Behaviour Therapy (CBT) has been found to be effective at reducing symptoms and improving functional outcome in many, but not all individuals with psychosis. Very few studies have investigated the individual patient factors that may predict outcomes following CBT or other treatments. The aim of this study was to examine the impact of theoretically-driven predictors of functional outcome following either CBT or a control therapy, called Befriending. Methods: Our previous randomized controlled trial (1) compared 14 weeks of CBT and Befriending in first-episode psychosis (FEP) and found the CBT group to have significantly better functioning, but not symptoms, at mid-treatment compared with the Befriending group. There were no significant differences in symptoms or functioning post-intervention and at 1-year follow-up. The current study sought to determine whether type of treatment moderated the relationship between individual patient characteristics and later functional outcome by examining such relationships in individuals with FEP who received either CBT (n = 28) or Befriending (n = 27). A range of a priori selected baseline attributes including demographics, symptoms, functioning and cognition (IQ) were examined by univariate regression with the outcome variable being 1-year functioning measured by the Social and Occupational Functioning Assessment Scale (SOFAS). Results: In the CBT group only, working or studying at baseline (R^2 = .212; P = .014) and better premorbid functioning (R^2 = .235; P = .01) was associated with better functional outcome at 1 year. In the Befriending group none of the variables significantly predicted outcome. There was a trend for Full Scale IQ to predict functioning in both groups (CBT: R^2 = .138, P = .088; Befriending: R^2 = .207, P = .050). Conclusion: These preliminary findings indicate that, with respect to functional outcome, individuals with better premorbid adjustment and baseline functioning may benefit significantly more from CBT compared with Befriending. For those individuals with poor premorbid adjustment and baseline functioning, it may be necessary to explore alternative treatments initially, such as vocational rehabilitation.
(1)Jackson, H.J. et al. Psychol Med. 2008;38:725–35.
This study was supported by funding from a NHMRC Project Grant #145760 (H. Jackson) & NHMRC Postdoctoral Clinical Research Fellowship #628884 (K. Allott).
ID: 978281

REMISSION, METACOGNITIVE PROCESSES AND QUALITY OF LIFE - OUTCOMES FROM OPUS TRIAL. A 10 YEAR FOLLOW-UP OF A RANDOMIZED MULTI-CENTER TRIAL OF INTENSIVE EARLY INTERVENTION VS. STANDARD TREATMENT FOR PATIENTS WITH FIRST EPISODE SCHIZOPHRENIA SPECTRUM DISORDER

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Background: The OPUS trial is the largest randomized clinical trial comparing intensive early intervention vs. standard treatment in people with first episode schizophrenia spectrum disorder. The Danish trial which ran from 1998 to 2000 recruited 547 newly diagnosed people with schizophrenia and randomly allocated participants to either standard community treatment or intensive specialized early intervention treatment. Results collected during intervention (1-year follow-up) and post intervention (2-year follow-up) revealed that the intensive intervention participants showed significantly lower psychopathology, rates of hospitalization and improved functioning compared with those patients that received standard treatment. Data collected at 5 year follow up, revealed that many of the differences in outcomes between treatment groups had disappeared, where the only significant difference was the intensive early intervention group had significantly fewer days in supported accommodation than participants in the standard treatment. The following study is interested in examining outcomes within the OPUS cohort (intensive early intervention vs. standard treatment), 8 years after the trial was completed. Methods: A sample of 547 patients included in the original OPUS trial conducted between 1998 and 2000 will be invited to participate in the study. The study is a randomized control trial with multiple follow up assessments Participants will complete a series of interviews and questionnaires to measure levels of psychopathology, quality of life, social/vocational functioning, meta-cognitive beliefs, general self efficacy and cognitive functioning. Results: Preliminary results on psychopathology, psycho-social functioning and quality of life from the OPUS cohort will be presented. Conclusion: The OPUS trial is the worlds' largest randomized control trial comparing early intensive intervention vs. standard treatment within schizophrenia spectrum disorder. Data gathered from this 10 year follow up will help identify factors for better treatment outcomes and the long term prognosis for schizophrenia spectrum disorders.
ID: 986671

EFFECTIVENESS OF AN EXERCISE PROGRAM USING A 5 KILOMETER (5 KM) EVENT AS AN ACHIEVABLE GOAL: A STUDY IN PEOPLE WITH SCHIZOPHRENIA

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Background: People with schizophrenia have a higher prevalence of obesity than the general population. Many people with schizophrenia struggle with weight gain, due, in part, to their medications, many obstacles to exercise, unhealthy eating and symptoms, such as avolition. Several studies have shown the benefits of behavioral weight loss and exercise programs for people with schizophrenia. Effectiveness of the exercise programs has been compromised by poor adherence to the program. Few studies have used tangible goals to increase adherence (Pendlebury, Bushe, Wildgust, & Holt, 2007). Methods: This study tested the feasibility of using an exercise program in preparation for the completion of a 5 kilometer (5 km) event in 2 cohorts of people with schizophrenia. The exercise program was a 10-week training program that consisted of 3 supervised walking/jogging sessions per week, and a weekly educational meeting on healthy behaviors. Results: Cohort 1: Eleven inpatients and 6 outpatients were enrolled. Sixty-five percent (11/17) of the subjects participated in all of the training sessions. Eighty-two percent of the participants (14/17) who enrolled in the exercise program participated in the 5K event. Participants did not lose a significant amount of weight during the exercise program. Weight changed from baseline to week 10 by 0.17 + 0.92 kg (t(101) = 0.19, P = .85, 95% CI −1.65, 1.98). Cohort 2: 6 inpatients and 5 outpatients were enrolled. Almost 75% (8/11) of the subjects participated in at least half of the exercise sessions. Eighty-two percent of the participants (9/11) who enrolled in the exercise program participated in the 5 km event. Weight changed from baseline to week 10 by 0.26 + 0.43 kg (t(47) = 0.59, P = .56, 95% CI −0.61, 1.13). Conclusion: These results suggest that the goal of 5 km event participation pro-

motes adherence to an exercise program and is feasible in a population of people with chronic schizophrenia. The exercise program did not impact weight in either of these samples.
ID: 979477

COMPUTER-BASED SIMULATED JOB INTERVIEW TRAINING FOR VOCATIONAL REHABILITATION: FEASIBILITY AND TOLERABILITY

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Background: A prototype version of a computer-based simulated job interview training, developed through an SBIR-1 from NIMH, was tested for its feasibility with clients of vocational rehabilitation programs. Methods: 10 participants reflecting diversity of age, gender, ethnicity, and mental illnesses were recruited from area service providers. They performed 3 complete "plays" of about 15 minutes each. The simulation included: e-learning content, a simulated job interview with a simulated employer, and a multilevel feedback system. The e-learning content included an overview of the technology and guidance on how to interview well. The on-screen interviewer asked the user a wide variety of questions related to employment history and job skills. The user selected from a list of scripted statements for spoken replies using voice-recognition software. The feedback system included an on-screen coach who provided feedback throughout the conversation and an after-action transcript and audio recording for review. Responses included participant ratings on 17 Likert-scale questions about their reactions to the simulation, 4 questions about their opinion of usability, and 2 questions about their overall opinion of usefulness of the simulation and likelihood that they would use this simulation when fully developed. Additionally, participants were asked 5 yes/no questions about the simulation as an alternative to role-plays. Results: The mean score for all Likert-scale (1–5) questions was above 4.0; especially encouraging is that the overall rating had only a range of 4–5 and the mean was 4.8. Despite cognitive or symptom limitations, participants rated the simulation high for ease of use; 9 out of the 10 found the simulation entertaining; and 8 out of 10 said they would be curious to play the simulation again. Some comments were, "It kept me interested and focused," "It was interesting to see how to improve my skills," "I was not as nervous as I would be in a real-life situation," and "It portrayed accurately what might be said in a job interview." Participants also expressed their appreciation for the help-coach and the immediate feedback on their conversational decision. Conclusion: The training provided exposure to a fearful situation and job interview skill training. Participants liked the training, were motivated to do it, and believed that it would help them decrease their fear of job interviews and increase their skills. Plans are to submit an SBIR-2 for full development.
ID: 978505

PHENOTYPE-GENOTYPE AND ENVIRONMENTAL INTERACTION IN FIRST PSYCHOTIC EPISODES. BASELINE RESULTS

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Background: A psychotic episode is characterized by positive, negative, cognitive and affective symptoms. Around 3% of the general population suffers a first episode of psychosis (FEP) along his life. Patients with a FEP are an excellent group to study the risk factors linked to the development of psychotic disorders. Our objectives are to characterize our sample of patients with a FEP, to ensure its validity as a population of interest in the study of a predictive model of the psychotic illness, to guarantee the correct matching of the control group with the recruited patients and to present some of the baseline demographic, clinical and functional characteristics of the sample. Methods: By September 2010, 34 patients, ages 7–35 years, who presented a FEP had accepted to participate in the study in our center. 24 healthy controls were recruited from the same geographic area, being matched for socioeconomic status, gender and age. Results: There were no significant differences between patients and controls in age, socioeconomic status, sex or race. Patients had worse premorbid adjustment ($P < .001$) and global functioning ($P < .001$) than controls. Male patients outnumbered females (24 vs. 10). On the PANSS, Young and Montgomery-Asberg scales, the mean total scores were 69.8 ± 23.7, 2.47 ± 5.9 and 11.4 ± 10.1, respectively. There were statistically significant negative correlations between all clinical scales and the global functioning scales ($P < .001$). A low positive correlation was found between negative and general symptoms and total PANSS score and the premorbid adjustment scale ($P < .5$). Diagnoses most used after the baseline evaluations were: psychotic disorder not otherwise specified (NOS) 35.3% and schizophrenia 26.5%. Conclusion: The present study confirms, in this Spanish sample, some previous findings about the characteristics of FEP. No statistical differences were found between patients and healthy controls in the matched variables. Worse premorbid adjustment and general functioning was found in FEP patients in comparison with healthy controls, and severity of symptoms was related to general disability. These results support the hypotheses that the FEP population of patients is a main target and a valid construct in the research of a predictive model in psychotic disorders.
ID: 976112

STAGES OF RECOVERY AND NARRATIVES FOLLOWING A FIRST EPISODE PSYCHOSIS

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Background: It has been proposed that the recovery of individuals with severe mental illness can be divided into 5 different stages: moratorium, awareness, preparation, rebuilding, and growth (Andresen et al., 2003). It has also been suggested that narratives might be a good way to access and better understand individuals' recovery processes. Even though most would expect that individuals would be more likely to be in the first stage of recovery following a first episode of psychosis, few studies have investigated this. In fact, it could be argued that some individuals may progress more quickly than others across stages. Methods: This study has 2 objectives: 1) to determine if individuals' narratives can be used to determine the stage of recovery, and; 2) to link the recovery stage to the richness of the narratives, as scored with the Scale to Assess Narrative Development (STAND; Lysaker et al., 2006). Participants were recruited in First Episode clinics in Montreal and were interviewed using the Indiana Psychiatric Illness Interview. Verbatim transcripts were coded using an analysis grid and a qualitative analysis software (QDA Miner v3.2) to assess the stage of recovery. They were also rated according to the STAND coding book by an independent evaluator. Results: Preliminary results with 25 participants reveal that 12 participants had reached the second stage of recovery (awareness), that one had reached the third stage (preparation), whereas 12 were

still in the initial stage (moratorium). There is a strong positive correlation between the stage reached and the score on the STAND (0.79, $P < .01$). Results from a larger sample will be presented. Conclusion: As expected, these results indicate that coding the recovery stage based on narratives is possible and that the stage reached is related to the richness of the narratives. Furthermore, half of the participants had progressed past the moratorium stage, implying that all individuals do not recover at the same rate. Given that treatment needs can vary according to the recovery stage, a better understanding of the different courses of recovery is warranted for clinicians and researchers. Acknowledgements: Funding for the project was provided by the Canadian Institutes of Health Research (CIHR). The first author is receiving a Doctoral Research Award from the CIHR.
ID: 976260

SELF-REPORTED QUALITY OF LIFE AND CLINICIAN-REPORTED FUNCTIONING IN SCHIZOPHRENIA: INTERRELATIONSHIPS AND SENSITIVITY TO NEUROCOGNITIVE CHANGE

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Background: Functional recovery has become a treatment priority in schizophrenia but it is a construct in need of a gold-standard operationalized definition. Divergent definitions may be in part due to emphases stemming from observer- vs. self-reports of functioning. Methods: In this study, correlations among schizophrenia subjects' ($N = 84$) self-reported quality of life (QOL; Sheehan Disability Scale) and case-manager rated observation of functioning (Specific Levels of Function Scale) were examined at baseline and following 3 months of a randomized controlled trial of cognitive remediation on 3 domains with conceptual overlap between the measures: Work/School, Interpersonal Behaviors, and Participation in Community Activities. The relationship of change scores in QOL and functional ratings to change in neurocognition (Brief Assessment of Cognition in Schizophrenia) and functional skills UPSA and SSPA) were examined with bivariate correlations. Change in functional measures was assessed with repeated measures ANOVA. Results: At baseline and endpoint, small, non-significant correlations were observed in Interpersonal QOL/Functioning (baseline $r = .12$; endpoint $r = .-.08$), Activities and Leisure QOL/Functioning (baseline $r = .09$; endpoint $r = .05$), and Work or School QOL/Functioning (baseline $r = -.19$; endpoint $r = -.23$). Following treatment, QOL Work/School and Interpersonal domains improved ($P < .01$); change scores in these domains were associated with improved psychomotor speed and information processing speed, as well as performance-based measure of adaptive competence (all P-values $< .01$). Following treatment, clinician ratings indicated small, non-significant changes in all 3 domains. However, change scores suggested that improvements in executive functioning, verbal memory and verbal fluency were associated with ratings of improved performance by case managers in the activities and work domains. Conclusion: Self-reported QOL and observer-rated functional behaviors appear to measure independent constructs and are associated with different neurocognitive constructs. Following treatment, during which cognitive and functional competence improved, self-rated QOL was rated as being more satisfied, but clinician ratings did not indicate real world behavior change. These findings have implications for how to index functional changes after short-term treatments.
ID: 978526

LINK BETWEEN OLFACTORY INDENTIFICATION AND KRAEPELINIAN SCHIZOPHRENIA: A PUTATIVE ARGUMENT FOR A NEURODEGENERATIVE PROCESS

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Background: Some recent data report deficits in olfactory identification among schizophrenic patients. These deficits are present at the beginning of the disease and should progress with the course of the illness. Likewise these deficits should be more present among schizophrenic patients with more severe symptoms and worse social functioning. The kraepelinian schizophrenia was defined in 1987 by Keefe and al. This sub-group is characterized by a very poor prognosis. Several clinical and biological studies showed differences with good outcome patients regarding pre-morbid functioning, negative and disorganized symptoms, specific cognitive deficits and polyuro-polydipsic syndrome. Studies in neuroimaging showed a posteriorization of the deficits in white and gray matter at baseline and the progression of the deficits in gray matter at 4 years among these patients in comparison with good outcome patients. These authors postulate that the kraepelinian schizophrenia may represent a very specific form of schizophrenia or of dementia. The aim of this study is to study the link between kraepelinian schizophrenia and olfactory identification. Methods: In 2010, we recruited a sample of 25 kraepelinian schizophrenic patients from the psychiatric departments in Picardie area (France), according to DSM-IV criteria and using Keefe's criteria. Then we recruited a sample of 24 no kraepelinian schizophrenic patients from the same area. Several socio-demographical data as well as the scores at the PANSS were collected for each patient. Olfactory identification was determined for each patient using a basic set of odors. To compare the 2 sub-groups we used first wilcoxon analysis then linear regression adjusting on age and duration of illness. Results: Results show a worse olfactory identification among kraepelinian patients ($P < 0, 004$) as well after adjusting on age and duration of illness ($P < 026$). Conclusion: First this result supports the validity of this entity with a specific etiopathology. Secondly as olfactory system is linked with several brain areas implicated in schizophrenia and above represent a marker of neuroplasticity, this worse olfactory deficit could express a neurodegenerative process. Then it will be interesting to use olfactory status to identify and study poor prognosis patients in a longitudinal way.
ID: 978753

MEASURING EVERYDAY FUNCTIONAL PERFORMANCE IN SCHIZOPHRENIA: RESULTS FROM A VIDEO ETHNOGRAPHY FEASIBILITY STUDY

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Background: The ecological validity of neurocognitive and functional measures in severe mental illness is poorly understood because of a lack of validated research methods to study community life-as-lived. We describe the development of a video ethnography method that measures everyday behaviors with codes called community performance indicators (CPIs). The method provides a strategy to measure everyday functional performance and test the ecological validity of neurocognitive and functional assessments. Methods: We gathered up to 18 hours of video ethnography data on each of 9 subjects with schizophrenia selected for high or low composite scores on the MATRICS Consensus Cognitive Battery (MCCB). We used video ethnography to capture behavior in naturalistic settings. We

established 4 CPIs that show excellent inter-rater and promising test-retest reliability: behavioral activity level, goal pursuit, social interaction, and problem solving. Results: 1) High and low NC subjects showed statistically significantly differences on all 4 CPIs. 2) MCCB composite scores were correlated with all 4 CPIs (r = .54–.77; $P < .01$–.07). 3) MCCB domain scores demonstrated specificity: working memory and visual learning had strong associations with all CPIs; verbal learning, reasoning/problem solving, and social cognition had strong associations with social interaction and problem solving; attention-vigilance and speed of processing were associated with goal pursuit ($r > .42$ or $P < .05$). Conclusion: We present a method for reliably measuring everyday functional performance in schizophrenia. Results from a small, select sample suggest that CPIs capture skills associated with neurocognition, supporting their use in a larger study of ecological validity.
ID: 978094

SOCIAL COGNITION IN SCHIZOPHRENIA AND BIPOLAR DISORDER: PRELIMINARY FINDINGS FROM A CROSS-DIAGNOSTIC COMPARISON STUDY

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Background: Deficits in social functioning are characteristic of many individuals with schizophrenia and bipolar disorder and include problems in establishing and sustaining intimate relationships, difficulties in maintaining employment, and a lack of involvement in community activities. Research examining cognitive processes that are operational during social interaction (what has been referred to as ''social cognition'') has helped to explain some of the observed variance in social functioning abilities across healthy and clinical populations. In this study, we assessed social cognitive performance in 2 groups of clinically stable outpatients with schizophrenia (n = 16) and bipolar disorder (n = 19), and a sample of healthy control participants (n = 15). Methods: Participants were evaluated on 3 social cognitive assessments: 1) a traditional Theory-of-Mind (ToM) social perspective-taking task; 2) a social reasoning and affect interpretation task, the Movie Clips Task (MCT); and 3) a social communication and interpersonal problem-solving task, the Interpersonal Block Assembly Task (IBAT). Results: Individuals with schizophrenia and those with bipolar disorder did not differ in performance on any of the 3 social cognitive measures. Consistent with previous findings, individuals with schizophrenia performed significantly worse than healthy controls on the ToM measure. Surprisingly, those with bipolar disorder performed significantly worse than healthy controls on measures of both cognitive (ToM) and social affect (MCT) perspective-taking, suggesting impairment in the ability to infer another person's mental and affective state. Finally, both clinical groups performed significantly worse on a measure of social communication and interpersonal problem-solving (IBAT) as compared with the healthy control group. Conclusion: Social cognitive impairments appear to be characteristic of individuals with schizophrenia as well as bipolar disorder. Future research should aim to identify deficits specific to each condition as well as those that are common to schizophrenia and bipolar disorder in order to advance the development of focused interventions that aim to enhance social cognition, social skills, and ultimately, better community functioning outcomes.
ID: 981215

TREATMENT OF NEGATIVE SYMPTOMS: WHICH PSYCHOSOCIAL INTERVENTIONS ARE EFFECTIVE?

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Background: Negative symptoms are important predictors for impaired social outcome in schizophrenia. Pharmacological and physical (eg Transcranial Magnetic Stimulation (TMS)) treatments of negative symptoms have only limited effects. Psychosocial interventions may contribute to improvement of negative symptoms. A literature study has been performed to identify psychosocial interventions that may contribute in treatment strategies. Methods: A systematic literature search was executed evaluating the effectiveness of psychosocial interventions on negative symptoms. Medline, EMBASE, Cinahl were searched for the period 1990–2010. Details on methods and results of the literature search are available on www.ggzrichtlijnen.nl (Dutch language). Studies reporting any effects (positive, negative or no effects) were included. Results were categorized into levels of evidence, level 1 standing for 2 or more randomized controlled trials (RCT's), level 2 for 1 RCT, level 3 for a non-controlled study or a RCT of low quality. Results: Cognitive behavioral therapy (CBT) does improve negative symptoms (small effect); effects last for at least 2 years (level 1) (12 RCT's, n = 976). Peer support groups may improve negative symptoms (small effect) (level 2) (1 RCT, n = 106, P = .02). Psychomotor (dance) therapy (level 2) may improve negative symptoms; effects (small) lasting 4 months. Arts therapy (level 3), drama therapy (level 3), social skills training (level 2) and music therapy (level 2) may improve negative symptoms (all small effects). A consumer run program directed on recovery may diminish negative symptoms (level 3). Cognitive remediation (level 2), family interventions (level 1) and ergo therapy (level 3) do not improve negative symptoms. Conclusion: Although most attention is paid on the pharmacological treatment, psychosocial interventions may be part of treatment protocols to improve negative symptoms. CBT is the most investigated and effective in improving negative symptoms, but like other psychosocial or pharmacological interventions, the effect sizes are small. Studies on new treatment strategies, including strategies combining pharmacological, physical and psychosocial treatments are needed to find better treatment options for negative symptoms.
ID: 979110

MULTI-DIMENSIONS OF MOTIVATION IN INDIVIDUALS WITH SCHIZOPHRENIA

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Background: Motivational deficit is a core symptom of schizophrenia and has critical implications for functional outcomes. The constructs of intrinsic and extrinsic motivation have recently received significant attention from schizophrenia researchers, although there is an overall dearth of evidence supporting the construct validity of motivation as measured specifically in schizophrenia samples. Methods: This study sought to investigate the factor structure of 2 representative measures of motivation, the Motivational Trait Questionnaire (MTQ; Heggestad & Kanfer, 2000) and the Intrinsic Motivation Inventory for Schizophrenia Research (IMI-SR; Choi, Mogami & Medalia, 2009), among individuals with schizophrenia (N = 29) participating in cognitive remediation research at Columbia University. Descriptive statistics were calculated to evaluate item characteristics (eg, item

means and standard deviations and item skewness), and exploratory factor analysis (EFA) was used to evaluate factor structure of the 2 measures. Results: Total and subscale scores on the MTQ and IMI-SR were comparable to scores reported in prior schizophrenia samples. EFA yielded 3 factors: intrinsic motivation (ie, interest/enjoyment, value/use), integrated regulation (ie, personal mastery and competitive excellence) and introjected regulation (ie, motivation related to anxiety). The 3 factor model explained 73.3% of the variance. Cronbach's alpha values for the 3 factors were .84, .73 and .58 for intrinsic motivation, integrated regulation and introjected regulation, respectively. Conclusion: Psychometric examination of measures assessing trait-like (MTQ) and state-specific (IMI-SR) levels of motivation yielded 3 primary factors, suggesting a multidimensional structure to the construct of motivation in schizophrenia. Future study utilizing confirmatory factor analysis will contribute to model specification to better understand and inform the measurement of this core construct of schizophrenia symptomatology.
ID: 978942

SUBTYPING SCHIZOPHRENIA PATIENTS BASED ON DEVELOPMENTAL TRAJECTORY: RELATIONSHIP TO MEASURES OF COGNITION, SYMPTOMS AND FUNCTIONING AFTER ILLNESS ONSET

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Background: Premorbid history varies widely in schizophrenia, with some individuals showing a slow and insidious onset and others becoming psychotic more suddenly. Further, premorbid adjustment has been shown to bear significantly on functioning, symptoms, cognition, and ultimate prognosis. Methods: In the current exploratory analysis, our measure of premorbid functioning was the Premorbid Adjustment Scale (PAS), a retrospective measure assessing social and academic function at several time points from early childhood to illness onset. In an effort to explore discrete developmental subtypes, we applied mixture modeling to data from the PAS in our sample of schizophrenia patients (N = 373), finding 4 latent trajectory classes. We then tested the different classes' associations with variables pertaining to cognition, symptoms, and functioning. Results: The first of the classes we identified showed consistently good-to-moderate function until onset; the second showed initially good function that deteriorated with time until onset; the third showed initially poor function that stabilized or improved until onset; and the 4th showed initially poor function that further deteriorated until illness onset. We found that developmental classes varied from one another in age at onset of prodromal symptoms (F(1,338) = 7.34, P = .007), Global Assessment of Functioning (GAF) score (F(1,348) = 12.21, P = .001), negative symptoms as measured by the Positive and Negative Syndrome Scale (PANSS; (F(1,262) = 4.53, P = .034), and general cognitive ability (F(1,354) = 4.33, P = .038). Further analyses confirmed the differences between the latent trajectory classes. In particular, the 4th class of individuals, who show the greatest degree of developmental compromise prior to formal illness onset, reliably show the greatest degree of cognitive and functional impairment, as well as more negative symptoms, relative to the other developmental classes. Conclusion: Our findings are particularly relevant to the problem of heterogeneity in the schizophrenia population; our use of a minimally-supervised modeling approach to for distinct patient subgroups confirms the notion that premorbid history represents a useful index for subtyping schizophrenia patients. The potential implications of this subtyping strategy, including those pertaining to potential genetics studies, are to be discussed.
ID: 979572

SUCCESS AND RESOURCE APPRAISALS AND NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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Background: Within schizophrenia, negative symptoms have strong relationships with unfavorable outcomes such as social isolation, unemployment, and decreased life satisfaction (Milev et al., 2005). Importantly, the majority of individuals with schizophrenia experience negative symptoms at some point during their illness, and approximately 25% experience unremitting negative symptoms (Buchanan, 2007). A recently proposed cognitive model hypothesizes that negative symptoms are related to low expectancies for pleasure, low expectancies of acceptance from others, low expectancies for success in daily life, and a perception of limited personal resources (Rector, Beck, & Stolar, 2005). The current study evaluates whether a newly developed measure assessing 2 of these belief domains (low expectations for success and perception of limited resources) is associated with negative symptoms in schizophrenia. Methods: 62 individuals with schizophrenia were rated on negative symptoms and completed a new measure assessing beliefs about the probability of success and perception of limited personal resources (Success and Resource Appraisal Questionnaire (SARA-Q), as well as items from the Dysfunctional Attitudes Scale assessing defeatist beliefs. Results: Analyses suggest that a greater degree of beliefs regarding low expectations for success and perception of limited resources (as assessed by the SARA-Q) is robustly associated with negative symptoms comprising the affect/motivation factor (avolition, asociality, and anhedonia), but not with negative symptoms reflecting diminished expressivity (blunted affect, alogia). Notably, the SARA-Q predicted unique variance in affect/motivation symptoms above and beyond the influence of depression, positive symptoms, and defeatist beliefs. Conclusion: Beliefs about diminished capability for success and beliefs about an inability to cope with difficult situations and sustain effort to complete tasks (ie, limited personal resources) are strongly linked with negative symptoms and are thus a potential treatment target for interventions targeting negative symptoms in schizophrenia.
ID: 977808

EFFECTS OF A MINDFULNESS INTERVENTION ON WORK OUTCOMES FOR ADULTS WITH SCHIZOPHRENIA

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Background: The purpose of this study was to evaluate the feasibility and efficacy of the Mindfulness Intervention for Rehabilitation and Recovery in Schizophrenia (MIRRORS), an adaptation of Mindfulness-Based Stress Reduction (MBSR) designed to enhance work quality and quantity in a vocational rehabilitation job placement. Methods: In this randomized controlled pilot study, 34 participants with schizophrenia or schizoaffective disorder were concurrently enrolled in vocational rehabilitation and were receiving outpatient services. After they were randomized to the 16-week MIRRORS program (N = 18) or to a weekly support group (N = 16) and had begun to work, hours worked were recorded weekly and work performance was assessed at baseline, mid-intervention and intervention end using the Work Behavior Inventory (WBI) by a rater who was not involved in the interventions. Groups were equivalent on baseline demo-

graphic variables but the MIRRORS group was significantly higher on PANSS positive symptoms. Results: *T* tests found no significant group differences for total hours or weeks worked. A repeated measures ANCOVA controlling for baseline PANSS positive symptoms was conducted comparing overall ratings of work performance assessed at baseline, mid-intervention and intervention end using the WBI for the 26 participants (MIRRORS = 15; Support = 11) who participated in at least the first half (8 weeks) of the interventions while working. This analysis revealed no time effect. However, the group effect was significant ($F = 4.74$, $P = .04$), indicating stronger overall work performance for the MIRRORS group, and there was an interaction trend ($F = 3.10$, $P = .054$). Conclusion: Results suggest that receiving a mindfulness-based intervention concurrent with a vocational rehabilitation job placement may improve quality of work outcomes for people who have schizophrenia.
This study was supported by a grant from Veterans Administration Rehabilitation Research and Development.
ID: 978414

DOES SUBSTANCE MISUSE AND COGNITIVE IMPAIRMENT PREDICT FUNCTIONAL OUTCOME IN THOSE WITH A FIRST-EPISODE OF PSYCHOSIS?

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Background: Comorbid substance misuse is highly prevalent in those with a first-episode of psychosis (FEP) and a detrimental impact on the course of illness, with more hospitalizations, treatment non-compliance and higher rates of relapse. A history of substance misuse may also have an impact on functional outcome in patients with psychosis. Those with a psychotic disorder have impairment in cognitive function relative to the general population, which has been associated with global functioning. This study therefore aims to investigate whether cognitive function and substance misuse at the FEP predict global functioning at 8 year follow-up. Methods: Neuropsychological tests were administered to 76 participants at their FEP, these participants were then followed-up after an average of 8 years (range 5–11). Substance misuse was defined as frequent or regular illegal drug use (more than once a month) or abuse or dependence of illegal substances using criteria based on the DSM-IV. The Global Assessment of Functioning (GAF) was completed at follow-up assessment. Linear regression analysis was conducted to investigate the individual predictors of functional outcome including neuropsychological test performance and a history of substance misuse plus baseline sociodemographic and clinical variables. A multiple regression model was subsequently constructed entering those variables that were significant individual predictors of GAF disability. Results: Male gender ($P = .001$) and a history of illegal substance misuse ($P = .035$) were associated with a lower GAF disability score at follow-up assessment, no further baseline clinical or socio-demographic characteristics were significant predictors. Worse performance on several tests of cognitive function were associated with poorer GAF disability scores at follow-up including premorbid IQ ($P < .001$), IQ ($P < .001$), auditory working memory ($P < .001$), immediate ($P < .001$) and delayed ($P < .001$) recall, verbal fluency ($P < .001$), executive function ($P = .002$) and psychomotor speed ($P = .002$). The final multiple regression model ($F(3,64) = 16.784$, $P < .001$, Adjusted $R^2 = .414$) included immediate verbal recall ($B = 0.343$, $P = .004$), premorbid IQ ($B = 0.307$, $P = .007$) and gender ($B = 0.235$, $P = .018$). Conclusion: Premorbid IQ, Immediate verbal recall ability and male gender were predictors of functional outcome measured using the GAF disability scale. A history of substance misuse is not a significant predictor of functional outcome when taking into consideration cognitive factors.
ID: 986751

ASSESSING RECOVERY IN PEOPLE WITH SERIOUS MENTAL ILLNESS

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Background: Mental health care in the United States and Western Europe is undergoing a seismic shift in values. The centerpiece of this shift is the recovery model, which assumes that all consumers have the capacity to improve and develop a life distinct from their illness. It emphasizes hope, empowerment, and control of one's life. This model stands in contrast to scientific and clinical models, which view recovery as an outcome, primarily involving reduced symptoms and improved functional capacity. Despite the importance of the recovery model, to date there are no empirically sound measures of recovery as defined by SAMHSA and only a handful that are based on other definitions. We have used an empirical strategy to develop a new instrument based on the SAMHSA definition and recovery domains: the Maryland Assessment of Recovery in People with Serious Mental Illness (MARS). We will describe the development of the MARS and present new data derived from a larger project to examine its validity as well as the construct validity of the consumer recovery construct. Methods: The MARS was developed using an iterative process by a group of experts in serious mental illness and recovery, supplemented by structured interviews with independent experts and consumers. The psychometric characteristics of the MARS were evaluated based on a sample of 166 participants with serious mental illness recruited from several outpatient mental health clinics in Maryland and Texas. Results: The MARS contains 25-items scored on 5-point Likert scales. Initial data demonstrate that the MARS has good internal consistency (Cronbach's alpha = .95) and test-retest reliability ($r = .868$). It has high content validity, and face validity based on ratings of consumers and scientific experts. Further, the data indicate that while the SAMHSA definition describes 6 distinct personal characteristics of recovery, the domains are highly inter-correlated and actually reflect a single factor. Conclusion: These data support the use of the MARS as a psychometrically sound recovery measurement instrument and suggest that it is practical for use in both community mental health settings as well as research.
ID: 986693

A COMPARISON OF A PATIENT SELF-REPORT MEASURE OF RECOVERY AND INTERVIEW BASED MEASURES OF FUNCTIONAL OUTCOMES AND SYMPTOMOLOTOGY

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Background: We investigated the relationship between patient rated recovery and measures of symptomatology and functional outcome in a group of 96 individuals with a diagnosis of schizophrenia or schizoaffective disorder (DSM IV-SCID). While once primarily viewed as a chronic, deteriorating

condition, schizophrenia is now often seen within a more hopeful, recovery based paradigm. Recent research, coupled with consumer-driven campaigns to change public opinion, have resulted in a Recovery Movement. Recently developed by Bellack and colleagues, the Maryland Assessment of Recovery Scale in Serious Mental Illness (MARS) is a 25 item self report measure developed to assess recovery status in people diagnosed with serious mental illness. Based on the SAMHSA definition of a recovery model, the scale focuses on beliefs about the self associated with the recovery process. In preliminary studies conducted by Bellack and colleagues, the MARS has been shown to be a unidimensional scale with good internal consistency and test/retest reliability. Methods: Participants in this study were administered the MARS, the Social and Occupational Functioning Assessment (SOFAS), the Multnomah Communities Abilities Scale (MCAS), the Brief Psychiatric Rating Scale (BPRS) and the Negative Symptom Assessment (NSA). We hypothesized that participants' level of reported recovery (MARS) would be positively correlated to community functioning (SOFAS, MCAS) and negatively associated with symptom measures (BPRS, NSA). Results: To correct for a skewed distribution, Spearman Ranked correlations were calculated to examine the relationship between these constructs. Confirming our hypothesis, results of the relationship between the MARS construct of recovery and measures of community functioning result in low to moderate positive correlations ($r = .21–.35$; MARS to SOFAS and MCAS respectively) suggesting that more positive beliefs about recovery are associated with better community functioning. In contrast, while a measure of more global symptoms (BPRS) was moderately negatively associated with higher levels of recovery ($r = -.30$) as hypothesized, there was no correlation between the MARS and NSA ($r = -.06$). Conclusion: These findings suggest that while there is a relationship between ideas about the self related to a recovery model and community functioning and global symptoms, current ideas about the relationship between negative symptoms and recovery attitudes may require further investigation.
ID: 988382

QUALITY OF LIFE IN METABOLIC RISK PATIENTS WITH PSYCHOSIS IN RELATION TO THE POPULATION

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Background: Background: The International Diabetes Federation (IDF)(2004) has defined criteria for metabolic syndrome and in patients with schizophrenia 4 of 10 meet this criteria (Mc Evoy 2005). Its important too study more about the influence of metabolic syndrome and obesity because there association with high morbidity and increased risk of influence on patients health and the treatment itself (Weiden et al 2004). The aim of the study was to investigate metabolic risk factors influence on quality of life in patients with schizophrenia and other psychosis Methods: The method was a prospective cohort study from specialized psychiatric outpatients departments in Sweden. The study recruits consecutively patients diagnosed with schizophrenia and other long-term psychotic disorders (ICD10). The prospective population based study of public health in south east of Sweden is serving as a population based control group. Patients are assessed with a psychiatric questionnaire which included CGI and GAF. Health-related quality of life assessed using the questionnaire EQ5D both in patients and population and health status outcomes was BMI, smoke habits and alcohol use. Results: The results on patients ($n = 777$) and population ($n = 7238$) showed significant differences in lower EQ5D Index for patients especially in younger age. The diagnosis of schizophrenia and schizoaffective were the most common in the patient group ($n = 481$). In patients was nearly 50% non alcoholic users compared with the population were the non users was 18 %. BMI over 35 were more common in the patient group than in the population 13.2% vs. 2.8 %.In patients 44% was smoking compare with population 21% but it was no difference in quality of life between smokers in patients compare with population. Conclusion: : In conclusion there were differences in quality of life between metabolic risk patients with psychosis and the control group from the population. There was also differences in BMI, smoking habits and use of alcohol.
ID: 978332

PROFILES AND CORRELATES OF WELL-BEING AMONG PEOPLE WITH SEVERE MENTAL ILLNESS RECEIVING SUPPORTED EMPLOYMENT SERVICES : DOES GETTING A JOB MATTER?

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Background: While some models in positive psychology suggest that people's level of well-being is biologically determined and may only temporarily be affected by life circumstances, some researchers have also found that lasting changes in happiness and well-being can be achieved through action or life events. According to a certain model, 50% of an individual's level of happiness (or life satisfaction or long-term balance of positive and negative affects) is based on genetic factors and this "happiness baseline" remains fairly constant. For the rest, 40% of the level of happiness would depend upon intentional activities and 10% upon life circumstances, the employment status for example. Furthermore, it seems that most life events would affect levels of well-being for less than 3 months and these changes would be followed by a return to the "baseline." Methods: Using a sample of 302 people with severe mental illness registered in supported employment programs, the present study aimed at assessing whether getting competitive employment was associated with changes in their psychological (PWB) and social well-being (SWB). Different questionnaires and interviews were administered to the participants. Results: The results revealed an increase between baseline and the 9-month follow-up in both PWB and SWB, but these increases were not related to whether people obtained a job or not. Further analyses indicated that people with lower levels of self-esteem were more likely to be found in the low-level PWB and SWB clusters at both time points while levels of clinical symptoms were not as consistently related to the clusters. Job satisfaction and number of accommodations implemented at the workplace were not related to the clusters. Conclusion: In accordance with the theories that postulate that life circumstances are not important factors in an individual's level of well-being, this study showed that gaining employment was not associated with significant changes in levels of PWB and SWB in people with a severe mental illness. Further analyses supported the point that it is intrinsic factors (self-esteem) rather than fluctuating ones (symptoms) that would best determine an individual's levels of well-being, happiness and life satisfaction. However, knowing that changes in life circumstances rarely impact the levels of well-being beyond a period of 3 months, it would have been interesting to gather longitudinal data.
The present study has been funded by the Canadian Institutes of Health Research (CIHR).
ID: 967397

BASELINE MOTIVATIONAL DEFICITS AS THE KEY PREDICTOR OF FUNCTIONING IN SCHIZOPHRENIA AT 1-YEAR FOLLOW-UP

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Background: The negative symptoms of schizophrenia are comprised of 2 key symptom subdomains: 1) diminished expression (affective flattening and poverty of speech); and 2) amotivation, and contribute to functional impairment in this illness. Recent data, including our own work, suggests that motivational deficits serve as a critical determinant to functioning. This study explores the longitudinal relationship between motivational and pleasure deficits, cognitive dysfunction, and functional outcomes at 1 year in schizophrenia. We hypothesize that motivational deficits are the critical predictor of longitudinal functioning in schizophrenia. Methods: Stable outpatients between the ages of 18 and 55 with schizophrenia were evaluated at baseline and 1 year later with: the Scales for the Assessment of Positive Symptoms (SAPS) and Negative Symptoms (SANS); the Apathy Evaluation Scale - clinician version (AES); the Temporal Experience of Pleasure Scale (TEPS); the Calgary Depression Scale (CDS); and the Brief Assessment of Cognition in Schizophrenia (BACS). The Quality of Life Scale (QLS) was used to evaluate functional status. Results: 23 participants (mean age of 42 years, mean duration of illness of 15 years) were assessed at baseline and 1 year later. Stepwise hierarchical regression revealed that baseline amotivation, as measured by the AES, was the strongest predictor of both baseline and future functioning. Specifically, AES scores accounted for 76% of the variance in baseline functioning (R^2 change = .756, $P < .001$), and 70% of the variance in functioning at 1-year (R^2 change = .697, $P < .001$). After exclusion of the Intrapsychic Foundations subscale of the QLS due to overlap in item content with amotivation measures, AES score continued to be the strongest predictor of functioning at baseline and follow-up, accounting for 66% and 58% of the variance in functioning, respectively. Positive symptoms (SAPS total score) explained an additional 5% of the variance, and cognitive dysfunction an additional 6% of the variance in functioning, at baseline only. Conclusion: Negative symptoms have been repeatedly implicated in poor functional outcome, with recent work suggesting that motivational deficits are the central link between negative symptoms and poor functioning. The present data extends previous findings and highlights the critical role motivational deficits play in predicting longitudinal functional outcomes in schizophrenia.
ID: 976492

EXAMINING THE EFFICACY AND FEASIBILITY OF EXERCISE COUNSELING IN INDIVIDUALS WITH SCHIZOPHRENIA

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Background: This pilot study examined the feasibility of a modified form of exercise counseling among obese individuals with schizophrenia and assessed its impact on increasing levels of physical activity and improving psychological mediators including self-efficacy, perceived benefits and barriers of physical activity. Methods: A pre and post single-case experimental design was used. Four obese adults with schizophrenia (2 men and 2 women) who were not in the action or maintenance stages of the Transtheoretical Model (TTM) (Prochaska & DiClimente, 1986) with respect to physical activity were recruited. The TTM allows clients to be assessed for their readiness to change particular behaviors and provides stage specific cognitive and behavioral strategies to assist with behavior change. Participants attended 4 exercise counseling sessions conducted by the lead researcher. Exercise counseling sessions consisted of exploring physical activity history and interests, setting weekly goals, and monitoring progress. Physical activity and psychological mediators were measured using the International Physical Activity Questionnaire (Craig et al., 2003) and the Patient-Centered Assessment and Counseling for Exercise Questionnaire (Long, et al., 1996) before, during, and 1 month after the intervention. Participants also wore accelerometers throughout the study to provide objective data of physical activity. Results: All participants found the intervention acceptable and attended all 4 exercise counseling sessions. Exercise counseling was successful in targeting key TTM psychological mediators; however, these changes were not associated with increased physical activity in 2 participants. These 2 participants indicated they experienced negative physical and mental health complications (eg, sore hips and muscles, anxiety attacks) and had difficulties with scheduling during weeks 3 and 4 of the intervention which interfered with regular physical activity participation. Conclusion: Findings from this developmental stage of research indicate that this modified form of exercise counseling can successfully target key psychological mediators of the TTM. Future behavioral interventions for exercise and physical activity should also include additional strategies to enhance barriers and scheduling efficacy in addition to other psychological mediators of behavior change.
ID: 979328

DEFEATIST BELIEFS, ASOCIAL BELIEFS, AND LOW EXPECTATIONS: THE EMERGING COGNITIVE BEHAVIORAL SCIENCE OF NEGATIVE SYMPTOMS AND THE DEFICIT SYNDROME

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Background: Reduced motivation and withdrawal from constructive activity have been observed in patients with schizophrenia because the earliest psychiatric reports and are important contributors to long-term disability. After 100 years of study, however, understanding of these negative symptoms is surprisingly limited, as are efficacious treatment options. Recent research has indicated that psychological factors such as negative attitudes and expectancies are significantly associated with the broad spectrum of negative symptoms. Specifically, defeatist beliefs regarding performance mediate between neurocognitive impairment and both negative symptoms and functional outcome. Additionally, asocial beliefs predict asocial behavior, and negative expectancies are associated with negative symptoms. The present study explored whether these dysfunctional beliefs and negative expectancies might also be a feature of deficit syndrome schizophrenia, which was proposed over twenty years ago as a separate negative symptom syndrome within schizophrenia that has a distinct neurobiological pathophysiology and etiology. Methods: Based on a proxy formula, 22 deficit and 20 non-deficit patients (from a pool of 125 negative symptom patients) were identified and received a battery of symptom, neurocognitive, and psychological measures. In addition, 22 healthy controls received a subset of this battery. Results: The deficit group scored significantly worse on measures of negative symptoms, insight, neurocognition, defeatist attitudes, asocial beliefs (a trend), and low expectations for pleasure but better on measures of depression, anxiety, and distress than the non-deficit group. Moreover, the deficit group showed a trend for higher scores on self-esteem. Conclusion: Based on these findings, we propose a more comprehensive formulation of deficit schizophrenia, characterized by neurobiological deficits and a cluster of psychological attributes that lead to withdrawal and protect the self-esteem. Although the patients have apparently opted-out of participa-

tion in normal activities, we suggest that a psychological intervention that targets these negative attitudes might improve their functioning and quality of life.
ID: 978259

BASELINE COGNITION AND SYMPTOM VARIABLES PREDICT THE ACQUISITION OF SOCIAL AND ADAPTIVE SKILLS DURING PSYCHOSOCIAL INTERVENTION

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Background: Functional recovery has become an important treatment target in schizophrenia. While pharmaceutical treatments for schizophrenia have been effective in reducing positive symptoms of the disorder, these improvements do not translate to improved independent living, community involvement, or interpersonal behavior. This study aims to identify baseline predictors for the acquisition of social and adaptive skills during psychosocial intervention. Methods: Schizophrenia patients ($N = 54$) in a clinical trial were randomized to receive a previously validated psychosocial treatment called Functional Adaptation Skills Training (FAST). FAST is a group treatment that uses props and role-plays to improve areas of functioning such as handling finances, living independently, and meeting people. Assessments were conducted pre- and post-treatment. Stepwise and hierarchical regression analyses determined if demographic and course of illness variables and baseline cognitive domains predicted the pre- and post-treatment change scores in acquisition of competence measures (social skills, adaptive living skills, medication management) and community behavior (community activity, interpersonal relationships). Results: Social Competence improvement was predicted by psychomotor speed ($R^2\Delta = .30$) and lower positive symptoms ($R^2\Delta = .16$). Improvements in Adaptive Competence were predicted by processing speed ($R^2\Delta = .13$). Medication Management Skill improvement was predicted by younger age at baseline ($R^2\Delta = .10$) in the first step and lower negative symptoms ($R^2\Delta = .16$) and better baseline processing speed ($R^2\Delta = .07$) in the second step. Community behaviors were differentially related to baseline cognitive and demographic variables. Interpersonal Behaviour was predicted by age of first hospitalization ($R^2\Delta = .18$) in the first step and working memory ($R^2\Delta = .13$) in the second step. Community Activity was predicted by age of first hospitalization ($R^2\Delta = .28$) in the first step and executive function ($R^2\Delta = .26$) in the second step. Conclusion: Cognitive and symptom variables limited the extent to which individuals with schizophrenia acquire skills through psychosocial intervention. Earlier onset and the amount of time hospitalized are additional rate limiters when examining how psychosocial treatment generalizes to real-world community behavior. Although they may acquire skills in treatment, individuals with earlier onset or long hospital stays might benefit from additional efforts to translate these gains to their community behavior.
ID: 978706

COGNITIVE FLEXIBILITY AS A PREDICTOR OF PERSPECTIVE-TAKING IN SCHIZOPHRENIA

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Background: Deficiencies of social perspective-taking have been consistently demonstrated in schizophrenia. However, the neurocognitive underpinnings of these deficits are yet poorly understood. Controlled laboratory tasks that challenge the participant to consider the perspective of another person have yielded evidence that individuals with schizophrenia have minimal difficulty in making simple inferences in regard to the perspective of a single individual. Deficits in perspective-taking are revealed when the task calls for 2-stage inferential reasoning, ie the ability to infer from a series of events what another person is thinking about a third person—what is referred to as "second-order" perspective-taking in the literature on Theory of Mind. Methods: This study examined the neurocognitive correlates of second-order vs. first-order perspective taking on a series of False Belief Tasks that involve standard oral presentation of stories and a more novel series of videotaped scenes. Subjects were 18 individuals with DSM-IV (SCID) Schizophrenia or Schizoaffective Disorder and 25 healthy control individuals (ages 18–60) who responded to public advertisements regarding the research. Neurocognitive functioning was assessed with a battery of information processing and neuropsychological tests. Results: Correlational and regression analyses yielded evidence that neurocognitive correlates of both first- and second-order perspective-taking differed for healthy control subjects vs. individuals with schizophrenia. Among individuals with schizophrenia, performance on both first- and second-order perspective-taking tasks was predicted by measures of cognitive flexibility (perseverative errors on the Wisconsin Card Sort Test), when controlling for working memory. In contrast, among healthy control subjects only, estimated IQ predicted performance, and only on second-order tasks alone. Other neurocognitive domains (attention, vigilance and complex problem solving) did not contribute to variance in performance on the 2 types of False Belief tasks—for either healthy control subjects or individuals with schizophrenia. Conclusion: Overall, results suggest that deficits in the ability to flexibly shift focus from one social target to another and/or to simultaneously hold in mind the perspectives of more than 1 individual may underlie basic deficits in representational thinking in the social domain among individuals with schizophrenia.
ID: 979992

AN INVESTIGATION OF A DATING SKILLS GROUP FOR YOUNG PEOPLE WITH PSYCHOSIS

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Background: There is evidence that despite initial symptomatic response there is poor functional recovery following an initial psychotic episode, yet treatments to address these needs are not widely available to this population. There is a need to develop treatments oriented to the development of social skills, such as dating, for individuals with first episode psychosis. The current study is a pilot study to investigate the feasibility and potential clinical benefits of a dating skills group designed for individuals who are in their first 5 years of psychosis. Methods: Participants ($n = 9$) were males(mean age = 25.9)who attended a dating skills group for 12 weeks. Assessments of well-being, life satisfaction, self-esteem, loneliness, fear of negative evaluation, social skills and symptoms were conducted at pre-treatment, post-treatment and 3 month follow-up. A client feedback questionnaire was administered at post-treatment. Paired t tests were conducted to compare means on all measures at baseline and post-treatment and 3 month follow-up. Results: Results showed a decrease in the mean score for phobic anxiety on the brief symptom inventory at post-treatment ($P = .02$). The difference in the mean level of self-acceptance, as measured by the Psychological Well-Being scale, between baseline and post-treatment also approached significance ($P = .06$)suggesting a trend for self-acceptance to increase at post-treatment. We also calculated response frequency for each answer on the client feedback questionnaire to explore client impressions. Clients endorsed that the group was easy to follow ($n = 7$), very enjoyable ($n = 6$), very useful ($n = 7$), and respectful ($n = 7$). The majority of clients

(n = 6) felt that the group "helped" in increasing confidence to meet new people. Conclusion: Research suggests(Pinkham et al., 2007) that young individuals with psychosis often lack the social skills to meet others and initiate dating and romantic relationships. This study suggests that dating skills groups could possibly reduce potential barriers to dating such as phobic anxiety and lack of self-acceptance. Overall our results indicate that dating skills groups are a novel, feasible and well-received intervention for individuals with first episode psychosis.

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ID: 978984

THE DIFFERENTIAL VALIDITY OF 6 DIFFERENT RATING SCALES FOR FUNCTIONAL OUTCOME IN SCHIZOPHRENIA: THE VALIDATION OF EVERYDAY REAL WORLD OUTCOMES (VALERO) STUDY RESULTS

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Background: Cognitive deficits are associated with disability in people with schizophrenia. However, several recent studies have found very minimal relationships between ratings of real-world functioning and cognitive performance. These studies typically relied on patient self-report and there is little information about which rating method or informant provides the best information. Thus, the Validation of everyday real world outcomes (VALERO) study was conducted which evaluated 6 real-world functional rating scales chosen by a RAND panel and examined their correlations with performance-based measures of cognitive functioning and the ability to perform everyday activities. Methods: 198 people with schizophrenia were tested with the MATRICS Consensus cognitive Battery (MCCB) and performed the UCSD performance-based skills assessment-B (UPSA-B), and the advanced finances subtest from the Everyday functioning battery (EFB). They and an informant (Friend, relative, or case manager) also reported their functioning on 6 real world functional status ratings scales; The Social Behavior Schedule (SBS), The Social Adjustment Scale (SAS), the Heinrichs Carpenter Quality of Life Scale (QLS), the Specific Levels of Functioning (SLOF), the Independent Living skills Survey (ILSS), and the Life Skills Profile (LSP). Best judgment ratings were generated by an interview who conducted both interviews. Results: HLM analyses were used to construct an ability latent trait and canonical correlation analysis was used to relate all 6 functional status rating scales to the latent trait. The overall model fit was quite good: Chi-squared = 78.100, degrees of freedom (df) = 56, P-value (P) = .027, and RMSEA = .078, with 41% variance shared between the ability latent trait and the 6 rating scales. The rating scales were systematically deleted from the model and the final model with 2 rating scales, the LSP and the SLOF, fit the data: Chi-squared = 32.059, df = 24, P = .126, RMSEA = .072. A regression analysis found that the LSP did not add any variance to the prediction of the ability latent trait above and beyond the SLOF. Conclusion: Systematic assessments of real world functioning are quite strongly related to performance on ability measures such as the MCCB and UPSA-B. Of the 6 rating scales selected as most suitable by the VALERO RAND panel, the Specific Levels of Functioning was best in this study.
ID: 948785

ABOVE AVERAGE INTELLECTUAL ABILITY AND FUNCTIONAL STATUS IN SCHIZOPHRENIA

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Background: Occasional reports of preserved and even above-average cognitive ability continue to appear in the schizophrenia literature. We were interested in the extent to which these high-performing patients also demonstrate advantage in practical cognition, daily living skills and functional independence. Methods: To explore the question we examined IQ scores in 96 patients meeting DSM-IV criteria for schizophrenia or schizoaffective disorder and in 77 non-patient comparison participants. This procedure yielded 18 patients with IQs above the average range (>110; AAP) as well as 27 controls in the same range (AAC). In addition, 16 patients (BAP) and 6 controls (BAC) scored below the low-average range(<80). These 4 groups were then compared on demographic, cognitive, clinical and functionality variables. Cognitive measures included the Wide Range Achievement Test-Reading (WRAT-4) and the MATRICS Consensus Cognitive Battery (MCCB). Clinical measures comprised the Positive and Negative Syndrome Scale (PANSS). Practical cognition measures included the Canadian Objective Assessment of Life Skills (COALS) and the University of California Performance Skills Assessment (UPSA). Community functionality was indexed with the Multidimensional Scale of Independent Functioning (MSIF). Results: Groups did not differ significantly in age, sex, parental education or race, but patient groups had higher rates of unemployment and less education than healthy comparison groups. The patient groups (AAP, BAP) were equivalent in the severity of their positive symptoms, but BAP had significantly more severe negative symptoms (PANSS). There were significant (P <.001) main effects of group on WRAT, MCCB, COALS and UPSA measures. In addition, post-hoc comparisons revealed significant (P < .05) cognitive differences between AAPs and BAPs, but no differences between the AAP and AAC groups. However, community functionality (MSIF) differentiated patient groups from each other as well as from the control groups. Thus BAPs showed significantly less community independence than AAPs, AACs and BACs, whereas AAPs were less independent than AACs. Conclusion: Schizophrenia patients with above average intellectual ability are cognitively indistinguishable from controls with this ability level. Moreover, high ability significantly offsets the severe dependence and functional impairment associated with the illness. Nonetheless, these exceptional patients still remain functionally disadvantaged relative to healthy people.
ID: 931133

COMMUNICATION ABNORMALITIES DIFFERENTIALLY PREDICT SPECIFIC ASPECTS OF SOCIAL FUNCTIONING IN SCHIZOPHRENIA

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Background: Neurocognitive deficits and communication abnormalities (CA) are central features of schizophrenia. Although neurocognition is often the most robust predictor of adaptive functioning, recent evidence suggests that CA better predict social functioning. Methods: This study examined the contribution of neurocognition and 2 subtypes of CA (ie, disconnected speech and poverty of speech, as measured by the Thought, Language and Communication Scale) to impairments in social functioning in a sample of community-dwelling subjects with schizophrenia (N = 85). Measures of social functioning included: social competence (Social Skills Performance Assessment [SSPA]; Social and Assertive scenes), social be-

havior in the community as rated by case-managers (Specific Level of Function Scale [SLOF]; Social Appropriateness and Interpersonal Behaviour domains), and subjects' self-rated quality of social life (QOL; Sheehan Disability Scale). Stepwise regression analyses determined if disconnected speech and/or poverty of speech predicted social outcomes after accounting for neurocognitive abilities. A MANOVA was conducted with global cognition as a covariate to determine whether groups trichotomized as "disconnected," "poverty of speech" or "without CA" had differences in various aspects of social function. Results: The SSPA Social Scene was predicted by Disconnected speech ($R^2\Delta = .37$), followed by Neurocognition ($R^2\Delta = .07$) and Poverty of speech ($R^2\Delta = .03$), whereas the SSPA Assertive Scene was predicted by Poverty of speech ($R^2\Delta = .19$) followed by Disconnected speech ($R^2\Delta = .06$). SLOF Interpersonal Behavior was predicted by Poverty of speech alone ($R^2\Delta = .18$), while SLOF Socially Appropriate Behavior was predicted by Neurocognition ($R^2\Delta = .10$) and Disconnected speech ($R^2\Delta = .06$). QOL was predicted by Poverty of speech ($R^2\Delta = .10$) followed by Neurocognition ($R^2\Delta = .07$). MANOVA tests revealed greater impairments for the poverty of speech group than the group without CA in both the SSPA Assertive Scene ($P = .01$) and the Interpersonal Behavior ($P = .02$). Subjects with disconnected speech performed worse than the group without CA on the SSPA Social Scene ($P = .04$) and reported more impaired QOL than the poverty of speech group ($P = .04$). Conclusion: Communication abnormalities predict social functioning even after accounting for neurocognitive factors. Discrete abnormalities are differentially associated with specific social competencies and behavior, and therefore may be considered treatment targets for social functioning.
ID: 979008

WORKING ALLIANCE AND COGNITIVE REMEDIATION THERAPY OUTCOMES IN PEOPLE WITH SCHIZOPHRENIA

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Background: Good working alliance has been associated with better outcomes in several studies of psychosocial interventions for people with schizophrenia. There have been no studies of the working alliance in the context of cognitive remediation therapy (CRT). Since working alliance may improve outcome, it is important to establish what factors promote an effective working alliance, improve the alliance and if the alliance can result in better outcomes in CRT. Methods: Forty-nine people with a diagnosis of schizophrenia enrolled in a cognitive remediation therapy trial that took place in combination with work placements. Working alliance ratings from participants and therapists were gathered at 3 points during the course of the intervention. Measures of neuropsychological performance, psychotic symptoms, depression, anxiety and work performance were also collected before and after therapy. Results: Depression was a significant predictor of both participant and therapist ratings of the working alliance early in therapy. Better work performance was additionally associated with higher participant ratings of the early therapy alliance. Cognitive ability was unrelated to either participant or therapist ratings of the alliance. Participant ratings of the alliance were stable over time while therapist ratings improved. At the end of therapy there was a moderate association between participant and therapist ratings, with no association early in therapy. Greater participant rated working alliance was associated with less severe target complaints at the end of therapy. Conclusion: The current study found it was more difficult to establish a working alliance with participants who were depressed. However, cognitive impairments did not interfere with participants ability to form a working alliance with their therapist. Participants who rated the working alliance more highly went onto report a greater improvement in the severity of their main complaint following therapy. The current study shows that the working alliance is an important factor in participants rating of therapy success. This suggests that the therapist has a key role to play in facilitating CRT.
ID: 979139

IMPACT OF NEGATIVE SYMPTOMS ON PSYCHOSOCIAL FUNCTION IN SCHIZOPHRENIA IN EUROPE

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Background: 70% of people with schizophrenia continue to experience disabling symptoms (positive, negative, affective) and cognitive difficulties that affect personal, social and occupational functioning. In Europe, over 80% of adults with schizophrenia have persistent problems with social functioning, yet live in the community. Positive symptoms have been the main priority for treatment, while negative and cognitive symptoms have been relatively neglected. The aim of this study was to examine the impact of negative symptoms on psychosocial functioning in order to assess the importance of such symptoms as potential treatment targets. Methods: 295 participants with DSM4R schizophrenia recruited in 11 European centers and assessed using: PANSS, GAF, Personal and Social Performance(PSP), Quality of Life Scale(QLS), Functional Recovery Scale in Schizophrenia(FROGS) and Psychosocial Remission in Schizophrenia(PSRS). Relationships between negative symptoms and functionality were examined using statistical modelling. The relationship between function (PSRS, FROGS, QLS, GAF and PSP) and PANSS Negative Subscale was examined using Spearman correlations and canonical correlation analysis(CCA). This examines linear combinations of items (variants)in the PANSS negative subscale and each functional scale that have the highest correlation with one another. Variants permit identification of key items in each scale that contribute most to the relationship between scales. Results: In this study, negative symptoms were highly correlated with poor psychosocial functioning in outpatients. This significant trend occurred across different scales for measuring functional assessment. Most functional items appear in the first 2 CCA variants. All of the PANSS negative items appear important in the relationship with measures of function, except N6, suggesting that this item is a less important contributor to the relationship with functionality. Conclusion: This study shows a close relationship between negative symptoms and psychosocial functioning. First & second generation antipsychotics have efficacy for positive symptoms in some people; however most antipsychotics have little impact on negative symptoms or other domains. This work supports the view that negative symptoms are a key target for drug development. Future drug development should target particular negative symptoms, and it is likely that drug combinations rather than monotherapy will be utilized to improve psychosocial functioning in the community.
ID: 979119

RECIPROCAL SOCIAL BEHAVIOR IN INDIVIDUALS AT CLINICAL HIGH RISK FOR DEVELOPING PSYCHOSIS

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Background: Individuals at clinical high risk (CHR) for psychosis typically exhibit significant social dysfunction (Addington et al., 2008); however, the specific social behaviors these individuals engage in have not been characterized. We used the Social Responsiveness Scale (SRS, Constantino, 2003) to examine reciprocal social behavior (RSB) – the ability to process social information from the environment and respond appropriately

in interpersonal interactions – in adolescents and young adults at CHR for psychosis. The SRS has been validated and widely used as a quantitative measure of autistic traits, but has not been applied in studies of the psychosis prodrome. Methods: CHR adolescents were recruited as part of an ongoing longitudinal study of risk factors for psychosis at UCLA. Parents of CHR participants ($n = 45$) and demographically comparable controls ($n = 18$) completed the SRS, a 65-item questionnaire that asks informants to rate the participants' behavior over the last 6 months. Items representing all 3-criterion domains for autism (ie, deficits in reciprocal communication, social deficits, and restricted/stereotypic behaviors or interests) are included. Results: CHR individuals had significantly higher overall scores on the SRS than healthy controls (66.5+/−15.4 vs. 45.3,+/−6.8; $P < .001$), indicating more severe deficits in RSB. CHR individuals had significantly higher scores across all SRS sub-scales: social awareness ($P < .008$), social cognition ($P < .001$), social expressiveness ($P < .001$), social motivation ($P < .001$), and autistic mannerisms ($P < .001$). The average T scores for CHR individuals were typical of scores obtained in individuals with high functioning autistic spectrum disorders (Constantino & Gruber, 2005). Conclusion: Although the SRS was specifically designed to tap social deficits inherent in autistic spectrum disorders, as opposed to those associated with other psychiatric disorders, youth at CHR for psychosis also showed highly significant deficits in RSB. These findings identify a novel set of social impairments in domains critical for adolescent social development, and provide a basis for further examination of social dysfunction in CHR individuals. Furthermore, the genetic overlap between autism and schizophrenia (Burbach and van der Zwaag, 2009), along with these findings, suggest that it may be important to screen for phenotypes typically associated with autism in those at clinical high risk for developing schizophrenia.
ID: 975271

PSYCHOSOCIAL STRESS, SOCIAL SUPPORT, AND THE ESCALATION OF SCHIZOTYPAL SYMPTOMS IN WHITES AND LATINOS

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Background: Although research suggests that psychosocial stress exacerbates symptoms of schizophrenia, little is known about how stress effects schizotypal symptoms. This study examined the effects of 2 types of psychosocial stressors (major life events and daily hassles) and social support on schizotypal symptom exacerbation in White and Latino individuals. Methods: 56 Latinos and 75 Whites between the ages of 18 and 35 who responded to advertisements inquiring about "odd or unusual experiences" completed a number of measures including the SPQ, Magical Ideation and Perceptual Aberration Scales, life events and daily hassles scales, and a measure of perceived social support. The questionnaires were completed again 4 to 6 weeks later. Results: For Whites who scored high on the schizotypal scales, an interaction between life events and social support was found ($t = 2.203$, $P < .05$) such that participants who had a high number of life events and low levels of social support showed a significant exacerbation of schizotypal symptoms from time 1 to time 2. For Latinos, however, only daily hassles were found to exacerbate symptoms for those scoring highly on schizotypy measures ($t = 2.12$, $P < .05$). Conclusion: The data suggest that cultural factors play an important role in the exacerbation of schizotypal symptoms. For Latinos, daily hassles appear to be significant in the escalation of symptoms; for Whites, however, major life events appear more critical. Moreover, social support buffered against the exacerbation of symptoms only for Whites, suggesting that for Latinos, either traditional measures of social support do not adequately assess support received or perceived social support does not buffer against the stress of daily living.
ID: 979625

TOWARDS A DYADIC VIEW OF EXPRESSED EMOTION

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Background: Expressed emotion (EE) is typically assessed only from the key relatives' perspective and the ways in which patients perceive EE are not well understood, even though EE is thought to be transactional in nature. Methods: Sixty Mexican Americans with schizophrenia or schizoaffective disorder and their key relatives completed the Brief Dyadic Scale of Expressed Emotion (BDSEE), a new self-report instrument, an average of 5.98 times over a 1-year period. Key relatives' EE was also assessed with the Camberwell Family Interview (CFI) at the beginning and end of the year. Relapse data were also collected, based on whether patients required hospitalization or experienced symptom exacerbation within the 1-year period. Results: Patients' perceptions of key relatives' emotional overinvolvement (EOI) were positively associated with their perceived criticism and were unrelated to their perceptions of warmth. In contrast, key relatives' perceptions of EOI were positively related to their perceptions of warmth, following the pattern of prior literature. Preliminary findings supported the reliability and validity of the BDSEE. The key relative version of the BDSEE was related to the CFI and the patient version of the BDSEE was related to 2 established parenting scales. Key relatives of patients who relapsed reported being more emotionally overinvolved than those caring for individuals who remained clinically stable. Conclusion: Key relatives and patients perceive EE in different ways. That patients perceive criticism and EOI in similar ways may suggest the existence of a common psychological pathway by which these caregiver behaviors affect patients. Including both perspectives of EE is informative and necessary to advance our understanding of the family context and how it relates to the course of illness. Giving patients a voice can further our understanding of the dyadic and interactional nature of EE. In addition, explaining to relatives that patients perceive EOI in a negative way may be an important part of future interventions. This preliminary study provides some support for the reliability and validity of the BDSEE. A main contribution of the instrument is that it is the first self-report measure of EE to assess warmth. Including warmth in the assessment of EE provides a more comprehensive view of the family context. Because of its brevity, this instrument can be easily applied in future research and clinical work, to "take the temperature" of the family frequently.
ID: 976975

ERRORLESS LEARNING AND SUPPORTED EMPLOYMENT IN SCHIZOPHRENIA: ADDRESSING COGNITIVE IMPAIRMENTS AS RATE- LIMITING FACTORS TO EMPLOYMENT SUCCESS

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Background: Schizophrenia is characterized by deficits in work functioning with unemployment estimates ranging from 65% to 90%. In examining factors related to work outcome, a number of studies have shown cognitive impairment to be a key variable. The present findings were drawn from

an ongoing study of cognitive rehabilitation and Individual Placement and Support (IPS) supported employment in a sample of schizophrenia and schizoaffective disorder outpatients. Methods: Study participants included 45 persons meeting DSM-IV criteria for schizophrenia or schizoaffective disorder. Baseline assessment, prior to job placement, included measurement of cognition using the MATRICS Consensus Cognitive Battery (MCCB). After job placement, study participants were randomized to 1 of 2 training groups (errorless learning plus supported employment vs. supported employment alone) for training to address specified work related problems identified by the Work Behavior Inventory. Study participants were followed for up to 12 months after their initial job placement. Results: Group comparisons of participants who attained community-based jobs through the supported employment program (n = 20) vs. those who did not (n = 25) revealed no significant differences in level of functioning on any of the 7 MCCB cognitive domains. Interestingly, of those who did get placed, 50% quit their jobs shortly after placement prior to initiation of training. Survival analyses revealed no significant differences between the 2 training groups on job tenure over the 12 month follow-up period, perhaps due in part to the sizeable proportion of participants who quit their jobs prematurely. Conclusion: These preliminary results indicate 2 important findings: a) IPS supported employment is effective in getting persons with schizophrenia placed at community-based jobs regardless of level of cognitive impairment, and b) early intervention after job placement appears essential to address the difficulties persons with schizophrenia face when attempting to meet the challenges of a new job.
ID: 978661

PSYCHOSOCIAL FACTORS CONTRIBUTING TO SUICIDAL IDEATION IN HOSPITALIZED SCHIZOPHRENIA PATIENTS IN KOREA

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Background: This study aimed to comprehensively evaluate psychosocial risk factors associated with suicidality in patients with schizophrenia in Korea. Methods: The study sample consisted of 84 hospitalized patients with schizophrenia. Suicidal thoughts and a clear desire to be dead within 2 weeks were defined as a current suicidal ideation. Socio-demographic and clinical variables, including family history of completed suicides and psychiatric illnesses, were collected, and the Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS), Beck Depression Inventory (BDI), Simpson-Angus Scale (SAS), Scale to assess Unawareness of Mental Disorder (SUMD), and Alcohol Use Disorders Identification Test (AUDIT) were administered to identify factors associated with a current suicidal ideation. Results: Forty-three subjects (51.2%) reported clear suicidal ideation. Multivariate analysis revealed that later age of illness onset, previous suicide attempt, family history of completed suicide, depression, or substance abuse, fewer than one family visitation to the hospital per month, and score on the CDSS were independently related to current suicidal ideation in these subjects. Age, education level, and scores on the SUMD were not significantly associated with current suicidal ideation in the multivariate analysis, but were associated with suicidal ideation in a univariate analysis on the level of $P < .1$. Conclusion: The above clinical factors should be evaluated to predict and prevent suicidal risk in patients with schizophrenia. In particular, modifiable factors such as depression should be managed to reduce suicidality of hospitalized patients with schizophrenia.
ID: 977346

FOLLOW ALONG SUPPORT AND JOB TENURE FOR PERSONS WITH SEVERE MENTAL ILLNESS IN SUPPORTED EMPLOYMENT

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Background: The Individual Placement and Support (IPS) of supported employment is effective helping clients with severe mental illness obtain competitive jobs, although job tenure continues to be a problem for this group. One component of the IPS model, ongoing support for clients who obtain employment, has not been well delineated or empirically validated. We hypothesized that intensity of follow-along support by employment specialists would be positively associated with job tenure over time. We also sought to identify the pattern and type of follow along support provided after job acquisition Methods: IPS employment specialists provided monthly data on 142 clients with severe mental illness who had obtained employment in the preceding 6 months. Clients were receiving rehabilitation services at 4 sites (3 community mental health centers and 1 psychiatric rehabilitation center) across the Midwest. Employment specialists recorded the frequency and components of follow-along support contacts, as well as competitive employment outcomes over a 2-year follow-up period. Results: Clients worked an average of 9.6 months at their initial job and 12.9 months total across the study period. Regarding follow-along support, prototypically, employment specialists made weekly contact immediately after a job start, within a few months reduced this to monthly, and maintained the frequency thereafter. Over 75% of support was provided face-to-face and at a variety of locations, including at the job site, other community locations, and at the agency offices. Frequency of follow-along support contact was significantly correlated with total months worked during follow-up (r = .27, $P < .01$). Frequency of contact made face-to-face was also positively correlated with total months worked (r = .26, $P < .01$). Location and duration of contacts were not significantly associated with job tenure outcomes. Conclusion: IPS typically provides support for 1 year or more after clients begin employment, with the majority of contacts made face-to-face. Ongoing IPS support from employment specialists promotes continued employment. Face-to-face seems to be the most beneficial form of contact, although there is no evidence to suggest that length of contact or location is related to outcomes. Future research should identify the specific characteristics of effective employment specialist interventions and examine other sources of support that may be helpful in promoting continued employment.
ID: 986721

NEUROCOGNITIVE PREDICTORS OF OBJECTIVE AND SUBJECTIVE QUALITY-OF-LIFE IN INDIVIDUALS WITH SCHIZOPHRENIA: A META-ANALYTIC INVESTIGATION

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Background: Quality-of-life (QOL) has been recognized as a crucial domain of outcome in schizophrenia treatment, and yet its determinants are not well understood. Recent meta-analyses suggest that symptoms have only a modest relationship to QOL (Eack & Newhill, 2007). Individuals with schizophrenia show 1–2 SD deficits on measures of elementary neurocognition, and links between these deficits and objective measures of community functioning (eg employment and independent living) are well established. While objective measures of community functioning and measures of QOL would appear to be closely related, studies investigating the ability of neurocognitive variables to predict QOL in individuals with

schizophrenia have yielded conflicting results. One potential explanation for these findings is the interchangeable use of objective and subjective indices of QOL in the schizophrenia literature. Methods: We conducted parallel literature searches in the PUBMED and PSYCINFO databases for all peer-reviewed, English-language articles published between January 1, 1980 and January 10, 2009 on cognition and QOL in schizophrenia. The software program DSTAT v. 1.11 was used to calculate effect sizes and to carry out subsequent homogeneity and moderator variable analyses. Results: A total of 20 studies (10 objective, 10 subjective) consisting of 1615 clients were aggregated from relevant databases. Weighted effect size analysis revealed that there were small-moderate relationships ($d \leq .55$) between crystallized verbal ability, working memory verbal list learning, processing speed and executive-function and objective indices of QOL. In contrast, results revealed either non-significant or inverse relationships for the vast majority of neurocognitive measures and measures of subjective QOL. Direct comparisons between studies using subjective vs. objective QOL measures showed that the neurocognitive domains of crystallized verbal ability, immediate prose recall, list-learning, processing speed, and executive function were differentially related to subjective and objective QOL. Conclusion: Consistent with our hypotheses, we found a disparity between the relationship of neurocognitive deficits to measures of subjective QOL and objective QOL in individuals with schizophrenia. Taken together, the markedly different pattern of relations between neurocognition and objective and subjective QOL has implications for the potential effects of intervention on cognitive deficits of individuals with schizophrenia.
ID: 978421

NEUROCOGNITION, INSIGHT INTO ILLNESS AND SUBJECTIVE QUALITY-OF-LIFE IN SCHIZOPHRENIA: WHAT IS THEIR RELATIONSHIP?

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Background: Subjective quality-of-life (SQOL) has been recognized as a crucial domain of outcome in schizophrenia treatment, and yet its determinants are not well understood. In a recent meta-analytic investigation of 10 studies of neurocognition and SQOL in schizophrenia (Tolman & Kurtz, Scz Bull, in press) measures of crystallized verbal ability and processing speed were moderately negatively correlated with SQOL. One potential explanation for inverse relationships between elementary neurocognition and SQOL is that higher levels of cognition may serve as a proxy for better insight into the illness, and better consequent recognition of illness-related functional impairment. This study sought to determine whether: (1) symptoms, neurocognitive variables, and insight into illness influence SQOL; and, (2) whether insight mediated or moderated a relationship between elementary neurocognitive function and SQOL. Methods: Seventy-one stabilized outpatients with schizophrenia or schizoaffective disorder were administered a neuropsychological test battery, symptom, insight and subjective quality-of-life measures. Results: Elementary neurocognitive measures, WAIS-Vocabulary ($r = -.37$, $P < .01$), Digit Span ($r = -.25$, $P < .05$), and PCET Categories ($r = -.27$, $P < .05$) were all inversely related to life satisfaction. Insight into illness ($r = -.34$, $P < .01$) and depression severity ($r = -.45$, $P < .01$) were also inversely related to life satisfaction. When depression ratings were entered first into a series of hierarchical regressions for the 3 elementary neurocognitive measure linked to satisfaction with life in the correlational analysis all remained significant predictors of scores on the SQOL scale. There was no evidence that illness insight mediated or moderated the relationship between elementary neurocognition and subjective QOL. Conclusion: First, we found that severity of depression, but not positive or negative symptomatology, was related to SQOL. Second, we found that 3 measures of elementary neurocognition, crystallized verbal ability, attention, and executive-function, were all inversely related to SQOL. Third, our results confirmed that illness insight was inversely related to SQOL. The inverse relationships between elementary neurocognition, insight into illness, and SQOL held even after controlling for depression severity. Fourth, the relationship between neurocognitive deficits and satisfaction with life was not mediated or moderated by a measure of insight into illness.
ID: 977646

TARGETING INFORMATION PROCESSING BIASES AND SOCIAL AVOIDANCE IN GROUP COGNITIVE BEHAVIORAL THERAPY FOR PARANOIA: A PILOT RANDOMIZED CONTROLLED CLINICAL TRIAL

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Background: The main objective of this study was to determine the preliminary efficacy of Paranoia-Focused Cognitive Behavioral Therapy (PFCBT) relative to standard care in the treatment of drug-refractory persecutory delusions. PFCBT is a manualized intervention that combines group and individual modalities to reduce paranoia-biased information-processing and social avoidance, and to increase insight and reality testing capacity. Methods: This was a randomized controlled clinical trial. Subjects were 24 adults ages 18–65 with the primary DSM-IV Schizophrenia and Schizoaffective disorder and drug-refractory persecutory delusions, recruited from outpatient clinics in New York City Metropolitan area. Participants were randomly assigned to either experimental or control group. The experimental group received PFCBT in addition to standard care and the control group received standard care alone. PFCBT included participation in 1 group session and 1 individual therapy session weekly over the 15 weeks. The efficacy of the intervention was evaluated using standardized measures by blind evaluators conducted at baseline, post-treatment, and at 6-months post-termination follow-up. The Persecution Severity score on the PANSS was the primary outcome measure. The differential treatment effects were examined using linear mixed effects modeling. Results: Participants treated with PFCBT had significantly greater reduction in severity of paranoia, which they maintained at 6-months follow-up. PFCBT also resulted in significant changes in cognitive biases targeted in treatment, and increases in insight. Thus, subjects who tended to interpret negative life events as caused by malevolent others began to attribute such events to situational causes, and they increasingly searched for additional factual information when making judgments. At the 6-month post-treatment follow-up evaluation there was a trend toward greater reduction in prescribed antipsychotic medication. Conclusion: The study demonstrated preliminary efficacy of PFCBT for patients with persecutory delusions.
ID: 980180

THE FEAR FACTOR: GOOD SOCIAL COGNITION MAKES HUMAN INTERACTION STRESSFUL

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Background: Patients with schizophrenia have been documented to show impairments on measures of social cognition. It is however unknown how these deficits found in laboratory measures relate to social functioning in daily life. The present study set out to determine whether social cognition

measured in an experimental setting is related to affective and psychotic reactions to (stressful) social situations in daily life. Methods: Fifty-three patients with psychotic disorder completed the Degraded Facial Affect Recognition task (DFAR), a computer test measuring recognition of positive and negative facial expressions. Social stress and affective and psychotic symptoms in daily life were assessed using the Experience Sampling Method (a random time sampling technique). A series of multilevel linear regression analyses were performed investigating the association between affective and psychotic reactivity to daily life social stress on the one hand, and scores on the DFAR on the other hand. Results: Patients performing better at recognizing negative facial expressions (anger and fear) show more affective ($B = 0.01$, 95% CI: 0.005, 0.014, $P = .00$) and psychotic ($B = 0.01$, 95% CI: 0.007, 0.013, $P = .00$) reactivity to social stress in daily life. In other words, these patients report more affective and psychotic symptoms in stressful social situations. Conclusion: The results of this study show that scores on a well established computer test assessing recognition of emotional faces are associated with the individuals' reaction to social stress in daily life. This indicates that scores on laboratory measures of social cognition translate to real life social interactions. A next important step is to investigate whether social cognitive functioning fluctuates over time, and thereby impacts on social interactions.
ID: 979106

REMISSION AND RECOVERY IN FIRST EPISODE PSYCHOSIS: AN EXAMINATION OF CLINICAL AND PERSONAL PERSPECTIVES

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Background: Relationship between syndromal remission and aspects of recovery such as functional outcome remain largely unexplored. The concept of recovery must incorporate a personal perspective from the individual as well as aspects of functional outcome with societal perspectives. Methods: Relationship between consensus definitions of remission and global functional outcome (SOFAS) at 2 years was examined in FEP ($N = 141$) patients. Data from a qualitative study of meaning of recovery and what influences it from the individual's perspective will be presented. FEP ($N = 30$), with 2–5 years of treatment were interviewed to elicit personal meanings of illness and recovery. The data, derived from transcripts of interviews conducted, were analysed using Interpretative Phenomenological Analysis (IPA) procedures. Results: Remission data showed that 54% and 70% of patients met criteria for syndromal remission using the 6 months and 3 month criteria, respectively. Rates of good (SOFAS >60) or very good (SOFAS >70) functional outcome were much lower (32% and 16%, respectively). There was a strong relationship between syndromal remission at 3 or 6 months and level of global functional outcome (SOFAS) at 2 years (using multiple analyses including, correlations, ROC/AUC and regression). Only 41(44%)remitted patients had a good functional outcome. None of the remitted patients had a good outcome. Individuals described recovery in one or more domains of ''symptom recovery,'' ''psychological recovery,'' and ''social recovery.'' There was 71% agreement between remission of positive symptoms (ratings on SAPS) and personal recovery and only 50% agreement on ''not in remission'' and ''not recovered.'' More than half considered themselves recovered according to their personal definition of recovery; 77% incorporated symptoms as part of their ''illness recovery,'' 66% considered themes of ''psychological recovery''; 53% engagement in role with ''meaningful activities'' and 40% ''peer and social relationships'' as part of ''social recovery.'' Patients identified side effects from medication and substance use as major obstacles and social and family support (52%–56%) and medication (44%) as aids to recovery. Conclusion: Consensus definition of remission is valid for early phase of psychosis and is highly associated with functional outcome. However, remission is not sufficient for functional recovery. Patients' perspectives on recovery may be different but not necessarily in disagreement with clinical evaluation of remission.
ID: 979621

A SHOT AT RECOVERY: A PILOT PROGRAM FOR INSTITUTING AN INJECTION CLINIC COMBINED WITH A PSYCHOSOCIAL RECOVERY GROUP IN A COMMUNITY MENTAL HEALTH CENTER

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Background: As many as 50% of patients with schizophrenia do not take oral antipsychotic medications as prescribed. Long-acting injectable (LAI) antipsychotic medications are a recommended alternative to oral medications for many of these individuals. Methods: We describe outcomes for a group of 24 individuals with schizophrenia switched from oral medications to long acting injections. Medication injection visits which occurred every 2 weeks were paired with a recovery-oriented psychosocial group called A ShoT At Recovery Club (A-STAR). We present a case series describing clinical changes in the LAI participants during treatment. In addition, we compare service utilization for this cohort for the 9-month period prior to the switch to the 9-month period following the switch to LAI medications, and we examine changes over time in symptomatology and functional outcome. Results: Results indicated fewer hospitalizations and significantly fewer crisis services in the 9 months following the switch to LAI. Adherence remained high throughout the 9 months of the trial (91.20%) and symptomatology as rated from the Brief Psychiatric Rating Scale-Expanded version improved ($P < .03$). Scores on the Multnomah Community Ability Scale and the Personal and Social Functioning Scale also revealed significant improvements in functional outcome over time (P's $< .01$). Conclusion: The data suggest that pairing injections with a recovery-oriented group may have benefits for individuals with schizophrenia.
ID: 979742

CLINICAL OUTCOME FROM A PRODROMAL CLINIC

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Background: There has been increasing interest in early detection during the prodromal phase of a psychotic disorder. A few treatment studies have been published with promising results. However, the focus of most treatment studies is on reducing conversion to psychosis and less on improving the clinical state of ''at risk'' individuals. In a recent study examining psychological treatments in a clinical high risk sample of individuals meeting criteria for prodromal risk syndrome for psychosis, 48 out of 51 individuals did not convert to psychosis over the 18 month course of the study. The purpose of this part of the study is to examine the extent to which clinical improvement was experienced in those who did not transition to psychosis. Methods: The sample consisted of 48 individuals (34 males, 14 females), mean age 21.07 years. All met criteria for attenuated positive symptoms based on the Structured Interview for Prodromal Syndromes. Treatment consisted of ongoing psychiatric management, individual psychological treatment of up to 20 sessions over a 6-month period, and regular monitoring of clinical symptoms. Anxiolytics and antidepressants were

prescribed and monitored as needed to treat mood and anxiety symptoms. Antipsychotics were not utilized. Measures used included the Scale of Prodromal Symptoms (SOPS), Global Assessment of Functioning (GAF), Calgary Depression Scale (CDSS), General Health Questionnaire (GHQ), Alcohol/Drug Use Scale (AUS/DUS), Social Functioning Scale (SFS), and 2 anxiety scales - SIAS and SAS. Assessments were conducted at baseline, and follow-up assessments at 6, 12 and 18-months. Results: A generalized linear mixed model for repeated measures was used to examine change over time. There were significant improvements in attenuated positive symptoms ($F = 31.65$, $P < .0001$), GAF ($F = 11.02$, $P < .001$), CDSS ($F = 5.10$, $P < .01$), GHQ ($F = 7.97$, $P < .001$) SFS ($F = 5.62$, $P < .01$) and both anxiety scales ($F = 8.75,7.65$, $P < .001$). Positive symptoms and social functioning improved up to 18 months, GHQ and anxiety by 6 months and all other measures up to 12 months. There were no changes in the rate of substance use but ratings were relatively low at baseline. Conclusion: Results demonstrate that individuals who meet criteria for prodromal risk syndrome do improve over time on a range of outcomes in particular positive symptoms. Although the actual impact of the treatment cannot be determined, the clinical improvement in this group of vulnerable patients occurred without the use of antipsychotics.
ID: 977715

RELIABILITY STUDY OF THE BRAZILIAN VERSION OF THE INDEPENDENT LIVING SKILLS SURVEY (ILSS) IN SCHIZOPHRENIC PATIENTS

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Background: Patients with schizophrenia show important impairments in social functioning, interpersonal relationship, work and leisure. Two versions for the Independent Living Skills Survey (ILSS) were developed ie one for relatives and another for cases to provide an evaluation of the living skills of psychotic patients. The aim of this study was to assess the reliability of the Brazilian version of the ILSS when reported by cases from the schizophrenia spectrum. Patients with a confirmed DSMIV diagnosis of schizophrenia, aged between 18 and 65 years, and availability to come for reassessments, were invited to participate. Methods: Two convenience samples from 2 mental health units of the Universidade Federal de São Paulo (UNIFESP), namely the out-patient Schizophrenia Program and the Psychosocial Care Center Luis da Rocha Cerqueira were selected, one for the inter-rater reliability study and internal consistency, and another for the temporal stability study. The scale was translated and back-translated by a bilingual translator, and some modifications were required to adequate the instrument to Brazilian culture. Patients able to come for 2 consecutive weeks were allocated to the test-retest study and the remaining were included in the study of internal consistency and inter-rater reliability. The test and retest were conducted by the same rater and agreement among observers was carried out by 2 professionals simultaneously. Results: Test-retest: A total of 46 patients participated in the study, with a mean age of 36.9 years (SD: 9.1); 65.2% were males; 89.1% were single; 47.8% had completed high school and 47.8% were unemployed. The temporal stability measured by ICC coefficients varied from 0.84 to 0.94, considered good. For the internal consistency and inter-rater reliability test, forty patients were included, with a mean age of 38.4 years (SD: 10,9); 70% were males, 84% were single; 60% had completed high school and 49% were unemployed. The ICC coefficients ranged from 0.80 to 0.99, and the Cronbach's alpha was 0.80 for the total score of the scale, varying from 0.23 to 0.98 for the domains of the scale. Conclusion: The scale presented a satisfactory internal consistency, high agreement between observers and a good temporal stability. These results showed that the Brazilian version of ILSS is a reliable and stable measure to assess the social functioning of patients with schizophrenia.
ID: 978818

THE CANADIAN OBJECTIVE ASSESSMENT OF LIFE SKILLS (COALS): A NEW MEASURE OF FUNCTIONAL COMPETENCE IN SCHIZOPHRENIA

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Background: There is little consensus on the best way to measure functional status in individuals with schizophrenia, and there are concerns about the accuracy, reliability and suitability of instruments currently in use. The Canadian Objective Assessment of Life Skills (COALS) was undertaken to address limitations of existing measures while building in features of our own analysis of functional competence. We hypothesize 2 key components in relation to successful independent living: procedural knowledge routines (PKR), or "knowing how" to carry out an adaptive action or activity, and executive operations (EXO), which reflect "knowing what to do and when to do it." These 2 components are evaluated in 5 domains relevant to independent functioning in the community: Health and Hygiene, Time Management, Trip Planning, Crisis Management and Domestic Activities. Methods: The COALS takes approximately 25 minutes to administer and we evaluated its reliability and validity in 99 patients meeting DSM-IV criteria for schizophrenia or schizoaffective disorder and in 80 non-psychiatric controls. Ninety-three patients and 63 controls were retested 1 month later. Additional measures included the Positive and Negative Syndrome Scale (PANSS), the Multidimensional Scale of Independent Functioning (MSIF) and the UCSD Performance Based Skills Assessment (UPSA). Results: The groups did not differ significantly in age, sex, or parental education; however, patients had less education and lower rates of full-time employment than the non-psychiatric controls. Results indicated that patients performed significantly worse on the COALS than non-psychiatric controls ($P < .001$), yielding a large effect size (Cohen's $d = 0.93$). Summary scores for both the PKR ($d = 1.06$) and EXO ($d = 0.89$) subscales also significantly differentiated patients from controls. The COALS demonstrated good test-retest reliability (0.88) and was significantly correlated in expected directions with other measures of functional outcome: UPSA (0.71) and the MSIF (−0.45). The COALS was not associated with positive symptoms as measured by the PANSS ($P = .31$), providing evidence of discriminant validity. Conclusion: These preliminary findings suggest that the COALS provides a valid and reliable alternative to existing measures of functional outcome in the schizophrenia population. Work is in progress to evaluate the validity and utility of the hypothesized component processes. This research is supported by the Ontario Mental Health Foundation.
ID: 975800

EARLY DETECTION AND INTERVENTION (EDI) IN FIRST EPISODE PSYCHOSIS: CAN IT INCREASE THE CHANCE FOR FULL RECOVERY? TIPS 10 YEAR FINDINGS

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Background: INTRODUCTION: We know duration of untreated psychosis (DUP) and outcome in first episode psychosis (FEP) are correlated, but we don't know if shortening DUP CAUSES better outcome. The TIPS

study tests this by changing DUP in 2 of 4 Scandinavian health care sectors and measuring outcome for all. Methods: INITIAL FINDINGS: Baseline assessments (N = 281) found DUP significantly reduced with educational campaigns and early detection teams. Shorter DUP in the Early Detection (ED) sites was significantly associated at intake with younger age, less positive and negative symptoms, and less suicidality than in the NoED sites. Follow-up at 3 months (262), 1 year (272), 2 years (259), and 5 years (197) documented persistent negative symptom advantages for ED. Ten year assessments (173) included symptom recovery, functional recovery, and full recovery (definitions to be detailed). A key question was whether EDI could increase the likelihood of full (ie both symptomatic and functional) recovery. Results: TEN YEAR FINDINGS: DROP OUTS: A strong drop-out selection bias emerged. In the ED sites, drop outs at their last interview (usually 5 year follow up) had significantly LESS negative symptoms than completers [P = .03]. In the NoED sites drop outs at their last interview had significantly MORE negative symptoms than completers [P = .03]. RECOVERY: Despite this attrition bias, the ED site had more recovered patients [30% vs. 14%, P = .003], and recovered ED patients had a more rapid remission and needed less treatment than recovered NoED patients. This advantage is likely a robust finding in that NoED sites appeared to lose few patients with a potential for recovery. Across sites fully recovered patients had a slightly shorter DUP than not fully recovered (ns), slightly milder positive symptoms, but significantly lower negative symptoms (PANSS negative component score (P = .002)). Conclusion: CONCLUSIONS: ED is associated with an increased chance for a very good course and outcome in FEP, and the ED effect appears partly related to intervening at a point of less intense negative symptoms. IMPLICATIONS: EDI works in psychosis and gives a lasting effect for a sizeable group. The ultimate limits to what can be gained by EDI have yet to be ascertained.
ID: 979468

MOVE: A PSYCHOSOCIAL TREATMENT FOR PERSISTENT NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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Background: Individuals with schizophrenia who have persistent and clinically significant negative symptoms (PNS) including, restricted affect, diminished emotional range, poverty of speech, decreased motivation and interests, diminished sense of purpose and diminished social drive typically have the poorest functional outcomes and quality of life. The NIMH-MATRICS Consensus Statement on Negative Symptoms indicated that these symptoms were a distinct therapeutic indication representing an unmet therapeutic need for large numbers of individuals with schizophrenia. While aspects of negative symptoms may be lessened with existing evidence-based practices, no model addresses the entire constellation of PNS. Methods: Based upon decades of work developing and employing evidence-based treatments for schizophrenia, we have developed a novel psychosocial treatment called the MOtiVation and Engagement (MOVE) Program specifically to target multiple domains of severe and persistent negative symptoms and their functional consequences. MOVE is a home based, manual-driven, multi-modal treatment that employs a number of cognitive and behavioral principles to address the broad range of factors contributing to a PNS presentation. Components of MOVE include: 1) Environmental supports and the organization of belongings to prompt initiation and persistence at tasks, 2) In vivo skills training to ameliorate skills deficits and encourage appropriate interaction with individuals in the client's environment, 3) Cognitive behavioral techniques to address self-defeating attitudes that mediate the relationship between negative symptoms and functional outcomes, 4) In vivo training in emotional processing to address affective blunting and problems in identifying the emotions, and 5) Specific techniques to address the deficits in anticipatory pleasure experienced by individuals with PNS. Results: Our research, and that of other groups, has provided support for many components of the model including improvements in motivation as measured by the Negative Symptom Assessment, and decreases in self-defeating attitudes. Conclusion: Available research suggests that further investigation of a comprehensive treatment for PNS, such as MOVE, is warranted.
ID: 979783

QUALITY OF LIFE AND RECOVERY IN PSYCHOTIC DISORDERS - 10 YEAR FOLLOW-UP OF THE TIPS STUDY

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Background: Subjective quality of life (sQoL) is increasingly recognized as a valid outcome measure in psychotic disorders, but not included in most definitions of recovery. The purpose of the current study is to investigate the relationship between sQoL and other outcome measures after 10 years in treatment. Methods: The results are based on a prospective longitudinal study of a catchment area patient sample with broad schizophrenia spectrum psychotic disorders (age 16–65, N = 301), followed from their first week in treatment and reexamined after 1, 2, 5 and 10 years. Of the original 301 patients, 185 participated in the 10 year follow-up. Patients that did not participate in the 10 year follow-up were significantly less satisfied with their life at start of treatment (but not at any other timepoints), compared with those who did. There were no other differences between the groups regarding age and gender or positive-, negative or depressive symptoms at previous follow-ups. Results: There was a small - but statistically significant and stable- improvement in sQoL from start of treatment throughout the 5 year follow-up, but with a subsequent fall from 5 to 10 years. There were also different patterns of change on the individual level, as indicated by modest levels of correlation between sQoL at 10 years and at previous timepoints including the 5-year follow-up. While sQoL at baseline mainly was determined by depressive symptoms and pre-treatment factors such as poor premorbid functioning and longer duration of untreated psychosis, sQoL at the 10-year follow-up was - as previously found at the 2-year follow-up - independently influenced by current affective symptoms, suicidal symptoms, global functioning and social relations in addition to alcohol use. Levels of positive and negative symptoms did not influence sQoL after correction for differences in affective symptoms (multiple linear regression analysis). Patients meeting recovery criteria had higher sQoL in bivariate analyses. The difference in sQoL between groups was no longer statistically significant after correcting for affective and suicidal symptoms, the presence of alcohol misuse and social relations. Conclusion: This implies that sQoL also taps other aspects than those covered by symptomatic and functional indices of recovery, and that an assessment of patients' experience of their own lives is an important addition to these recovery measures in evaluating treatment outcomes and course of illness.
ID: 979088

ASSESSING THE STABILITY OF "REAL WORLD" FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA AND NON-PSYCHIATRIC ADULTS

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Background: Impairments in the ability to perform basic activities of daily living, obtain competitive employment, and interact socially among peer groups affect most individuals diagnosed with schizophrenia (Green, 1996). Given the well-documented relationship between cognition and these various markers of functional outcome (Couture et al, 2006; Green, 2004), recent treatment efforts to enhance cognition have necessitated the review of current efforts to assess and quantify functional impairment (Leifker et al, in press). One particular measure of interest is the Multidimensional Scale of Independent Functioning (MSIF; Jaeger et al., 2003). This instrument has demonstrated exceptional discriminability between patients and non-psychiatric controls and has shown clinical utility in assessing the range of functional deficits seen in this population (Miles et al., in press). However, there is little information on the psychometric properties of this instrument in schizophrenia (Leifker et al., in press). Accordingly, the aim of this study was to assess and compare the stability of the MSIF, relative to a commonly used measure of functional capacity, in schizophrenia patients and non-psychiatric controls. Methods: This study assessed 97 patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder and 79 non-psychiatric controls. Participants were retested 1 month later, including 93 patients and 58 controls. All participants were administered the MSIF and the UCSD Performance Based Skills Assessment (UPSA; Patterson et al., 2001). Results: The groups were statistically similar in terms of age, sex, country of birth, and parental education. However, the non-psychiatric participants had higher levels of education and higher rates of full-time employment. Test-retest reliabilities of the MSIF, as assessed using intraclass correlations (ICC), ranged from 0.63 to 0.90 for the patient group and 0.64 to 0.87 for the control group. The ICCs for the UPSA ranged from 0.15 to 0.61, and 0.19 to 0.68 for the patient and control groups, respectively. Paired *t* tests were also used to assess test-retest reliability. There were no differences over the 1 month interval for any MSIF domains, but some differences were noted on the UPSA. Conclusion: The MSIF demonstrated high test-retest reliability over a 1 month interval and was shown to be more stable than the UPSA. This research was supported by the Ontario Mental Health Foundation and the Canadian Institutes of Health Research.
ID: 976684

ABNORMAL MOVEMENTS AND THE LONGITUDINAL COURSE OF SOCIAL AND ROLE FUNCTIONING IN ADOLESCENTS AT HIGH-RISK FOR PSYCHOSIS

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Background: The prodromal period immediately preceding the onset of overt psychosis is characterized by emerging subthreshold psychotic symptoms, motor abnormalities, and a broad decline in functioning. Recent evidence suggests that basal ganglia dysfunction, which is implicated in the development of psychotic symptomatology, may manifest in the form of movement abnormalities and deficits in processes integral to psychosocial functioning. However, little is known about the longitudinal relationship between abnormal motor function and the observed psychosocial deficits. Understanding a potential link between these phenomena can refine etiological models of cortico-striatal dopamine dysfunction and inform intervention strategies to improve functioning of these affected youth. Methods: In the present study, 40 clinical high-risk participants meeting criteria for a prodromal syndrome were assessed for movement abnormalities and global role and social functioning at baseline. Role and social functioning was then followed up over a 1-year period. Results: At baseline, severity of movement abnormalities was strongly associated with poor role functioning. Further, when controlling for baseline social functioning and medication status, movement abnormalities at baseline predicted a significant decline in social functioning 1-year later, with a trend in the same direction for role functioning. Conclusion: Results suggest that movement abnormalities potentially reflective of basal ganglia dysfunction are closely associated with deficits in psychosocial functioning and predict a decline in functioning in youth at risk for psychosis.
ID: 937250

GENDER DIFFERENCES IN CLINICAL PRESENTATION OF FIRST EPISODE PSYCHOSIS: RELATIONSHIP TO PREMORBID ADJUSTMENT

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Background: Premorbid functioning in childhood, early adolescence and late adolescence has a great impact on the developmental course of schizophrenia and schizophrenia spectrum disorders. The impact of premorbid adjustment on the clinical presentation of first episode psychosis in the context of gender differences is not clearly understood. Findings suggest that males have poorer premorbid adjustment, and negative and non affective symptoms relative to their female counterparts. Methods: In an analysis combining 4 studies, we studied a sample of 80 male and 22 female patients presenting with their first episode of psychosis. The study investigated the relationship between premorbid adjustment, gender, and clinical presentation of patients presenting with their first episode of psychosis. Currently, 26 male and 17 female controls are used for comparison of levels of premorbid adjustment. Premorbid functioning during 3 stages (childhood, early adolescence and late adolescence) was assessed using the Cannon-Spoor et al. Premorbid Adjustment Scale (PAS) and studied with respect to gender and to its impact on the clinical presentation (positive and negative symptoms) of first episode patients as measured by the Brief Psychiatric Rating Scale (BPRS). In each stage we studied 2 domains of functioning: 1-Socialization domain that includes sociability and withdrawal and peer relations. 2-School functioning domain that includes scholastic performance and adaptation to school. Regarding clinical presentation of patients presenting with their first episode of psychosis, we studied their BPRS scores on specific symptoms that are delusions, hallucinations, blunted affect, psychomotor retardation, emotional withdrawal and conceptual disorganization. Results: The age range of male patients was 14–36 years (mean = 22.2 years) and 13–30 years (mean = 20.6 years) in female patients. In the control group, the age range of male controls was 13–29 years (mean = 19.9 years) and 13–26 years (mean = 18.8 years) in female control group. Control recruitment is still ongoing. Conclusion: Analyses from our study are ongoing to test the hypothesis that there are gender differences in premorbid functioning as well

as in clinical presentation of patients presenting with their first episode psychosis.
ID: 986814

DIFFERENCES IN COURSE OF ILLNESS AND PREDICTORS OF BAD OUTCOME AND RECOVERY IN THE OPUS I COHORT AFTER 5 AND 10 YEARS

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Background: Descriptions of outcome and clinical course of schizophrenia-like psychosis are based on findings from few cohorts who were not treated after modern principles. We aim to investigate the huge differences in outcome and to identify predictors of different outcomes. Methods: A cohort 496 patients with first episode psychosis were followed for 10 years with comprehensive research interviews carried out at baseline, after 1, 2, 5 and 10 years. Independent researcher carried out interviews focusing on clinical status, cognition and functional outcome. Recovery was defined as working or studying, having a GAF- function score of 60 or above, having remission of negative and psychotic symptoms, and not living in a supported housing facility or being hospitalized during the last 2 years before the 5-year and 10-year follow-up interviews. Two different bad outcomes were defined 1) continuous psychotic condition and 2) institutionalization in psychiatric supported housing facility or at least 6 month in the last 2 years before follow-up. Results: At 5 year follow-up, 267 were interviewed, 40 (15.7%) were found to be recovered, and 76 (29.8%) had a job or were studying, and 125 (46.8%) were continuous psychotic. Based on register based information for the total sample 53 (10.7%) were institutionalized at 5 year follow-up. Recovery after 5 years was predicted by female sex (OR = 2.4, 95% CI 1.0, 5.8), higher age (OR each increasing year 0.91, 95% CI: 0.83, 0.99), premorbid social adaptation (OR = 0.72, 95% CI 0.56, 0.93), growing up with both parents (OR = 2.6, 95% CI 1.0, 6.8) and low level of negative symptoms (OR per one point increase 0.51, 95% CI 0.33, 0.77) at baseline. Institutionalization was predicted by male sex (OR = 2.41, 95% CI 0.91, 6.35), young age (OR (each increasing year) 0.92, 95% CI 0.84–1.00), psychotic dimension at baseline OR per 1 point increase 1.71, 95% CI 1.14, 2.57) negative dimension at baseline OR per one point increase 1.61, 95% CI 1.05, 2.47). Neither recovery nor institutionalization was completely stable and there were changes in status between 2 and 5 year follow-up. Ten years follow-up data are currently being collected, and these data will be presented. Conclusion: Our findings indicate that the outcome in first episode psychosis is very varied and that it is predicted mainly by early markers of illness severity but also to some degree by social circumstances.
ID: 979039

PARDONED BUT NOT FORGIVEN: POST-AMNESTY REHABILITATION ISSUES IN A CASE OF SCHIZOPHRENIC HOMICIDE

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Background: The perpetration of homicide in the context of schizophrenic illness has long been documented in literature. Murder and schizophrenia are significantly stigmatizing dysfunctions and both occurring in the same individual present limitations to adequate social re-integration during rehabilitation. Methods: A detailed case report is presented alongside review of relevant literature. A re-integration model is proposed based on current clinical experience. Results: The patient is a 53 year old single male, with a long standing history of paranoid schizophrenia who was indefinitely committed to an asylum at the age of 26 following his fatal stabbing of his father. He was found "Not guilty by reason of Insanity" and his committal order lasted for 22 years before he was granted amnesty. Despite the legal relief, his rehabilitation and social re-assimilation have suffered significant challenges on account of the heinous nature of his offence against the background of chronic mental illness. Conclusion: There exists a matrix of clinical, psychosocial and legal considerations in the social re-integration of a schizophrenic who has committed homicide. This complex interplay of factors makes rehabilitation difficult. However, strategic multi-disciplinary management, positive engagement of supportive family members and phased re-entry into the community, all undertaken in a culturally appropriate manner, are vital to successful rehabilitation.
ID: 979845

REMISSION IN SCHIZOPHRENIA - HOW THE SYMPTOMATIC REMISSION CRITERION IS REFLECTED IN DAILY LIFE

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Background: In 2005, Andreasen proposed criteria for remission in schizophrenia, aiming at providing a framework for assessment of outcome. These criteria define symptomatic remission based on a structured interview. It is however unclear whether they also reflect symptom reduction and improved social functioning in daily life. Therefore, the current study investigates (i) positive symptoms (hallucinations and paranoia), (ii) negative symptoms (flat affect and anhedonia) and (iii) social functioning in the flow of daily life in patients meeting the remission criteria compared with patients not meeting these criteria. Methods: The Experience Sampling Method (a structured diary technique) was used to explore positive and negative symptoms and social functioning in the context of daily life in 184 schizophrenia patients. Positive symptoms were measured using the items "I hear voices," "I see things" and "I feel suspicious." Flat affect was defined as reduced intensity of positive and negative affect. Anhedonia was defined as a diminished capacity to generate positive affect after pleasant events. Social functioning was conceptualized as time spent in social company and change in positive and negative affect when being in company compared with being alone. The Positive And Negative Syndrome Scale (PANSS) was used to define symptomatic remission (score $\leq$3 on delusions, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerisms/posturing, blunted affect, passive social withdrawal and lack of spontaneity and flow of conversation). Results: 73 of 184 patients meet criteria for symptomatic remission. Remitted patients report significantly less hallucinatory experiences ($P < .001$) and lower levels of paranoia ($P < .001$). Next, remitted patients report higher intensity of positive affect ($P = .001$) and lower intensity of negative affect ($P = .001$) compared with non-remitted patients. Furthermore, they react with significantly more positive affect on pleasant events ($P = .006$). Patient groups however do not differ on time spent in social company ($P = .88$) and the effect of social company on their affect levels ($P = .665$). Conclusion: This study provides proof of good ecological validity of the proposed symptomatic remission criteria, showing that patients meeting these criteria report less positive and negative symptoms in the flow of daily life compared with non-remitted patients. A remitted state, however, is not related to improved social functioning.
ID: 979820

SLEEP PATTERNS OF INDIVIDUALS WITH SCHIZOPHRENIA

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Background: Poor sleep quality has been associated with overall quality of life in individuals with schizophrenia. Sleep disturbances associated with schizophrenia have been linked to worsening of positive symptoms. Furthermore, improvement of disordered sleep has been shown to correlate with a decrease in negative symptoms. Sleep is known to play an important role in the consolidation of memory. Deficits in slow wave sleep have been shown to be associated with level of cognitive impairment seen in schizophrenia. In this study, we aimed to explore sleep disturbances, patterns, and behaviors, as well as ties to quality of life and cognitive functioning in this population. Methods: In the context of a clinical trial of eszopiclone for the treatment of insomnia in schizophrenia, 150 outpatients with diagnosis of schizophrenia or schizoaffective disorder were assessed for insomnia. Individuals were recruited from an urban community mental health center. Participants were assessed for current sleep quality and behaviors, quality of life, processing speed, and current psychiatric symptoms. Results: 43% of subjects met clinical criteria for insomnia. Individuals who reported clinical levels of insomnia scored lower on the Quality of Life Enjoyment and Satisfaction Questionnaire (M = 55.3 ± 12.3 vs. M = 61.3 ± 14, P = .007)and higher on the Calgary Depression Scale (M = 8 ± 4.8) as compared with those without sleep difficulties (M = 4.4 ± 3.6, P = .000). Individuals with clinical insomnia also reported higher scores on the Night Eating Questionnaire (M = 24 ± 7.3 vs. M = 18.2 ± 7.7, P = .000). Those with insomnia also had a higher Body Mass Index (M = 35 ± 9.7 vs. M = 31.8 ± 8.1, P = .037). No significant differences in processing speed were detected, however higher impairment in the cognitive dimension of the Clinical Global Impression Scale-Schizophrenia Version was found (M = 3.5 ± 1 vs. M = 2.9 ± 1, P = .005). Significant differences were detected in specific sleep hygiene sub-scales. Those with insomnia reported irregular sleep times and more frequently went to bed feeling stressed, angry, and upset. They also reported more thinking, planning, and worrying while in bed. Conclusion: Insomnia is not a well recognized symptom in routine care of schizophrenia, however it is a substantial and frequent clinical problem which should be addressed given its negative impact on quality of life and psychiatric symptoms. Acknowledgements: This research was partly supported by a NARSAD young investigator grant and an investigator initiated grant from Sepracor, Inc. to Cenk Tek.
ID: 978694

COGNITIVE-SELF CONSCIOUSNESS AND OTHER METACOGNITIVE BELIEFS: INFLUENCES ON SYMPTOMS AND STRESS IN INDIVIDUALS AT ULTRA-HIGH RISK OF DEVELOPING PSYCHOSIS

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Background: Cognitive models of psychosis suggest that metacognitive beliefs (MCB) guide information and attention processes, increasing affective and symptomatic reactions to stressful events. Increased cognitive self-consciousness (CSC) may make an individual more aware that their MCB are incongruent with environmentally driven intrusive thoughts. This study tested the hypothesis that MCB would moderate the association between perceived stress, affect and symptoms in individuals at ultra-high risk of developing psychosis and healthy controls. Additionally, it examined the prediction that greater CSC would precede subtle fluctuations in psychotic symptoms. Methods: 27 individuals at ultra-high risk of developing psychosis, and 27 age and gender matched healthy controls completed a self-report diary when prompted by an electronic wristwatch several times a day for 6-days (experience sampling). Questionnaire assessments were also employed. Results: MCB moderated the association between affective, but not symptomatic, responses to stress. An increase in CSC preceded the occurrence of hallucinations in individuals who reported strong beliefs about the need to control their thoughts. Conclusion: The results tentatively suggest that MCB sensitize an individual to stress, and that increased CSC may trigger the onset of hallucinations. This may be indicative of a mechanism by which cognitive behavioral therapy has sometimes been found to improve hallucinations.
ID: 978235

SOCIAL FUNCTIONING IMPAIRMENTS IN INDIVIDUALS WITH SOCIAL ANHEDONIA ARE NOT ASSOCIATED WITH SOCIAL COGNITION

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Background: Anhedonia, the inability to experience pleasure, is a core negative symptom of schizophrenia and is one of the strongest predictors for the development of schizophrenia-spectrum disorders (eg, Kwapil, 1998). However, much is unknown about the social lives of individuals with social anhedonia (SA). The current study investigates the social functioning of individuals elevated in social anhedonia in comparison to controls and examines the role of social cognition. Methods: 96 individuals recruited from a large Mid-Atlantic campus participated in the study. Based on individuals' scores on the Revised Social Anhedonia Scale (Eckblad et al., 1982), participants were divided into SA and control groups. Social functioning was assessed with the Social Adjustment Scale (Weissman & Bothwell, 1976). Participants also completed the Social Support Questionnaire (Sarason et al., 1987; Sarason et al., 1983) to assess for number of social support contacts and satisfaction with social support. Social cognition was assessed with the Penn Emotion Recognition Test (Kohler et al., 2004), the Reading the Mind in the Eyes Test (Baron-Cohen et al., 1997; Baron-Cohen et al., 2001), and the Movie for the Assessment of Social Cognition (Dziobek et al., 2006). A series of one-way ANOVAs and correlational analyses were then used to assess for group differences and interrelationships among the variables. Results: Compared with controls, individuals elevated in SA self-reported greater impairments in social functioning, fewer numbers of social support contacts, and lower satisfaction with social support (P's $< .01$). The groups did not differ on any of the social cognitive measures (P's = n.s.). Further, social cognition was not significantly correlated with any of the social functioning measures (P's = n.s.). Conclusion: These data indicate that individuals with SA do demonstrate greater impairments in social functioning. Further, self-report data shows that individuals with elevated SA also have fewer social support contacts and are less satisfied with their social support network. However, the 2 groups did not differ on 3 measures of social cognition, and scores on these measures were not correlated with social functioning. Thus, social cognitive deficits do not appear to underlie the social impairments seen in individuals with elevated SA, suggesting the need to examine how other domains such as emotion and motivation may explain the functional impairment.
ID: 976535

NEUROPSYCHOLOGICALLY NORMAL SCHIZOPHRENIA PATIENTS HAVE FUNCTIONAL DISABILITIES?

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Background: Neuropsychological deficits are considered to be a core feature of schizophrenia. It has been established that cognitive impairments in schizophrenia are correlated with functional disability. Nonetheless, tests of the association between neurocognition and the functional status of the neuropsychological non-impaired patients have been limited and inconclusive. This study investigates 2 different methods of establishing normality in a sample of patients with chronic schizophrenia from a neuropsychological perspective. Additionally, the putative relationship between functioning and neurocognition in neuropsychological non-impaired patients is tested. Methods: A cross-sectional analysis of 190 chronic outpatients with DSM-IV schizophrenia diagnosis and 30 healthy controls were carried out from neuropsychological, symptomatic and functional perspectives. All participants completed a comprehensive neuropsychological battery including composite cognitive domains: Verbal IQ, attention, verbal memory, non-verbal memory, psychomotor speed and executive function. To establish normality, cognitive scores were compared with standardized norms. Alternatively, rates of significant intra-person differences between Verbal IQ vs. the 5 other cognitive abilities were examined. Furthermore, functional status of each participant was determined by the Social Functioning Scale. Patients' severity of psychopathology was assessed with the Positive and Negative Syndrome Scale. Results: Even establishing neuropsychological "normality" with the more restrictive method of intra-person discrepancy, we found that about 25% of the sample ($n = 47$) of outpatients with chronic schizophrenia might be considered as non-impaired. Non-impaired patients demonstrated better functional status than impaired patients ($t = -0.8548$, $P = .28$) in despite of showing similar rates of PANSS scores ($t = -0.48$, $P = .528$) and other clinical variables. However, compared with healthy controls, the neuropsychological normal patients manifested disability in several real-world domains, including levels of autonomy and pro-social activity. A significant relationship between neurocognition and functioning ($r^2 = .42$, $P = .017$) were found in both subgroups: impaired and non-impaired. Conclusion: Thus, scoring in the normal range of neurocognitive tests does not preclude having functional impairments in chronic schizophrenia.
ID: 979376

THE LONG-TERM EFFECTIVENESS OF COGNITIVE BEHAVIOUR THERAPY FOR PSYCHOSIS WITHIN A ROUTINE CLINICAL SERVICE

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Background: Over 30 Randomised Controlled Trials (RCTs) have been conducted into the efficacy of Cognitive Behaviour Therapy for psychosis (CBTp; Wykes et al, 2008), leading to its current status within the NICE (UK) and PORT (USA) guidelines for schizophrenia. However, relatively few studies have considered the long term effectiveness of CBTp within a routine clinical setting. The aims of the present study were to (i) report on the effectiveness of CBTp delivered in a psychological therapies service (the Psychological Interventions Clinic for outpatients with Psychosis (PICuP), South London and Maudsley NHS Foundation Trust) and (ii) investigate whether gains were maintained at a follow-up of 6 months and above. Methods: Clients ($n = 181$) who had received a minimum of 5 therapy sessions were assessed at 3 time points (baseline, pre-therapy and end of therapy), on a battery of measures assessing current symptoms of psychosis, emotional problems, and general well being, as part of PICuP's routine outcome measurement over the past 7 years. Clients stayed on the waiting list between 4–6 months, and received a median number of 17 therapy sessions from 74 therapists (average of 2.5 clients per therapist) over approximately 6 months. All therapists received fortnightly or weekly supervision from a CBTp expert. All clients who had completed therapy 6 or more months previously were contacted to take part in a follow-up assessment. Data were collected on 43 of the 150 eligible clients at an average of 21.4 months post therapy. Results: Outcomes were analysed using mixed effects regression models. Clients showed no significant change on any measure during the waiting list period. In contrast, significant improvements following therapy were found on all measures: voices and delusions, depression, anxiety, and quality of life. All gains were maintained at follow-up. Effect sizes ranged from moderate (.44) to very large (1.49). 25% and 44% of the sample showed clinically significant change post therapy on voices and delusions, respectively. Conclusion: These results provide support for the effectiveness of CBTp on a range of meaningful outcomes, delivered in a psychological therapies service with access to regular supervision, but outside of the controlled environment of most RCTs. They further suggest that gains are maintained post therapy, although the follow-up assessments may not have been conducted on a generalizable sample.
ID: 976562

A SELF-REPORT MEASURE OF FATIGUE SEVERITY IN EARLY PSYCHOSIS PATIENTS: THE PSYCHOTIC DISORDERS TIREDNESS SCALE (PDTS)

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Background: Recovery from psychosis may be complicated by fatigue symptoms. Studying this problem is hindered by a lack of valid and reliable measures for psychosis patients. The purpose of this study was to qualitatively explore fatigue experience in early psychosis patients in order to construct a valid self-report rating scale of fatigue severity. Methods: We investigated the a priori construct: "the experience of fatigue/tiredness in early psychosis patients." Competent patients enrolled in the Early Psychosis Treatment Service in Calgary, Alberta, Canada who endorsed the question: "Is being tired a problem for you?" were eligible. Those with medical conditions which could cause fatigue were excluded. Patients were asked to describe aspects of their lives impacted by fatigue in audiotaped, semi-structured interviews conducted in 3 waves of $N = 3$ to $N = 5$ patients. After each wave, interviews were transcribed and analysed before interviewing the next wave of patients. Transcribed interviews were analysed for emergent themes related to fatigue experience by coding participant narratives into "nodes" using NVivo 8.0 software. Nodes were organized into categories representing the main themes in the data. The investigators independently generated candidate scale items based on the themes. Candidate items were jointly discussed and examined for redundancy, ambiguity and poor scalability to establish a final set of items by consensus. Results: Three waves of interviews totaling 17 patients resulted in data saturation. Investigators independently generated a total of 90 candidate scale items from 16 identified categories of fatigue experience. Categories and scale items were combined or eliminated by consensus resulting in 8 categories containing a total of 37 candidate scale items. The areas most identified as severely affected by fatigue were impact on relationships, functioning, and cognition. It was notable that physical symptoms of fatigue were not as endorsed in these interviews as in conventional fatigue populations, suggesting that currently available fatigue scales have insufficient face validity to support their use with early psychosis patients. Conclusion: Fatigue significantly impacts early psychosis patients. This study shows that currently available fatigue

scales have poor face validity in early psychosis patients. Further study is warranted to establish the reliability and validity of the PDTS to measure fatigue severity in early psychosis patients.
ID: 979051

DIFFERENT OUTCOMES OF PERSONS WITH SCHIZOPHRENIA IN DEVELOPING AND DEVELOPED COUNTRIES

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Background: Currently there is an axiom in international psychiatry that schizophrenia has a better course and outcome in developing countries than that in developed countries. Is the axiom of the outcome of schizophrenia reliable? Methods: Previous international outcome studies of schizophrenia in developing and developed countries were reviewed, and the results of a series of longitudinal follow-up studies of patients with schizophrenia in China were analyzed. Results: There were limitations of previous international collaborative studies (eg, WHO's studies) in which withdrawals or attrition due to death and homelessness and outcome of never-treated patients were not included in follow-up analyses. The results of longitudinal studies in rural China indicated that compared with patients 14 years ago (55.2%), more patients' family economic status (74.6%) was lower than the mean level. Compared with never-treated patients 14 years ago (51.4%), there were still 30.7% patients who never received any antipsychotic treatment. The outcome of these never-treated patients was poor than those once received medication. Many patients (8.2%) were homeless in the 14-year follow-up. The outcome of these homeless patients was poor than those with family caregivers. The rates of mortality and suicide in these patients were 8.3 times and 37.4 times higher respectively than that in general population. The outcome of patients with schizophrenia was quite similar in developing countries. Conclusion: The higher rates of mortality, homelessness and never-treated among people with schizophrenia in developing countries might challenge presumed axiom about schizophrenia outcome in these countries. It is time to reexamine presumed wisdom about schizophrenia prognosis in developing countries. Given the culture is an important factor affecting the outcome of persons with schizophrenia, further systematic and comprehensive assessments of the outcome (eg, never-treated, mortality, homelessness, etc) should be conducted.
ID: 950898

CROSS-CULTURAL COMPARISONS OF ATTITUDES TOWARD SCHIZOPHRENIA AMONGST THE GENERAL POPULATION AND PHYSICIANS: A SERIES OF WEB-BASED SURVEYS IN JAPAN AND THE UNITED STATES

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Background: Negative attitudes toward schizophrenia are prevailing worldwide, with literature suggesting that there are substantial cross-cultural differences in such attitudes. To our knowledge, however, no studies have compared attitudes toward schizophrenia amongst the general public or of healthcare professionals between the United States and Japan. Methods: In our previous study in Japan (Hori et al., in press), 197 subjects in the general population and 112 physicians (excluding psychiatrists) enrolled in a web-based survey using an Internet-based questionnaire format. The present research employed the identical web-based survey method in the United States, which was facilitated by the same Internet research company used in Japan. After screening, 172 subjects in the general population and 45 physicians were newly enrolled in our American study. To assess their attitudes toward schizophrenia, we used the English version of the 18-item questionnaire used in our previous Japanese survey, which had been created based on the original questionnaire of Ucok et al. (2006). The items in this questionnaire were subjected to the exploratory factor analysis, using the principal axis factoring method with oblique rotation. This factor analysis was performed within the combined 2 general population groups. Factors were compared between the 4 groups using analysis of covariance (ANCOVA) with age and sex as covariates. Results: The factor analysis identified 5 factors, which were labeled "social distance," "pessimism regarding psychiatric treatment," "belief of dangerousness," "underestimation of patients' abilities," and "pessimism regarding prognosis." The ANCOVA on the 5 factors controlling for age and sex, and its post-hoc analysis with Bonferroni correction, showed that the general population group in Japan scored significantly higher than the general population in the US on the factors "social distance," "pessimism regarding psychiatric treatment," and significantly lower on "pessimism regarding prognosis." The 4 groups held similarly negative attitudes in terms of "belief of dangerousness." Conclusion: The present results indicate that while negative attitudes toward schizophrenia are prevalent among the lay public both in Japan and the US, Japanese hold even more stigmatizing attitudes. This finding points to the importance of taking into account cross-cultural differences when examining attitudes toward mental illness.
ID: 979022

THC IN URINE IN SCHIZOPHRENIA: ASSOCIATIONS WITH SYMPTOM LEVELS AND NEUROCOGNITIVE FUNCTIONING

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Background: Experimental studies have shown transient deterioration in clinical and cognitive outcome measures in patients with schizophrenia after iv administration of tetrahydrocannabinoid (THC). Substance use is generally related to poorer course and outcome in schizophrenia, but clinical studies are not consistent and some show improved negative symptoms and cognition in patients with self-reported cannabis use. There are no studies of the relationship between outcome measures and THC in urine in schizophrenia in a clinical setting. The present study aimed to investigate the relation between THC in urine and levels of symptoms and neurocognitive functioning in schizophrenia. Methods: Cross sectional naturalistic study of 400 patients with schizophrenia spectrum disorder consecutively recruited from catchment area based hospitals in Oslo. Clinical assessments included urine analyses for substances, SCID-I, PANSS, IDS, GAF, premorbid adjustment (PAS) and neurocognitive testing. Multiple hierarchical regression analyses were used to assess the role of THC in urine and potential confounders on outcome measures. Results: Twenty one patients had THC in their urine; this group was characterized by more men, poorer premorbid academic functioning and more substance abuse disorder. THC in urine was associated with poorer PANSS scores and poorer outcomes on specific neurocognitive domains, independently of cannabis abuse. Conclusion: In schizophrenia, presence of THC in the urine is associated with poorer outcome measures independently of confounding factors, including abuse of cannabis. These results suggest that the associations are dependent

on the pharmacological effects of cannabis, but the design does not allow for causative conclusions.
ID: 986654

ECOLOGICAL VALIDITY OF THE SOCIAL COGNITION SCREENING QUESTIONNAIRE (SCSQ)

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Background: Social cognition, the mental operations underlying social interaction, is a high priority research area in schizophrenia because of its relationship to social functioning. However, research progress has been hindered by measurement limitations. Extant instruments have been criticized for having poor or unknown psychometric properties, ceiling effects, overlapping excessively with traditional neurocognitive domains (eg, verbal memory), and being too narrowly focused. The Social Cognition Screening Questionnaire (SCSQ) was designed to address these limitations. The SCSQ provides estimates of the core domains of mentalizing and social perception, and an overall social cognition score. SCSQ scales have shown initial evidence of convergent and discriminant validity (Roberts et al., under review). In the current study we examined the ecological validity of SCSQ scales by evaluating whether they correlate with measures of social functioning as strongly as do other measures of social cognition. Methods: Thirty individuals with schizophrenia completed the SCSQ, the Social Functioning Scale (SFS, Birchwood, 1990), the Social Skill Performance Assessment (SSPA, Patterson et al., 2001), and 3 commonly used measures of social cognition: the Hinting task (Corcoran et al., 1995), the Internal, Personal, Situational Attributions Questionnaire (IPSAQ; Kinderman & Bentall, 1996), and the MSCEIT—Managing Emotions subtest (Mayer et al., 2003). Results: Results revealed 4 significant correlations between social cognition and social functioning measures. The SCSQ's mentalizing scale correlated with the SFS Interpersonal Communication scale (r = .422, P = .023) and Employment scale (r = .368, P = .049). The MSCEIT correlated with the overall SFS score (r = .405, P = .033), and the IPSAQ Personalizing scale correlated with the SFS Prosocial scale (r = −.525, P = .003). Notably, the SCSQ total score, Hinting task, and MSCEIT all exhibited trend level correlations with the SSPA (r's = .307–.356). Conclusion: These preliminary results suggest that the SCSQ's ecological validity is as strong as that of other common social cognition measures. Ongoing development of the SCSQ and other novel measures will improve understanding of social cognition and treatment of social functioning deficits in schizophrenia.
ID: 979694

A PROSPECTIVE TRIAL OF CUSTOMIZED ADHERENCE ENHANCEMENT PLUS LONG-ACTING INJECTABLE ANTIPSYCHOTIC (CAE-L) IN HOMELESS INDIVIDUALS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

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Background: Non-adherent patients with schizophrenia have a risk of relapse that is 3.7 times greater than adherent patients. While long-acting injectable antipsychotic is a theoretically useful option, fewer than 1 in 5 individuals with known non-adherence receive long-acting medication. Additionally, medication alone is unlikely to modify long-term attitudes and behaviors. This is a 25-week prospective trial of customized adherence enhancement therapy (CAE) and long-acting injectable antipsychotic (L) in homeless individuals with schizophrenia or schizoaffective disorder and treatment non-adherence. Methods: 30 adults with schizophrenia/schizoaffective disorder confirmed with the Mini International Neuropsychiatric Inventory (MINI) are being recruited for this on-going study. Additional inclusion criteria include meeting the Federal definition for homelessness within the past 12 months, sub-optimal treatment adherence as assessed by the Tablets Routine Questionnaire (TRQ), and willing to take long-acting injectable haloperidol. Outcomes include TRQ, symptoms (Brief Psychiatric Rating Scale/BPRS), global psychopathology (Clinical Global Impression/CGI), and functioning (Social and Occupational Functioning Scale/SOFAS). Individuals receive monthly injections of haloperidol decanoate and 8 sessions of a CAE, a manualized intervention developed by these investigators. CAE targets: 1) inadequate or incorrect understanding of mental disorder; 2) lack of medication-taking routines; 3) poor communication with care providers; and 4) substance use which interferes with adherence and healthy behaviors that promote recovery. Results: Out of 10 individuals screened (mean age 38.6 years/SD 10.4, 90% male, 80% African-American, 10% Native American), 4 individuals fit entry criteria and agreed to study participation. All who enrolled reported legal problems and 75% reported drug problems. Mean (SD) baseline TRQ, BPRS, CGI, and SOFAS, were 38.4% (16.3), 50.0 (15.7), 4.7 (.58), and 37.3 (5.5), respectively. Conclusion: Men, minorities, and those with legal and substance abuse problems are over-represented among homeless individuals with schizophrenia and non- adherence. Injectable medication plus psychosocial treatment that specifically addresses adherence appears relatively well-accepted and may potentially improve outcomes. Acknowledgements: Sponsored by Grant from The Reuter Foundation.
ID: 979323

PERCEIVED NEGATIVE ATTITUDE OF OTHERS PREDICTS TRANSITION TO PSYCHOSIS IN PATIENTS AT RISK OF PSYCHOSIS

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Background: Risk of psychosis is defined by the presence of positive psychotic-like symptoms, subtle self-perceived cognitive and perceptual deficiencies or by decreased functioning with familial risk of psychosis. Our previous study suggested that also the subjective experience of negative attitude of others (NAO) towards oneself may be an early indicator of psychotic development. This hypothesis was tested in a prospective follow-up study. Methods: A total of 55 young psychiatric outpatients assessed as being at current risk of psychosis (CROP) were followed for up to 60 months and rates of transition to psychosis (TTP) identified. CROP was assessed employing the Bonn Scale for Assessment of Basic Symptoms and the Structured Interview for Prodromal symptoms. TTP was defined by a psychotic episode lasting for more than 1 week. Associations between NAO at baseline and TTP was analysed by a Cox regression survival analysis. Results: 8 (14.5 %) TTP were identified: 4 (57.1 %) within 7 NAO patients and 4 (8.7 %) within forty-six non-NAO patients. In the multivar-

iate Cox regression analysis, NAO at baseline significantly ($P = .007$) predict TTP. Conclusion: The prospective follow-up results support our hypothesis that subjective experience of NAO is an early indicator of psychotic in development.
ID: 946906

WILL YOU MOTHER?: TREATMENT OF A 50 YEAR OLD CLIENT WITH SEVERE PSYCHOSIS USING DEPTH PSYCHOLOGICAL APPROACH

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Background: The encroachment of the medical model into the realm of psychology is driven by paucity of information on the long term effects of antipsychotic medication, coupled with lack of information on the efficacy of alternative methods of healing. This paper attempts to address the gap through a case study. The patient was 50 year old homeless woman, a victim of childhood sex abuse starting at age 3 and lasting well into her 40s. She was diagnosed severely psychotic, with hallucinations, flashbacks and seizures several times per day, leading to severe psychological distress and impaired ability in day to day functioning. The pharmacological interventions for the last 7 plus years provided little benefit, but seemed to have caused severe neural and organic damage - the patient continued to experience significant instability and distress, leading to suicidal behaviors; intense paranoia about being raped, depression, and hallucinations of images that commanded her to kill herself several times every day. In the last 30 years she had attempted several suicides leading to disability and a continuously distressed self that could not be left alone for more than 15 minutes at a time. Methods: Single subject case study. Treatment program consisted of psychodynamic interventions with a Depth Psychological approach. Results: Program offered immediate psychological relief leading to increased emotional stability and ego strength and symptom reduction by 80% over a period of 8 months after which more dedicated relational and rehabilitation work and symbolization process became possible. Conclusion: It is hoped that this case will provoke questions and enable the public and psychotherapy professionals to re-envision chemical imbalance theory in metaphorical terms, so that physiological distress and psychosis can be understood and treated as an externalized manifestation of intrapsychic conflicts, the biological model providing an avenue that allows for manifestation of the what is essentially a psychological storm. This paper proposes that an understanding of the internal conflicts and resolution of psychological impasses in therapy may effectively contribute to immediate mood stabilization and containment of hallucinations and affect for some patients that suffer from psychosis. Such reduction in distress may allow for gradual withdrawal of medications.
ID: 980262

NEGATIVE SYMPTOMS BUT NOT COGNITIVE ABILITY PREDICTS EARLY RESPONSE TO A SOCIAL LEARNING PROGRAM

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Background: A number of patients with schizophrenia remain chronically hospitalized. Social learning programs have been shown to treat successfully and transition to the community many of these patients. Located at a private, academic psychiatric hospital, the Second Chance Program has treated over 500 patients with psychotic disorder who have been institutionalized in or referred to the state hospital due to inability to function in the community. Over 80% of the patients have been discharged to the community with 50% in the community after 1 year. Though most patients respond to the program, the goal of this analysis is to determine those patients who are likely to respond faster to the program in order in the future to lower the length of stay of the average patient from 330 to 180 days. Methods: 33 patients were placed into 4 groups based on weekly total score at weeks 1 and 8 after admission. This score is based on the sum of points for socially appropriate behavior (adls, going to groups, interactions with others) minus points lost for inappropriate behavior (noncompliance, social isolation, bizarre behavior). It is used as a functional measure of progress in the program with a higher score indicating more community appropriate behavior. The 4 groups were: high scores both times ($n = 11$), high going to low ($n = 5$), low both times ($n = 12$), and low going to high ($n = 5$). An ANOVA analysis was performed to compare groups based on demographic variables, symptom measures (PANSS, SANS), and cognition (MATRICS) done in the first 5 weeks of admission. Results: The only significant difference was based on the SANS score ($P = .026$, $F = 3.6$, $df = 3$) with the high both times (SANS 42.2) being significantly different particularly compared with the low both times group (SANS 59.9). The 2 smaller groups had similar SANS scores (high to low 56.5, low to high 61.8). There was no statistical difference between groups with the PANSS (total or 3 factor subscales, demographic variable, or cognitive ability). Conclusion: This preliminary analysis indicates that lower though still severe negative symptoms predict success in a social learning program. It is likely that motivation is better in patients with less severe negative symptoms and patients with better motivation are likely to respond to a reward based program. This data will need to be replicated in a prospective manner with a larger sample and to determine if these early responders are more likely to have successful community placements.
ID: 978420

THE IMPORTANCE OF COGNITION, NEGATIVE SYMPTOMS AND SUBJECTIVE PARAMETERS FOR FUNCTIONAL RECOVERY IN SCHIZOPHRENIA

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Background: A wealth of research has been conducted on the relevance of neurocognition, social cognition, negative symptoms and functional outcome as treatment targets in schizophrenia. However, the interdependent relationships between these variables are not yet fully understood. Definitions of recovery put special emphasis on subjective and process oriented factors, but very little is known how these subjective experience variables are associated with neurocognition, social cognition, negative symptoms and the typical functional outcomes as well as more subjective outcomes like quality of life. Methods: First, by the means of structural equation modeling (SEM) we tested models with social cognition and negative symptoms serving as mediator variables between neurocognition and functional outcome. Additionally subjective parameters (hope, psychological strain, helplessness, initiative, knowledge, denial of the disorder, self-efficacy) were included into the model. We investigated their interrelationships with neurocognition, social cognition as well as negative symptoms and their predictive value for functional outcome. Second, we tested the same model but used quality of life instead of the traditional outcome measures. Again, the interrelationships with subjective variables and their role as predictors of quality of life were investigated. Data were collected in the context of an international RCT. Until now 169 outpatients with a diagnosis of schizophrenia according to ICD-10 or DSM-IV-TR participated in the study. We chose a longitudinal design. Results: 1. Social cognition and negative symptoms mediated the relationship between neurocognition and psychosocial functioning. Only few subjective variables (eg hope) were

associated with functional outcome. 2. Cognitive functions had no significant predictive or mediating influence on quality of life. Instead subjective variables (eg hope, psychological strain, self-efficacy) and negative symptoms functioned as significant predictors and were strongly related to each other. Conclusion: The results of the study provide further evidence for social cognition and negative symptoms being essential mediators between neurocognition and psychosocial functioning in schizophrenia. A combined treatment may reveal synergistic effects. Including relevant subjective variables seems to be a promising possibility to generalize therapy effects to quality of life.
ID: 979526

ROLE OF SYMPTOM REMISSION IN DETERMINING MEDICATION ADHERENCE IN EARLY PSYCHOSIS

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Background: Adherence to medication confers significant benefits on patients with psychotic illness, but achieving adequate adherence remains a clinical challenge. Because adherence tends to be stable over time, understanding the determinants of medication-taking in early psychosis is crucial. Efficacy of medication has been shown to be an important factor in adherence among patients with established illness. This study examines the influence of efficacy on adherence in a sample of patients being treated for a first episode of psychosis. Methods: In this study, data regarding medication efficacy and adherence were obtained from 260 early psychosis patients. ''Efficacy'' was assessed as the ability of the medication to reduce positive and/or negative symptoms to a level below established thresholds for clinical remission (defined by ratings on SAPS and SANS). Adherence was evaluated as adequate (>75%) or not. Both were assessed at treatment entry and months 3, 6 and 9 of treatment. Results: We found no relationship between medication adherence and rapid remission of positive symptoms (by month 3 of treatment), but found an association between sustained positive symptom remission (at month 3 and 6) and adequate adherence at month 6. In contrast, we found a negative association between rapid remission of negative symptoms and adherence: patients whose negative symptoms rapidly resolved by month 3 of treatment were less likely to be adequately adherent at months 3 and 6. We found no demographic differences between subjects who were non-adherent despite negative symptom remission and those who had not experienced negative symptom remission, or whose negative symptoms had remitted but who were adherent, except for the fact that the non-adherent subjects were more likely to have been non-adherent at treatment entry. Finally, we found that the overall rate of adequate adherence declined over time from 85% at program entry to about 60% at months 6 and 9. This was despite the fact that most patients experienced remission of positive symptoms, and 30% experienced remission of negative symptoms. Conclusion: These results suggests that medication efficacy may promote adherence if it produces sustained remission of positive symptoms, but that many patients are at risk to reduce or stop medication, despite its benefits. In particular, those who experience rapid symptom remission may be less likely to view themselves as ''ill'' and have more difficulty adhering to medication treatment.
ID: 978367

METHODS OF ASSESSING ALLIANCE IN INPATIENT SETTINGS

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Background: The purpose of this poster is to present 10 different methods of assessing alliance in an inpatient setting. The assessment is used to help talk about and improve alliance. Methods: The Colorado Mental Health Institute at Pueblo has an inpatient population of about 400 in twenty different units. The average length of stay varies from days (adolescent unit) to a decade (not guilty by reason of insanity). As part of the hospital's ''recovery initiative'' each unit is tasked with assessing and improving alliance between patients and staff. Ten different assessment tools have been developed. Some have sound psychometrics, some have been developed for practical use without psychometric analysis. Some have patient rating, some have staff rating. Some are anonymous, some not. Some rate staff, some rate a team or unit in general, some are self-ratings by patients. Some are used as a ''talking tool'' in 1:1 sessions, some are used in community meetings, some are summarized and reported. Results: This poster has 10 8.5 × 11 sheets of paper, each summarizing one tool, with representative items, how it is used, psychometrics (when available) and general opinions of results and usefulness. Each is non-copyright. Scales and more detailed psychometrics will be shared if there is interest. Conclusion: Assessing alliance is an ongoing process that can be done.
ID: 927235

MALADAPTIVE SCHEMAS IN YOUNG PEOPLE AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: In depression research it is accepted that adverse early social experiences can lead to enduring cognitive vulnerabilities that are characterized by negative schemas or beliefs about the self, others and the world. In schizophrenia research there are studies suggesting a role for social risk factors (eg child abuse, early social adversity, urban upbringing, social isolation, immigrant status) in the development of schizophrenia. One proposal by Selten (2005) is that social defeat may be the mechanism that links these ''adversities'' and is a contributing factor to psychosis. At the same time the development of cognitive models suggesting that people's beliefs and appraisal processes are very important in the onset and persistence of psychosis. The aim of this study was to examine if maladaptive schema and self beliefs are a link between social defeat and the onset of psychosis, ie that young people at clinical high risk (CHR) of developing a psychotic illness, who were characterized by a sense of social defeat would also have developed maladaptive self beliefs and self schema that increased their risk of developing psychosis. Methods: In a sample of 38 CHR individuals (28 males, 10 females, mean age 19.7 years) who met criteria for prodromal risk syndrome based on the Structured Interview for Prodromal Syndromes, we examined attenuated positive symptoms (SOPS), social defeat and cognitive schemas (Brief Schema Scales, Attitude Scale, Schema Questionnaire). Results: Relative to published norms the sample demonstrated high levels of social defeat and feelings of both internal and external entrapment, endorsed negative evaluations of the self and others and demonstrated maladaptive schemas (eg emotional deprivation, shame, failure, mistrust). All negative evaluations and maladaptive schemas were significantly associated with a greater sense of social defeat and entrapment (r ranged from .47 to .82, $P < .01$ for all correlations) and with high levels of attenuated positive symptoms (r ranged from .41 to .47, $P < .01$ for all correlations). Conclusion: In conclusion, those at clinical high risk of psychosis who have developed maladaptive self- beliefs and self-schema

have higher levels of attenuated positive symptoms. This could offer some support for the notion that maladaptive self beliefs may play a role in the onset of psychosis and have implications for prevention because these maladaptive schemas are malleable factors for which we have effective psychological interventions.
ID: 977705

UNDERSTANDING SELF-EFFICACY AND WELL-BEING IN PATIENTS WITH SCHIZOPHRENIA

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Background: Quality of life in patients with schizophrenia can be adversely affected by factors such as impaired cognitive functioning and other symptoms. However, positive intrapersonal characteristics may offset these factors and improve their well-being. Therefore, identifying positive psychological resource factors is crucial, particularly those that may improve quality of life. This study had 2 aims: 1) to examine the relationship between self-efficacy and well-being, and 2) examine psychosocial factors that are associated with increased self-efficacy. Methods: Participants were 62 middle-aged or older participants (Mean age = 50.4, SD = 6.2), with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder. Self-efficacy was measured using the Revised Self-efficacy Scale (RSES). Participants' perceived well-being was measured using the Recovery Assessment Scale (RAS). Factors we anticipated would be associated with self-efficacy were: a) Behavioral Activation, measured using the Behavioral Activation for Depression Scale (BADS), b) depression, measured using the Calgary Depression Scale (CDS) c) social contact, measured using the Lehman Quality of Life Index (QOLI). Results: Significant correlations were found between social self-efficacy and total RAS scores, $r(60) = .63$, $P < .001$. A simultaneous multiple linear regression was then performed. For this analysis, social self-efficacy was the criterion variable, and BA, social contact, and depression were the predictor variables. The model including all variables accounted for 32.3% of the variance in social self-efficacy, $R2 = .323$, $F(3,54) = 10.06$, $P < .001$. Significant predictor variables included BA ($\beta = .277$, $P = .019$), social contact ($\beta = .282$, $P = .016$), and depression ($\beta = -.341$, $P = .003$). Conclusion: Participants' self-efficacy is associated with greater well-being. Also, greater behavioral activation, greater social contact and less depression significantly predict high levels of social self-efficacy. Our data are correlational; therefore, caution should be used when interpreting these effects. However, increasing behavioral activation and social contact via psychosocial interventions may help to increase social self-efficacy and improve quality of life in patients with psychosis.
ID: 979890

DETERMINANTS OF OBJECTIVE AND SUBJECTIVE QUALITY OF LIFE IN SCHIZOPHRENIA: ARE THEY DIFFERENT CROSS-SECTIONALLY VS. LONGITUDINALLY?

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Background: The ultimate test of a treatment's effectiveness is improvement in quality of life (QOL) for the patient being treated. Both subjective QOL (life satisfaction) and objective QOL (level of functioning in activities and relationships) should be measured, as their correlates are different. Better neuropsychological functioning and higher depressive symptoms tend to be associated with worse subjective QOL cross-sectionally, lending credence to the notion that "sadder is wiser." However, it is unknown whether improving cognition via cognitive training (CT) can change QOL. Methods: 51 schizophrenia outpatients completed a randomized controlled trial of a 12-week, group based, compensatory cognitive training (CT) intervention vs. standard pharmacotherapy alone. Results: We found positive effects of CT intervention on attention ($P = .022$), memory ($P = .045$), functional capacity ($P = .014$), negative symptoms ($P = .003$), and subjective QOL ($P = .008$; all P-values derived from hierarchical linear modeling of group by time effects). Further, the effect size for subjective QOL at immediate post-treatment, $d = .50$, increased to $d = .84$ at 3-month follow-up. Conclusion: Better neuropsychological functioning is associated with worse subjective QOL cross-sectionally, possibly because more cognitively intact individuals are better able to see the impact of their illness and its limitations on their potential. However, treatments to improve cognition in schizophrenia may also increase QOL. Predictors of improved QOL within this trial will be discussed.
ID: 978938

AN ONLINE SELF-MANAGEMENT TOOL FOR PEOPLE SUFFERING FROM PSYCHOSIS

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Background: In many countries today, service user empowerment has become an important agenda item in health care for people suffering from psychosis. Developments of self-management programs so far seem promising in enabling service users to take up an active role in the daily management of their condition. The Dutch WEGWEIS project seeks to add to these developments by supporting self-management through smart web-based technology. The aim of the WEGWEIS project is to develop and evaluate an online self-management tool, which supports service users to regain more control over their lives. Methods: Our 4-year project consists of 3 phases. First, we will execute a survey of service users' needs as well as of technological possibilities of the web system. Second, we will develop a web application in iterations, in close collaboration with a focus group of service users. Third, we will do a randomized controlled trial (RCT) to measure the effectiveness of face-to-face online contact between service user and practitioner and the effect of feedback and advice given to service users, related to problems and goals they report. We will measure the effect on feelings of empowerment (MHCS), working alliance (WAI), and duration and frequency of admissions. This last phase is considered crucial, as RCTs in this area of research have been rare. Results: Based on survey results, a web application prototype has been developed which is designed to provide health care users up-to-date information about their health condition, offer them individualized and evidence-based advice and enables interactive ways of communication with clinicians and peers. Furthermore, the system is designed to support processes of shared-decision making by encouraging users to reflect upon their personal needs and goals in life, which can strengthen their voice in negotiations with clinicians. Smart technology is used to tailor the offered information to each user individually. Conclusion: The use of ICT in psychiatry seems promising. However, its effectiveness has yet to be established in RCTs.
ID: 977610

EFFECT OF CANNABIS USE ON THE COURSE OF SCHIZOPHRENIA IN MALE PATIENTS: A PROSPECTIVE COHORT STUDY

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Background: The impact of the use of cannabis on the course of schizophrenia is not clear and results of current studies are inconclusive. Our objective was to study the effect of cannabis use on the course of schizophrenia. Methods: A prospective cohort study with assessments at baseline, 6 months and 12 month follow up. Results: In a representative cohort, comprising 145 male patients of whom 67 (46.7 %) used cannabis, the mean age at onset of cannabis using patients was significantly lower than non using patients. No other cross-sectional differences were seen between users and non-users with respect to demographics and psychopathology. In longitudinal analyses, relapse in terms of number of hospitalizations, was significantly higher in cannabis using patients, although no significant correlations were found between cannabis use and increased psychopathology. Conclusion: Cannabis using patients with a schizophrenia-spectrum disorder are more frequently hospitalized than non using patients, independent from psychopathology. Mechanisms that contribute to the negative impact of cannabis use on the course of the disease are discussed.
ID: 978808

VISTA: A NOVEL PSYCHOSOCIAL TREATMENT TO IMPROVE METABOLIC RISK FACTORS FOR PATIENTS ON ATYPICAL ANTIPSYCHOTICS

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Background: In a community participatory research study, we increased the frequency of metabolic monitoring for all individuals with SMI on atypical antipsychotic medication. However, appropriate monitoring of metabolic syndrome (MetS) is only the first step in improving health outcomes in this population who are known to have a 20% shorter life span than the general population due primarily to cardio-metabolic illness. Methods: We developed a novel psychosocial program called in VIvo cuSTomized life style Alteration (VISTA), an individually tailored behavioral health intervention that utilizes motivational interviewing, in-home dietary instruction and organization (eg placing less desirable foods out of sight), and personalized exercise built around the individual's preferences and environment to improve illness management, health behavior and outcomes for individuals with metabolic risk factors. In a pilot study conducted at a community mental health center, individuals on second generation antipsychotic medications, with at least one metabolic risk factor were randomized to 1 of 3 treatment groups. Here, we describe preliminary data for VISTA compared with enhanced treatment as usual (TAU) (n = 30). Individuals in VISTA were seen weekly to monthly during home visits designed to encourage follow-up with primary care, customize life style changes to their environment, prompt and cue healthy behavior, and provide customized education and illness management. Results: Pilot data indicate that individuals in VISTA had a shorter duration to face-to-face contact with a primary care provider (PCP) following identification of a metabolic risk factor and a significantly higher number of appointments for medical follow-up with a PCP than patients in TAU ($P < .01$). Clinically, improvements in diet and increases in physical activity were seen for patients in VISTA, and adherence to psychiatric and non-psychiatric medications remained above 80% for the duration of treatment. While the difference was not significant in this small sample, a greater proportion of patients in VISTA (78%) than TAU (60%) improved with respect to the metabolic risk factor that qualified them for study. Conclusion: Psychosocial treatments such as VISTA may decrease long-term illness burden. Larger scale studies and studies of individuals who meet full criteria for MetS are warranted.
ID: 979716

METACOGNITIVE TRAINING IN SCHIZOPHRENIA: FROM BASIC RESEARCH TO INTERVENTION

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Background: Recent research suggests that cognitive (thinking) biases play a prominent role in the formation of delusions, and combinations may contribute to relapse and delusional states. Metacognitive training (MCT; www.uke.de/mkt) attempts to bring these biases to the awareness of clients (metacognition is thinking about thinking), for the purpose of increasing the abilities of clients to regulate thinking and deploy appropriate coping strategies. MCT primarily focuses on promoting awareness of the biases themselves, through general content material. MCT has an extension, referred to as MCT+, which focuses on using MCT material to apply this knowledge to an individual's own delusions. Methods: MCT is designed to be delivered by a health care specialist (trainer) with a group of 3–10 schizophrenia spectrum patients. It comprises 8 modules consisting of pdf-converted PowerPoint slides. MCT targets the cognitive errors and problem solving biases most characteristic of schizophrenia. The main objective of the training is to raise the patient's awareness of these cognitive distortions and to prompt them to critically reflect on, complement and alter their current repertoire of problem solving skills. Results: Several studies have been conducted because the introduction of the MCT in 2005. In the initial controlled pilot study, patients favorably rated their experience with MCT. Since then, 2 randomized controlled studies with blind assessors have found positive effects of MCT modules, including an accelerated decline in positive symptomatology, reductions in delusional distress, and reductions in the impact of cognitive biases. The MCT combined with the individualized MCT+ modules have also been submitted to a randomized controlled trial, and the positive impact on delusion conviction was replicated. Conclusion: The goal of the MCT is, through engaging interactive sessions, to introduce patients to the research findings on cognitive biases, with the goal of sharpening patients' (metacognitive) awareness of these biases, and to carry over this metacognitive knowledge to their daily life. Although the effectiveness of the MCT is still under investigation, given the high rates of relapse in schizophrenia, the noncompliance under antipsychotic medication, cognitive interventions such as the MCT are now being given consideration by mainstream practitioners.
ID: 979459

8-YEARS FOLLOW-UP OF THE MESIFOS FIRST EPISODE PSYCHOSIS COHORT

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Background: Long-term outcome predictors of first episode psychosis have not been thoroughly studied, nor the impact of a discontinuation challenge of antipsychotics on long-term outcome compared with maintenance treatment. Methods: A first episode psychosis cohort (n = 131) showing positive symptom remission for 6 months within the first year of treatment was fol-

lowed-up for 8 years. All patients participated in an RCT comparing a discontinuation challenge with maintenance antipsychotic treatment, during 18 months after achievement of remission. Results: At 24 months follow-up 52% were in symptomatic remission, 26% were functionally remitted and 19% met both criteria sets and thus met criteria for clinical recovery. Baseline differences between recovered and non-recovered patients were duration of untreated psychosis (DUP, mean 320.9 vs. 31.8 days, P = .001) and social functioning. A logistic regression analysis showed that predictors of recovery were DUP (OR = .531, df = 1, P = .008) and baseline social functioning (OR = .858, df = 1, P = .021). No recovery occurred in patients with DUP >6 months. The mean daily dose of antipsychotics did not differ between recovered and non-recovered patients, nor did baseline cannabis abuse. Patients were followed-up after 8 years. Data will be presented on symptomatic and functional remission and clinical recovery after 8 years, as well as the predictors of these outcomes. The potential consequences of the discontinuation challenge will be reviewed, as well as the long-term outcome of successful withdrawal of antipsychotics in the original study. Conclusion: A withdrawal challenge of antipsychotics in remitted first episode patients is a feasible way to find out whether long-term maintenance treatment is necessary or not; only a small proportion of patients will be able to stay off drugs definitively; a relatively large proportion of patients were in remission or recovered at 8 years of follow-up; data will be presented on predictors of remission and recovery.
ID: 978676

CANNABIS USE: DEFINING THE TARGETS FOR PSYCHOLOGICAL TREATMENT

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Background: There have been many reports that cannabis use is related detrimentally to outcomes such as delayed remission, relapse, suicidal behavior, violence, social instability and homelessness. But it is not clear whether this negative association arises from the specific effects of cannabis on psychotic symptoms or to confounding variables that are common to both poor mental health outcomes and cannabis use. If it is the former then clearly the focus on improving outcomes should be to reduce cannabis use if it was the latter then psychological treatments need to focus on these confounding issues which lead to poorer outcomes. Methods: A secondary analysis of data from a multicentre RCT that provided motivational interviewing and CBTp over a 9 month period of people with dual diagnosis. There were 160 people reporting cannabis use. Repeated measures of substance misuse (Time line follow-back) and symptoms (PANSS) at month 0, 12 and 24 months were collected as were covariates at baseline and averaged across the 3 data collection points. The 2 key questions are: (i) is amount of cannabis use associated with symptomatic outcomes when controlling for baseline correlates (including treatment allocation) and other potential confounds and (ii) are changes in cannabis use associated with changes in symptoms (especially positive symptoms) Results: Increasing the frequency or the amount of cannabis used is related to increases in symptoms (1–2 more days per week predicts increase in PANSS general of nearly 1.0 and positive symptoms of nearly 0.5). But if cannabis use decreases during the time of the trial then (after covarying for confounds) there is no association with positive, negative or general symptoms on the PANSS. Preliminary latent models suggest different patterns of use for different people with about 5 patterns identified. Conclusion: In people with existing psychosis, relationship between cannabis use and poor symptom outcomes and for some people is not attributable to specific effects of cannabis but to associated factors eg other substance use, lifestyles, treatment non adherence. For some people with psychosis, reducing cannabis use per se may have limited impact on clinical outcomes at least for longstanding users. Addressing cannabis use may be a priority but other issues may need to be addressed to improve outcomes. Psychological treatments therefore need to be comprehensive if they are to be successful in the majority of people with cannabis use.
ID: 979403

PEER ADVOCATES AS IMPLEMENTERS OF EVIDENCE-BASED SUPPORTED EMPLOYMENT/EDUCATION SERVICES: PRELIMINARY FINDINGS ON FEASIBILITY AND EFFICACY

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Background: Peer support is based on the notion that persons with serious mental illness (SMI) are uniquely positioned, based on their personal experience in dealing with a mental disorder, to provide support and encouragement to others with SMI who are in the process of recovery. Although evidence exists to support the contribution of peer support in providing conventional services such as supportive therapy, we are unaware of previous efforts to teach peers a set of competency-based skills required to provide evidence-based practices. The present preliminary results address the feasibility and efficacy of teaching persons with SMI the skills required of a supported employment/education specialist under the Individual Placement and Support (IPS) model, the leading evidence-based model of supported employment/education. Methods: Four persons with histories of SMI were hired as peer advocates at a local community mental health center and then trained to provide IPS services to persons with schizophrenia and schizoaffective disorder. The training was guided by behavioral learning principles and was conducted by experts in psychosocial rehabilitation and IPS. Training addressed 4 skill areas: a) establishing a professional relationship with clients, b) job development, c) job support/maintenance, and *d*) integration of employment services with mental health treatment. Competency of each peer was measured using the Kansas Employment Specialist Job Performance Evaluation, a 5-point scale (1 = poor, 3 = average, 5 = superior) that assesses 6 areas (eg, conducting vocational profile assessments, demonstrating job development skills), and was conducted by 2 experts on IPS. Results: Results show all 4 peers to be performing at or above average levels on each of the skill areas with the exception of integration with mental health services (mean range = 2.7–4.2). Each of the peers has acquired a caseload (n = 6–11), and has successfully placed at least one client at a competitive job or school activity in the community. Conclusion: In terms of its significance, we believe this effort takes the role of peers into a new realm, namely, demonstrating that clients who have recovered from their clinical disorders could actually learn and effectively perform the role of supported employment/education specialists that heretofore has traditionally been fulfilled by non-peer mental health professionals.
ID: 983420

21. Therapeutics: Pharmacologic Probes

PARTIAL OCCUPANCY OF THE GLYCINE TRANSPORTER TYPE 1 IN RAT BY RG1678 LEADS TO EFFICACY IN MODELS RELEVANT TO SCHIZOPHRENIA

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Background: Multiple lines of evidence support the notion that hypofunction of glutamatergic neurotransmission via NMDA receptors is implicated in the pathophysiology of schizophrenia. Blockade of the glycine transporter type 1 (GlyT1) will increase glycine levels in the NMDA synapse and subsequently enhance NMDA receptor function that could normalize hypofunctional receptor signaling. A novel and highly selective GlyT1 inhibitor, RG1678, was recently shown to have a beneficial effect in a Phase II trial in patients with schizophrenia. Using both behavioral and biochemical methods, data are described that link target receptor occupancy, plasma exposure, and efficacy of RG1678. Methods: Behavioral experiments were conducted with NMRI mice and Wistar rats; the chief outcome measure was locomotor activity. Mice received graded doses of RG1678 prior to D-amphetamine or L-687414, a glycine site antagonist at the NMDA receptor complex. Rats were given PCP for 14 days and, after the last dose, treated with RG1678 then D-amphetamine. For in vivo binding, Wistar rats pretreated with vehicle or RG1678 (3–60 mg/kg p.o.) received 1 mCi/kg [3H]RO5013853 i.v. and were sacrificed 30 minutes later. Sagittal brain sections were exposed to tritium-sensitive imaging plates for 5 days in a high-resolution phosphor imager. The amount of [3H]RO5013853 bound in brain regions of interest was quantified by image analysis. Results: RG1678 (0.1–10 mg/kg) attenuated the hyperlocomotion induced by D-amphetamine or L-687414 in mice and the hyper-response to D-amphetamine in rats treated chronically with PCP. Pretreatment with RG1678 produced a dose-dependent decrease of the in vivo binding of [3H]RO5013853 in brain regions known to express high levels of GlyT1. The plasma concentration of RG1678 required to produce 50% GlyT1 occupancy in the thalamus was 751 ± 110 ng/ml. Also, aligned with this finding, the plasma concentrations of RG1678 measured at active doses in the behavioral assays produced a maximal GlyT1 occupancy of about 50% in the thalamus. Conclusion: In summary, RG1678 is a potent GlyT1 inhibitor that can modulate both glutamatergic and dopaminergic tone. In vivo binding studies in the rat with [3H]RO5013853 facilitated a better understanding of the relationship between target receptor occupancy, plasma exposure, and efficacy, showing that a maximal brain GlyT1 occupancy of approximately 50% was needed to attain efficacy in behavioral models relevant to schizophrenia.
ID: 979378

ANTIPSYCHOTIC-LIKE PROFILE AND REVERSAL OF COGNITIVE IMPAIRMENT WITH THE POSITIVE ALLOSTERIC MODULATOR OF THE M4 MUSCARINIC ACETYLCHOLINE RECEPTOR VU0152100

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Background: Muscarinic acetylcholine receptors (mAChRs) mediate the metabotropic actions of the neurotransmitter acetylcholine. Of the 5 subtypes, M1 and M4 are of interest for the treatment of schizophrenia. The M1/M4-preferring agonist xanomeline was promising in clinical trials for Alzheimer's disease and schizophrenia, but dose-limiting adverse effects halted further development. Previously, a major limitation to testing the hypothesis that M1 and/or M4 mediate the antipsychotic-like effects of xanomeline was the lack of highly selective ligands for each mAChR subtype. Recently, we have reported on the highly selective M4 positive allosteric modulator VU0152100, which is brain penetrant. Here we describe the efficacy of VU0152100 in preclinical models of schizophrenia. Methods: For amphetamine and phencyclidine-induced hyperlocomotion assays, rats were pretreated with VU0152100 30 minutes before psychostimulant administration. For studies of contextual fear conditioning, a hippocampal-dependent learning and memory task, rats were pretreated with VU0152100 30 minutes before amphetamine or phencyclidine administration. After 15 minutes, rats were trained (4 shocks, 74s ITI); 24 hours later, they were exposed to the same context and percent freezing was assessed. Pharmacologic magnetic resonance imaging (phMRI), used to assess the effects of specific agents on regional changes in brain activity and their associated hemodynamic effects, were performed on a 9.4T Varian scanner in anesthetized rats. Functional images were acquired using MION as the contrast agent in order to calculate fractional CBV changes and time courses with and without pretreatment of VU0152100. Results: VU0152100 dose-dependently reversed amphetamine- and phencyclidine-induced hyperlocomotion. VU0152100 also reversed both amphetamine- and phencyclidine-induced deficits in contextual fear conditioning. As phMRI can be used to study the modulation of one neurotransmitter system on another at a systems level, evaluating how the cholinergic system affects dopamine transmission points to the underlying correlates of therapeutic efficacy of this compound. Conclusion: VU0152100 produced antipsychotic-like activity and cognition enhancement at doses that did not lead to adverse effects associated with peripheral mAChR activation. These results reveal that highly selective M4-targeting compounds have potential as novel antipsychotics that may address the positive symptoms and cognitive deficits of schizophrenia.
ID: 978074

IMPLICATIONS OF CLOZAPING AND DESMETHYLCLOZAPINE BLOOD LEVELS TO CLINICAL RESPONSE IN TREATMENT REFRACTORY SCHIZOPHRENIA

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Background: Desmethylclozapine (NDMC), one of clozapine's major metabolites, has become a recent focus of study for both its antipsychotic and metabolic effects and It has been shown in vitro that acts as an agonist of the serotonin 2A receptor as D2 receptor partial agonist. The potential therapeutic role for the NDMC has been proposed based on recent studies show that high proportions of NDMC/clozapine are associated with improved cognitive function and quality of life (Weiner et al., 2004;Mendoza and Lindenmayer, 2009) Methods: The aim of this study is to examine ratio of NDMC'/clozapine and NDMC and Clozapine plasma levels as predictors of clinical response of clozapine in schizophrenic resistant patients In this study, we investigated the pharmacokinetic profile of CLZ in Spanish patients and examined the association between serum CLZ parameters and clinical outcome. Results: There were pronounced interindividual variations of the steady-state plasma concentrations of CLZ and Desmethylclozapine (CLZ : 82.00–849. 00 ng/ml [319.40 ± 197.26 ng/ml]; (NDMC: 67–660 ng/ml [221.60 ± 148.31 ng/ml]; The ratio of CLZ and NDMC ranged from 0.41 to 2.65 (0.75 ± 0.6.). Approximately 3–35-fold interindividual variations in the plasma concentrations of were of CLZ and NDMC identified. In whole sample, the application of measurement drug plasma level at 8 weeks revealed significant correlation between CLZ dosage (mg/day)

and CLZ plasma levels at steady state (r = .41, P = .003), also, NDMC plasma levels at steady state((r = .38, P = .012) and sum of plasma levels (r = .42, P = .005) of CLZ and NDMC. It can be observed that responders subjects have presented a high correlation between dose of clozapine and plasma levels of CLZ (r = .5829, N = 52, P < .000), plasma levels of NDMC (r = .58, N = 65, P < .000) and total serum level in responders (r = .66, N = 52, P < .000). For nonresponders, there not was significantly correlation between doses of clozapine and its plasma levels (r = .42, N = 28, P < .069)) nor total plasma level (r = .31, N = 28, P = n.s.). For all sample, there was not correlation between doses of drug administered and presence of response at 8 weeks (r's = −.056, N = 82, P = n.s.) but higher NDMC/clozapine ratios was associated with response Conclusion: Higher NDMC/*N*-Desmethylclozapine, clozapine ratios may be associated with greater symptom improvement;
ID: 979534

"GONE TO POT": EVIDENCE FROM LABORATORY STUDIES WITH Δ-9-THC

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Background: Recent advances in knowledge about cannabinoid receptor function have renewed interest in the association between cannabis and psychosis. Converging lines of evidence suggest a relationship between cannabinoids and psychosis. Laboratory studies with delta-9-tetrahydrocannabinol (THC) have been a useful approach to investigate this relationship. Furthermore, cannabis is frequently used and misused by individuals with schizophrenia - and while cannabis appears to have a negative impact on the course and expression of schizophrenia, individuals with schizophrenia report deriving "benefits" from its use. Laboratory studies with THC may be useful in understanding the effects of cannabinoids in individuals with schizophrenia. Methods: We have characterized the dose-related behavioral, subjective and cognitive effects of intravenous THC in more than 250 healthy individuals in a series of double-blind, randomized, placebo-controlled laboratory studies conducted over the past 15 years. A range of doses (1–5 mg) of THC given at varying rates of infusion (5–20 minutes) have been studied. The sample has included healthy individuals, light users of cannabis and individuals with schizophrenia. The effects of THC on schizophrenia-relevant outcomes were measured including psychosis (PANSS) and perception, subjective effects, top-down processing ("babble" task), memory, attention, executive function, temporal processing, event related potentials (P300) and neural synchrony (ASSR). Furthermore, the influence of dopaminergic and GABAergic function on the THC response was characterized by studying the interactions of THC with haloperidol and iomazenil, respectively. Results: THC produces an array of transient schizophrenia-like positive and negative symptoms, perceptual alterations, verbal memory deficits, attentional deficits, working memory deficits and psychophysiological abnormalities in healthy individuals. THC also exacerbates symptoms in individuals with schizophrenia. Haloperidol pretreatment does not appear to attenuate the effects of THC and Iomazenil pretreatment may increase the vulnerability to THC. Conclusion: Cannabinoids can produce a range of transient schizophrenia-like phenomena. However, why some individuals are more vulnerable to these effects is not fully understood. Genetic factors and previous exposure to cannabis may influence the response to Δ-9-THC in the laboratory, and these factors will be discussed.
ID: 977980

GLYCINE TRANSPORTED INHIBITION ATTENUATES THE PSYCHOTOMIMETIC EFFECTS OF KETAMINE IN HEALTHY HUMAN SUBJECTS

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Background: Enhancing glutamate function by stimulating the glycine site of the NMDA receptor either with glycine and D-serine or with drugs that inhibit glycine reuptake may have therapeutic potential in schizophrenia. The objectives of this study were to investigate the effects of pretreatment with a glycine reuptake inhibitor (GLY-T Inhibitor), on ketamine-induced schizophrenia-like psychotic symptoms, perceptual alterations, and subjective effects. Methods: In the prepilot open-label, nonplacebo controlled phase the safety of escalating doses of a GLY-T Inhibitor were investigated in the ketamine paradigm. Once safety was established, the effects of a single oral dose of GLY-T Inhibitor and placebo pretreatment on ketamine-induced schizophrenia-like psychotic symptoms, perceptual alterations, and subjective effects were evaluated in 12 healthy male subjects in a randomized, counter-balanced, cross-over design. Two and a half hours after administration of a GLY-T Inhibitor or placebo, subjects received a ketamine bolus (0.23 mg/kg bolus over 1 minute) followed by a constant infusion (0.58 mg/kg/hour × 30 minutes, followed by 0.29 mg/kg/hour × 69 minutes). There was a wash-out of at least 7 days between test days. Psychotic symptoms, perceptual alterations and a number of subjective effects were assessed. These measures were collected in a repeated measures design before and several times during and after completion of ketamine administration. Results: Ketamine produced psychotomimetic and subjective effects consistent with its known effects. GLY-T inhibition reduced the peak increase in ketamine-induced PANSS total, positive symptoms subscale and general symptoms subscale scores. GLY-T inhibition also reduced ketamine-induced perceptual alterations measured by the clinician-rated subscale of the clinician administered dissociative symptoms (CADSS) scale. The magnitude of the effect of GLY-T inhibition on ketamine-induced increases in total PANSS and CADSS Clinician-rated scores was 0.68 and 1.03, respectively. None of the behavioral effects of ketamine were increased by GLY-T inhibition pretreatment. Conclusion: In this exploratory study, gly-t inhibition appears to reduce the psychotomimetic effects of ketamine. the findings of this study provide preliminary support for the antipsychotic potential of GLY-T inhibitors.
ID: 935248

DEPLOYING AN INTERACTIVE PROGRAM ON MEDICATION PERCEPTION AND ADHERENCE FOR PSYCHOTIC PATIENTS

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Background: Supporting adherence is recognized as a major issue in treating schizophrenia. However, there are very few clinical tools available to professionals to help patients maintaining their treatment (1,2). Methods: The workshops The DJ's choices have been developed to promote adherence using psycho educational notions, cognitive behavioral techniques and motivational approach. This material was adapted for group discussions

around medication perceptions, believes and challenges over long-term adherence. Workshop 1 Make up your mix shares psychoeducational notions on relapse prevention and treatment efficacy; Workshop 2: Get your beat allows to share on side effects and impression on medication; Workshop 3: Explore leads facilitates discussion on families' perceptions and influences of environment on adherence and Workshop 4: Keep the tempo states an individual action plan on daily integration of adherence. Results: The program was tested in a first episode clinic in Quebec city. Mean retention rate was 87%. A total of 30 patients participated to the workshops. Patients particularly appreciated the use of videotapes testimonies to discuss together their perception of treatment. Perception of efficacy, tolerance and knowledge remained unchanged. Proportion of patients with a positive impression according to DAI-10 increased slightly, from 75% to 85% (3). Conclusion: The workshops are now to be implemented at the hospital, Institut Universitaire en Santé Mentale de Québec. Steps yet to be accomplished include the elaboration of a formal program assessment and its implementation at the hospital. This initiative has gathered professionals from different perspectives of treatment, ie, pharmacists and psychologists. It represents a unique occasion to develop new skills in supporting adherence in an original intervention.

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ID: 980014

ROLE OF M4 MUSCARINIC CHOLINERGIC RECEPTORS IN PSYCHOSTIMULANT-MEDIATED EFFECTS IN MICE

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Background: Many central actions of acetylcholine are mediated by muscarinic (M1–M5) receptors and disturbances in the central muscarinic cholinergic system have been implicated in several pathophysiological conditions, including schizophrenia and drug addiction, conditions that involve the dopaminergic system. Behavioral and neurochemical studies of M4 receptor knockout mice have shown that the M4 receptor subtype plays an important role in the regulation of dopamine neurotransmission. Methods: Locomotor activity measurements and microdialysis were used to investigate cocaine-induced hyperlocomotor activity and cocaine-induced striatal dopamine release, respectively in fully back-crossed M4 receptor knockout mice. We also investigated the effect of a potent and selective allosteric potentiator of M4 receptors (VU0152100) on locomotor activities and striatal dopamine release in wild type mice. Results: Enhanced cocaine-induced locomotor activity and enhanced cocaine-induced striatal dopamine release was observed in M4 knockout mice. In accordance with this observation, the selective allosteric potentiator of the M4 receptor, VU0152100 inhibited cocaine-induced hyperactivity and striatal dopamine release in wild type mice. Conclusion: The present data suggest that the M4 muscarinic receptor is a possible new target in the medical treatment of psychosis and drug addiction.

ID: 979667

DECONSTRUCTING CLOZAPINE: TOWARD MEDICATION DEVELOPMENT FOR ALCOHOLISM IN SCHIZOPHRENIA

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Background: While typical antipsychotic medications such as haloperidol (HAL) do not limit alcohol use in patients with schizophrenia, our studies and those of other groups suggest that the atypical antipsychotic clozapine (CLOZ) does limit alcohol drinking in these patients. We have proposed that CLOZ's ability to decrease alcohol drinking relates to its broad pharmacologic profile, which includes weak dopamine (DA) D2 receptor antagonism, potent norepinephrine (NE) alpha-2 receptor antagonism, and the ability to increase NE levels in both plasma and brain. In order to understand more fully the actions of CLOZ in patients with schizophrenia, we have tested the ability of CLOZ (and other medications and medication combinations) to limit alcohol drinking in the Syrian golden hamster, an out-bred rodent that, like patients with schizophrenia, drinks steady yet moderate amounts of alcohol. Methods: Hamsters were either acclimated to alcohol drinking and then treated chronically with medications, to examine drug effects on chronic, established drinking patterns, or pretreated with medications and then introduced to alcohol, to examine drug effects on the initiation of drinking behavior. Results: While CLOZ dramatically and persistently decreased alcohol drinking in the hamster, HAL did not alter alcohol drinking, and the atypical antipsychotic risperidone (RISP) produced a transient decrease in alcohol drinking. Adding the potent DA D2 receptor antagonist raclopride to CLOZ diminished the ability of CLOZ to decrease alcohol drinking, while addition of the NE reuptake inhibitor desipramine (DMI) increased the ability of both HAL and RISP to limit alcohol drinking, more than DMI alone. Conclusion: Data from these experiments suggest that the ability of CLOZ to decrease alcohol drinking may derive, in part, from both a relatively weak DA D2 receptor blockade and its capacity to increase levels of NE in plasma and brain. These findings may contribute to the development of new pharmacologic strategies for the treatment of alcoholism in patients with schizophrenia.

ID: 979294

CARIPRAZINE, A D_3-PREFERRING DOPAMINE D_3/D_2 RECEPTOR PARTIAL AGONIST ANTIPSYCHOTIC CANDIDATE DEMONSTRATES ANTI-ABUSE POTENTIAL IN RATS

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Background: Cariprazine, a D_3-preferring Dopamine D_3/D_2 Receptor Partial Agonist is in Phase III clinical development for treatment of schizophrenia and bipolar mania. Substance abuse is a frequent comorbidity of both disorders. Dopamine D_3/D_2 receptor partial agonists showed anti-abuse efficacy in animal models of drug taking, attenuating relapse to cocaine seeking (1,2). We explored the anti-abuse potential of cariprazine at pharmacologically active antipsychotic doses in 2 cocaine abuse models in rats; D_2/D_3 partial agonists aripiprazole and bifeprunox were used as comparators. Methods: In the continuous cocaine self administration (SA) paradigm, rats previously trained in operant boxes to stably self-administer i.v. cocaine were challenged with cariprazine, aripiprazole, bifeprunox, haloperidol or 7-OH-DPAT and the number of cocaine self-infusions was measured. In a cue-induced relapse to cocaine seeking paradigm, stably cocaine self-administering rats were kept for 2 weeks without cocaine and its cues. During relapse tests, rats were treated with aripiprazole, bifeprunox or car-

iprazine, placed in the operant boxes in the presence of cues but without cocaine availability and the number of lever presses was recorded as a measure of cocaine-seeking. Antipsychotic-like activity of the compounds was assessed by inhibition of amphetamine-induced hyperlocomotion. Results: In the cocaine SA method, the D_2 antagonist haloperidol (0.25 mg/kg PO) significantly increased, while the D_3/D_2 agonist 7-OH-DPAT (0.1 mg/kg SC) significantly attenuated SA. Cariprazine, aripiprazole and bifeprunox dose-dependently increased SA reaching significance at the doses of 0.17, 3.0 and 0.1 mg/kg PO, respectively. In the relapse model, cariprazine, aripiprazole and bifeprunox dose-dependently inhibited cocaine-seeking with ED_{50} values of 0.2, 4.0 and 0.17 mg/kg PO, respectively. By comparison, the potency of these compounds in the amphetamine assay was 0.12, 3.9 and 0.09 mg/kg PO, respectively. Conclusion: These results indicate that dopamine D_3/D_2 receptor partial agonists such as cariprazine reduce the rewarding effect of cocaine in rats on a continuous SA regimen. These compounds can also potently attenuate cocaine-seeking. Cariprazine may have antiabuse potential in addition to its antipsychotic and antimanic efficacy.

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ID: 976933

USE OF EX VIVO TARGET OCCUPANCY TO IDENTIFY SELECTIVE BRAIN PENETRATING INHIBITORS OF CASEIN KINASE 1 DELTA

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Background: While kinases represent an attractive class of molecules for pharmacological intervention, developing highly selective, potent, brain-penetrating kinase inhibitors with desirable pharmacokinetic properties for treating neurological diseases poses notable challenges. To help facilitate identification of such inhibitors of the circadian gene Casein Kinase 1 delta (CK1d), we employed in vitro and ex vivo target occupancy (EVTO). Methods: IACUC approved procedures were carried out in compliance with the NIH Guide for the Care and Use of Laboratory Animals (1996). Sprague Dawley rats were dosed subcutaneously with vehicle or test compounds (1–100 mg/kg) 30 minutes prior to euthanasia. The brain regions were rapidly dissected and frozen on dry ice. Trunk blood and half of each brain region were used to determine compound exposure. Homogenized brain extracts were incubated (20 minutes at 4°C) with 1–8nM of ligand (3H-labelled reference CK1d inhibitor) or 10μM non-specific ligand; reactions were stopped by filtration and the amount of specific binding assessed. Some compounds were also evaluated for their ability to induce a phase delay when dosed at zeitgeber time 11. Pilot experiments were performed to determine the optimal experimental parameters for performing in vitro and EVTO. Results: Similar to immunolocalization data, the greatest concentration of CK1d binding was found in the hypothalamus. Binding saturation analyses were performed to assess Kd and Bmax. Compounds were then screened by in vitro TO to assess their ability to bind native enzyme. In vitro compound potencies did not always correlate with EVTO, primarily due to differences in brain penetration. There appeared to be a good correlation between EVTO and in vivo potency. In general, compounds with $\geq$50% relative EVTO produced a 2 hour circadian phase delay. Conclusion: EVTO has facilitated our efforts to assess the relationship between target binding of CK1d inhibitors in the CNS and pharmacokinetics, and is the backbone of our structure-activity relationship (SAR) understanding. While EVTO requires more compound than in vitro TO studies, it has the notable advantage of assessing the relative target binding and brain-penetrating capacity of compounds. Finally, the EVTO studies described here constitute a pre-clinical target biomarker, and provides the groundwork for translation to a PET ligand and assessing the ability of a drug candidate to bind to its target clinically.

ID: 932648

HOW MENTAL HEALTH CLIENTS WITH SCHIZOPHRENIA AND OTHER MAJOR MENTAL ILLNESSES IDENTIFY AND COMMUNICATE TREATMENT PREFERENCES TO CLINICIANS USING A COMPUTERIZED DECISION SUPPORT PROGRAM

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Background: This study tested the feasibility of an online software product ''CommonGround'' used by persons with serious mental illness, the majority with schizophrenia. Computerized decision support tools identify and communicate treatment preferences to clinicians. Prior to appointments clients work within the Decision Support Center (DSC) and are assisted in completing a one-page computer-generated report for use in the medication consultation, are provided access to health-related information via the Internet, and are supported with completing decision aids to address areas of decisional conflict related to medication use. During the 12-month pilot study 189 clients used the program. Methods: Focus groups were conducted with all medical staff and a subset of clients to describe experiences with the DSC. The audiotaped sessions were transcribed and coded to identify themes. Data on utilization and common concerns were aggregated. Results: The medical staff agreed that the one-page report generated by the software helped to create efficiencies in the consultation, helping them focus more quickly on clients' concerns. They observed that there were a number of instances in which clients were willing to disclose information via the computer not previously disclosed in face-to-face assessments. They noted that the software program acted as assistive communication technology for clients who were experiencing acute psychosis, organizing clients' concerns into a succinct report at a time when clients could not organize their story orally. Medical practitioners felt that it helped to build their skills in shared decision making and helped to activate clients' involvement in the consultation. Scheduling and supporting clients to arrive at the DSC 30 minutes before seeing the prescriber were the most significant organizational challenges in implementing this intervention. In client focus groups, the software's 3-minute recovery vignettes were a popular feature that helped to generate hope. Clients expressed that the program helped to amplify their voice and ensure that their concerns were noted and addressed during the busy consultation. They valued gauging their progress over time using the numeric scales on the one-page report. Patterns of utilization and common concerns will also be described. Conclusion: This study demonstrates that decision support technology can be incorporated into psychiatric medication clinics, with promise for widespread utilization in routine mental health settings.

ID: 976901

NMDA-INDUCED DOPAMINERGIC INSTABILITY, COGNITIVE DYSFUNCTION AND GLUTAMATE-BASED TREATMENT APPROACHES FOR SCHIZOPHRENIA

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Background: *N*-methyl-D-aspartate (NMDA) dysfunction plays a critical role in the pathophysiology of schizophrenia, and contributes to instability

of both subcortical dopaminergic systems leading to positive symptoms, as well as to impaired cortical function leading to negative symptoms and cognitive deficits. Over recent years, increasingly specific biomarkers of cognitive dysfunction in schizophrenia have been developed. The present studies investigate effects of NMDA antagonists on dopaminergic and glutamatergic models of schizophrenia, and as a model system for glutamatergic drug development. Methods: Dopaminergic function was studied using both microdialysis and PCP-induced hyperactivity in normal and serine racemase knockout (SRKO) mice. Cognitive effects of NMDA antagonists were assessed using intracranially recorded mismatch negativity (MMN) and N1 refractoriness in rats, and auditory 40 Hz response in mice. Results: PCP effects on dopaminergic function were reversed by novel glycine transport inhibitors, as well as by a combination of D-serine and a D-amino acid oxidase inhibitor. Levels of D-serine achieved during preclinical rodent studies were significantly higher than those achieved in recent clinical trials of D-serine, suggesting need for combined treatment strategies. SRKO mice also showed dopaminergic metabolic disturbance in vivo but not in vitro, suggesting alteration in local NMDA function. Subchronic (2 week) PCP treatment led to reduction in MMN generation over time, which was prevented/reversed by simultaneous subchronic treatment with glycine. Studies with combined D-serine/DAAO inhibitor treatment are ongoing. Conclusion: Dopaminergic instability in schizophrenia may reflect underlying disturbance in local and distributed NMDA function. The ability of NMDA-based treatments such as D-serine or high-affinity glycine transport inhibitors to reverse dopaminergic instability supports recent clinical studies showing effectiveness vs. positive as well as negative symptoms of schizophrenia. Pathophysiological biomarkers of schizophrenia, such as MMN, may also be induced in subchronic NMDA antagonist treatment models of schizophrenia and reversed by NMDA-based treatment approaches, suggesting utility in developing cognition-enhancing compounds in schizophrenia. Finally, addition of DAAO inhibitors may significantly ameliorate beneficial effects of D-serine in schizophrenia.
Funding: R01DA03383, P50MH086385
ID: 979186

NICOTINE ENHANCES AUTOMATIC TEMPORAL PROCESSING AS MEASURED BY THE MISMATCH NEGATIVITY WAVEFORM IN INDIVIDUALS WITH SCHIZOPHRENIA

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Background: Nicotine can improve sustained attention, processing speed, simple motor functioning and working memory. Little is known, however, of whether nicotine can enhance temporal processing, a process important for the moment to moment timing of activities, the sequencing of behaviors, and attention. Mismatch negativity (MMN) has been utilized as a physiological measure of automatic temporal processing, and in an initial study in healthy controls, nicotine enhanced mismatch negativity amplitudes from baseline recording to post-drug recording greater than in the placebo condition. Deficits in temporal processing have been documented in schizophrenia. Because nicotine is a cholinergic agonist, and because administration of this drug has been shown to improve other cognitive functions in these individuals, the present study was designed to test whether nicotine leads to improvements in temporal processing in this population. Methods: Twelve subjects participated in a 2 visit single-blind placebo-controlled cross-over study of the effect of nicotine on MMN indices in response to an interstimulus-interval deviant. Results: Nicotine enhanced mismatch negativity amplitudes from baseline recording to post-drug recording greater than in the placebo condition. Conclusion: This is the first study to demonstrate a nicotine related enhancement of mismatch negativity amplitude to an interstimulus-interval duration deviant in individuals with schizophrenia and confirms our hypothesis that nicotine enhances pre-attentive temporal processing. Nicotinic agonists may represent a potential therapeutic option for individuals with abnormalities in early sensory or temporal processing related to cholinergic system abnormalities.
ID: 979660

SUBCORTICAL/CORTICAL EFFECTS OF MODAFINIL DURING COGNITIVE CONTROL IN SCHIZOPHRENIA

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Background: Cognitive deficits are a core feature of illness in schizophrenia; they predate overt illness onset, persist during periods of symptom remission, and are strong predictors of long-term functional outcome. Critically, they are not effectively treated with the current antipsychotic pharmacopoeia. We used the combined NET/DAT inhibitor modafinil to test whether modulation of catecholamine systems is effective to remediate the altered function of the cortical/subcortical cognitive control network in schizophrenia. Methods: 27 clinically-stable patients with DSM-IV-TR-defined schizophrenia participated in a randomized, double-blind, counterbalanced, placebo-controlled within-subjects study of modafinil, administered as a single oral 200 mg dose. Patients were scanned on a 3T MRI while they performed the Preparing to Overcome Prepotency (POP) Task, a cued visual stimulus-response mapping task requiring proactive control, with a slow event-related design. Results were evaluated within this group, and compared with a healthy control group who participated in the identical protocol and data analysis procedures. Results: Patients improved performance on drug vs. placebo. Patients showed significant task-independent deactivation in the locus coeruleus (LC) and the substantia nigra/ventral tegmental area (SN/VTA), with some evidence of Treatment-by-Task effects to increase prefrontal cortex (PFC) activity. Compared with the control group, the patient group showed A) excessive cue-independent deactivation in VTA and striatum; B) attenuated cue-independent deactivation in LC; C) impaired Treatment-by-Condition increases in both VTA and LC to the Cue; D) greater Treatment-by-Condition increases in VTA to the Probe; E) a varied set of increases and decreases throughout the PFC, as a function of Treatment-by-Condition in the patient group relative to controls, both to Cue and Probe. Conclusion: Modafinil modulates the subcortical catecholamine nuclei giving rise to ascending systems that modulate the PFC. While these effects coincide with increased Treatment-by-Condition activity in the PFC (suggestive of enhanced gain control) and enhanced performance, they are altered in patients compared with healthy controls. This pattern is consistent with the underlying effects of chronic antipsychotic treatment on catecholamine neuron firing. Further work should directly address this problem to establish the optimal conditions for pro-cognitive drug action in schizophrenia.
ID: 979876

EFFECTS OF PREGABALIN ON THE BEHAVIORAL ALTERATIONS INDUCED BY KETAMINE IN RATS

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Background: The study of alternative pathways that could be involved in the pathophysiology of schizophrenia involves the use of substances that modulate neurotransmission in other pathways besides dopamine. Scientific attention has been drawn by other receptor systems like glutamate, GABA, and serotonine. Pregabalin is a new antiepileptic drug, a different GABAergic agent, acting as a ligand of α2δ type 1 and 2 subunits of voltage-gated calcium channels. The aim of this study was to investigate the effects of pregabalin on the behavior of mice under the influence of ketamine, an NMDA antagonist that mimics the positive, negative, and cognitive symptoms of schizophrenia. Methods: Rats were injected with saline or 25 mg/kg ketamine, intraperitoneally (i.p.) at a volume of 1 ml/100 g, then behavior modifications were evaluated, by the evaluation of stereotypy, hyperlocomotion and elevated plus maze task, after these rats have been treated with pregabalin (at doses of 30 mg/kg or 100 mg/kg) or placebo (saline solution, i.p.). Results: The administration of pregabalin after ketamine infusion was related to reduced hyperlocomotion indices: the group that received pregabalin 30 mg/kg had a mean value of 22.234 mm, and the group that received pregabalin 100 mg/kg had a mean value of 20.283 mm, ($F = 5{,}868$; $P < .0001$). Pregabalin was effective in preventing ketamine induced stereotypy at both doses, at 30mg/kg ($F = 4{,}242$; $P < .05$) and 100 mg/kg ($F = 4, 932$; $P < .036$). At the elevated plus maze task, the use of pregabalin did not showed differences when compared with placebo. Conclusion: This is the first study to investigate the effects of pregabalin using an animal model of psychosis. Our results indicate that behavioral changes induced by ketamine in rats can be reversed with the use of pregabalin, which highlights the importance of investigating the effects of this new drug in greater depth and of looking beyond the dopamine model of schizophrenia in the search for more effective treatment strategies.

ID: 986930

CONTRIBUTION OF IMPAIRMENT IN TOP-DOWN PROCESSING TO THE PSYCHOTOMIMETIC EFFECTS OF DELTA-9-TETRAHYDROCANNABINOL

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Background: Schizophrenia is characterized by a disruption in top-down processing. Delta-9 tetrahydrocannabinol (THC) has been shown to induce a range of schizophrenia-like effects in healthy controls and exacerbate symptoms in individuals with schizophrenia. However the extent to which a disruption in top-down processing contributes to the psychotomimetic effects of THC is not known. The purpose of the study was to assess the effects of THC on top-down processing using the McGurk task. Methods: The data was collected as part of a number of ongoing double-blind, placebo-controlled, randomized, cross-over trials of THC in adult healthy subjects. Subjects received both a high dose of intravenous THC (0.03 mg/kg) or low dose(0.015 mg/kg) or placebo. Several tasks of top-down processing were studied in a pre- post fashion, both before and 15min after the THC/Placebo infusion. The McGurk task, a test of auditory and visual integration was the principal measure. In addition, data was collected using the "Babble task," the "Thatcher Illusion" and "Reading the Mind in the Eyes task." The psychotomimetic effects of THC were measured using the Positive and Negative Syndrome Scale (PANSS) and the Clinician Administered Dissociative Symptom Scale (CADSS). The subjective effects of THC were measured using a Visual Analogue Scale (VAS). Data was available for 8 test days (THC = 4, Placebo = 4) and was analyzed using SPSS. Results: THC resulted in a greater disruption of top-down processing as measured by "change from baseline" scores on the McGurk task than placebo. The postinfusion total score on the McGurk task and individual scores on "Ba" and "Ga" sub-tasks were lower in the THC group reflecting impaired auditory-visual integration with THC. Changes in measures of top down processing correlated with changes in psychosis and perceptual alterations. Conclusion: Preliminary data from ongoing studies suggest that THC disrupts top-down processing as measured by the McGurk task and this impairment correlates with the psychotomimetic and subjective effects of THC. The relevance of these findings to the psychotomimetic effects of cannabinoids will be discussed.

ID: 979543

MODULATION OF BDNF EXPRESSION AFTER CHRONIC TREATMENT WITH THE NOVEL ANTIPSYCHOTIC LURASIDONE IN RATS: BASAL CHANGES AND STRESS RESPONSIVENESS

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Background: Although rapid control of schizophrenia symptoms by antipsychotics (APDs) depends on their ability to modulate neurotransmitter function, it is now generally accepted that neuroadaptive changes taking place following repeated administration of APDs may be relevant for the improvement of core disease symptoms (such as cognitive deficits). Long-term APD treatment leads to a variety of cellular changes that may boost neuronal plasticity. Within this context, a potential target is represented by neurotrophic factors, such as the neurotrophin BDNF, which plays a crucial role in neuronal plasticity and cellular resiliency. Methods: In the present study we have investigated the ability of sub-chronic treatment with the novel APD lurasidone (10 mg/kg) to modulate BDNF expression in hippocampus and prefrontal cortex, 2 brain structures that play a central role in schizophrenia dysfunction. We also evaluated whether treatment with lurasidone could alter the rapid modulation of the neurotrophin after an acute stress, a major precipitating element in psychiatric disorders. Results: We found that chronic lurasidone treatment increases the expression of BDNF in rat prefrontal cortex (+41%, $P < .01$) and, to a lesser extent, in hippocampus (+27%, $P < .05$). We also found that rats that have been chronically treated with lurasidone show a selective enhancement of BDNF mRNA levels in hippocampus when exposed to an acute swim stress (+92%, $P < .05$ vs. unstressed animals). Basal and stress-induced changes of BDNF are due to the modulation of different neurotrophin transcripts suggesting that different intracellular mechanisms may contribute to such effects. One interesting finding,

which emerged from this analysis, is the significant increase of exon IV mRNA levels in the prefrontal cortex of animals treated with lurasidone and exposed to the acute swim stress (+36%, $P < .01$): It may be inferred that prolonged exposure to the novel APD lurasidone leads to a facilitation of activity-dependent exon IV transcription, which may represent a coping response set in motion following exposure to the challenging condition. Conclusion: Our data suggest that adaptive changes produced by repeated treatment with lurasidone may contribute to the amelioration of functional capacities, closely associated with neuronal plasticity, which are deteriorated in patients with schizophrenia, bipolar disease and depression. Further studies will need to be done to determine the functional implications of these findings.
ID: 976705

IMPAIRMENT OF TIME ESTIMATION AND REPRODUCTION BY DELTA-9-TETRAHYDROCANNABINOL

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Background: Delta-9-tetrahydrocannabinol (THC) has been shown to induce a range of schizophrenia-like effects in healthy controls and to exacerbate symptoms in schizophrenia patients. A change in the subjective passage of time is a characteristic finding in schizophrenia, and has in turn been related to deficits in working memory and attention. Similarly, alterations in temporal processing have also been observed with cannabis intoxication. The aim of this study was to characterize the effects of THC (the principal active ingredient of cannabis) on temporal processing and relate these effects to the psychotomimetic effects of THC. Methods: These data were collected as part of 4 ongoing double-blind, placebo-controlled, randomized, cross-over trials of THC in 33 adult healthy subjects. Subjects received placebo ($n = 31$), low-dose (0.015–0.018 mg/kg; $n = 17$), medium-dose (0.03–0.036 mg/kg; $n = 12$), or high-dose (0.05 mg/kg; $n = 10$) THC intravenously. A temporal processing task consisted of 5 trials during which the subject had to estimate and also reproduce time periods ranging from 5 seconds to 30 seconds at baseline, during the period of maximal drug effect, and again after drug effects had ended. A second, longer task required that subjects estimate a time interval ranging from 7.5 to 20 minutes. All tasks were performed in the presence of a distractor. Psychotomimetic effects of THC were measured using the Positive and Negative Syndrome Scale (PANSS) and the Clinician Administered Dissociative Symptom Scale (CADSS). The subjective effects of THC were measured using a Visual Analogue Scale (VAS). Data were analyzed using SPSS. Results: Time estimation in the seconds range was impaired, with estimated times exceeding actual by 13%–39%. Time estimation in the minutes range was likewise impaired, with estimated times exceeding actual by 5%–10%. Both of these results indicate a speeding up of the "internal clock." Time production was impaired with produced times less than actual by 8%–10%, again indicating a speeding up of the "internal clock." These impairments correlated with the psychotomimetic and subjective effects of THC. Conclusion: These findings shed light on the overlap between the temporal processing deficits observed in schizophrenia and those produced by cannabinoids.
ID: 980025

EFFECTS OF LOW DOSE RISPERIDONE ON NEUROCOGNITIVE, CLINICAL AND SOCIAL FUNCTIONING IN SCHIZOTAXIA: RESULTS FROM THE CHANGSHA STUDY

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Background: The Changsha study identifies adult, non-psychotic relatives of patients with schizophrenia who show deficits in neurocognitive, social, clinical and other dimensions, and who meet proposed diagnostic criteria for a liability syndrome for schizophrenia ("schizotaxia"). In this study, we investigated whether a low dose (2.0 mg) of risperidone, a second generation antipsychotic medication, could attenuate negative symptoms, neurocognitive deficits, and other measures of clinical and social function in subjects who met our research criteria for schizotaxia. Methods: One hundred eighty nine relatives were assessed at the Mental Health Institute, Second Xiangya Hospital of Central South University, Changsha (Hunan Province, China), between December 2006 and December 2008. Eighty six of these individuals met criteria for schizotaxia, and 36 agreed to enter a 6-week, double-blind, placebo-controlled protocol. Results: Side effects of risperidone were mild. ANCOVAs using age and gender as covariates showed significant improvement in the risperidone group ($n = 20$) on neurocognitive function (Wisconsin Card Sorting Test Total Errors and Perseverative Errors) and on a self-report measure of social function (Social Adjustment Scale), compared with the placebo-control group ($n = 16$). Effect sizes were small to medium. Notably, risperidone effect sizes were larger (medium to large) in a subset of subjects (risperidone = 15; placebo = 10) whose membership in the schizotaxic group was confirmed by cluster analysis. Negative symptoms did not decline significantly in either analysis. Conclusion: The results are generally consistent with previous open-label investigations of risperidone administration in subjects with schizotaxia, and provide evidence that significant neurocognitive and clinical problems are amenable to remediation in non-psychotic relatives of people with schizophrenia.
ID: 979778

THE NICOTINE METABOLITE, COTININE, IMPROVES PERFORMANCE OF A 5 CHOICE SERIAL REACTION TIME TASK (5C-SRTT) IN RATS AND ATTENUATES GLUTAMATE (NMDA) ANTAGONIST-RELATED IMPAIRMENTS

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Background: It is well documented that a significant percentage of schizophrenia patients are heavy cigarette smokers, thus exposing themselves to considerable quantities of the tobacco alkaloid, nicotine, as well its most predominant metabolite, cotinine. Cotinine has a pharmacological half-life (15–19 hour) that greatly exceeds nicotine (2–3 hour) and accordingly, heavy smokers typically maintain significantly higher plasma levels of cotinine than nicotine over the course of a 24 hour day. However, until recently, few studies had been conducted to systematically characterize the neuropharmacological and behavioral effects of cotinine. Previous work in

our laboratories indicated that cotinine improves prepulse inhibition of the auditory startle response in rats (in pharmacological impairment models relevant to schizophrenia) and that it improves working memory in non-human primates. The objective of the experiments described here was to test the hypothesis that cotinine improves sustained attention in rodents and attenuates the deficits in performance induced by glutamate (NMDA) antagonists (ie, studies potentially reflective of cognitive deficits observed in schizophrenia). Methods: Cotinine (dose range 1.0–3.0 mg/kg s.c.) was initially evaluated in a variable stimulus duration version of the 5 choice serial reaction time task (5C-SRTT). Subsequently, cotinine (dose range 0.03–1.0 mg/kg s.c.) was evaluated for its ability to attenuate MK-801-related impairments in performance in the standard (single, 5 seconds stimulus duration) version of the task. Results: Depending on dose, cotinine improved deficits in the performance of the 5C-SRTT induced by the presentation of variable stimulus durations. Moreover, cotinine effectively attenuated MK-801-related impairments in accuracy and it increased the number of completed trials. Cotinine did not significantly affect the increases in premature responses elicited by MK-801 and it did not affect response or reward latencies. Conclusion: These animal data suggest that schizophrenic patients who smoke may be self-medicating deficits in attention (ie, with nicotine and/or cotinine) and they also support the argument that cotinine could serve as a prototype for the development of new drugs used to treat the attentional deficits associated with schizophrenia.
ID: 978771

22. Therapeutics: Treatment Trials

STUDY QUALITY ASSESSMENT FOR PLACEBO-CONTROLLED RANDOMIZED TRIALS IN SCHIZOPHRENIA CONDUCTED 1966–2009

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Background: Diminished drug-placebo differences have been observed in recent psychiatric clinical trials. Variations in study quality can substantially affect the likelihood of detecting efficacy signals in these studies. We searched the MEDLINE database for double-blind, placebo-controlled RCTs in schizophrenia published 1966–2009, and reviewed 63 publications as a basis for this quality rating analysis. Methods: Study quality was evaluated using a rating checklist system developed for RCTs by AHRQ (1). The checklist contains 10 domains: 7 key items are worth 2 points each for scoring purposes (study populations, randomization, blinding, interventions, outcomes, statistical analysis, and funding sources), 3 non-key items are each worth 1 point (study questions, results, and discussions) and the maximum score is 17 (100%). The relationships between study quality factors and dropout rate with placebo response were also investigated using meta-regression analysis. Placebo response was defined as mean change from baseline in BPRS total score (derived from PANSS in 11 studies). Results: The overall mean study quality rating score was 15 (SD 1.4), with lower mean score observed in studies published before 1990 ($P < .01$). Forty-nine articles (79%) did not meet the randomization standard (specifying the use of adequate concealment and sequence generation methods). The outcomes quality criteria were derived from best practices (specifying primary/secondary outcome measures); only 36 (58%) studies met the criteria. Forty-one (65%) articles provided detailed funding and sources of support. The majority of studies provided adequate, clear information on interventions (94%), study population (94%), discussion (98%), results (100%), and study hypothesis (100%). All 36 articles meeting the outcomes criteria were published during 1989–2009, and showed relatively larger placebo response ($P < .05$). When incorporating the quality score in the meta-analysis of placebo response, the effect size was estimated to be −0.25 compared with −0.3 in an unadjusted analysis. Smaller placebo response was observed in studies with higher completion rate ($P < .05$). Conclusion: Our findings confirm that large study quality differences in psychiatric clinical trials exist, especially in the areas of randomization, outcomes, and funding support sources. These factors are critical for bias reduction, trial reproducibility, decreasing variability, and hence improving the likelihood of detecting a treatment effect if one truly exists.
ID: 977481

A NON-PHARMACOLOGICAL INTERVENTION FOR WEIGHT GAIN MANAGEMENT FOR PATIENTS WITH SCHIZOPHRENIA: MULTICENTRIC, RANDOMIZED CONTROLLED CLINICAL TRIAL - ARE MODEST EFFECTS IMPORTANT FOR CHALLENGING OUTCOMES?

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Background: Patients with schizophrenia are more likely to be overweight or obese, in comparison to the general population. Strategies for weight gain management that have been proven effective in clinical trials include regular check-ups, lifestyle and medication counseling, medication assessments, behavioral control programs, and pharmacological intervention. Objectives: Evaluate the efficacy of a non-pharmacological intervention in weight gain management. Methods: A multicentric randomized clinical trial was conducted comparing schizophrenic patients on intervention vs. patients on a standard care group. Patients concerned with weight gain were included in this study and received a 12-week 1-hour group intervention. The intervention was focused in nutrition counseling, lifestyle, physical activity and self-esteem. Weight, waist circumference, blood pressure, fasting blood glucose, total cholesterol, HDL and LDL cholesterol, triglycerides and insulin were measured before the intervention, and after 3 and 6 months. Treatment as usual including antipsychotic drugs and/or mood stabilizers was maintained. Data were analyzed using intent to treat (ITT). Results: 160 patients were enrolled in the study (81 intervention × 79 standard care), 60% female, 36.3 (SD: 9.9) years, 78.8% single, and 56.2% with 9–11 years of study. After 3 months intervention group lost 0.48 kg (DP: 2.8), and standard care gained 0.48 kg (DP: 3.18) ($t = -1.938$, 144 gl, $P = .05$). After 6 month, intervention group lost 1.15 kg (DP: 4.2), ADN standard care gained 0.01 kg (DP: 4.6) ($t = -2.4$, 144 gl, $P = .01$). Conclusion: Patients that participated on intervention presented a small weight loss after 3 and 6 months, with questionable impact on health. Further studies are necessary with longer periods of follow up, because the results suggest a trend of those patients to improve the anthropometric profile.
ID: 978884

MONEY FOR MEDICATION: A RANDOMIZED CONTROLLED STUDY ON THE EFFECTIVENESS OF FINANCIAL INCENTIVES TO IMPROVE MEDICATION ADHERENCE IN PATIENTS WITH A PSYCHOTIC DISORDER AND CO-MORBID SUBSTANCE ABUSE

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Background: Non-adherence to antipsychotics is often problematic, particularly among patients with psychotic disorders and co-morbid substance abuse. In a pilot-study, our study-group investigated the feasibility and possible effects of providing financial incentives for acceptance of antipsychotic depot-medication: Money for Medication. Aim: In a randomized controlled trial we will more thoroughly assess both the effectiveness and side-effects of Money for Medication. The primary aim is to improve adherence to antipsychotics in patients with psychotic disorders and substance abuse. Methods: 168 patients will be randomly assigned to the Money for Medication group ($n = 84$) or the control group ($n = 84$) during 12 months. The latter will receive treatment as usual without financial rewards. Effects of discontinuing the intervention will be monitored during 6 months follow-up. Outcome measures include: depot acceptance (during and after the intervention, the longest period of uninterrupted depot acceptance, time expired before the depot is taken, effort of clinicians, attitudes towards medication and intervention), psychosocial functioning (including number and days of admissions, symptomatology, substance use, side-effects, and quality of life), and cost-utility. Results: Pilot-study ($n = 5$). In the year financial rewards were offered, the percentage accepted depots of 5 patients increased from 44% to 100%. While patients were hospitalized for an average of 100.2 days in the previous year, only 1 was re-admitted for 17 days during the intervention-year. Conclusion: Our pilot-study revealed

a large effect of Money for Medication on medication acceptance and hospitalizations. A randomized controlled trial is currently being executed to further assess the effectiveness of this intervention.
ID: 979832

A RANDOMIZED CONTROLLED TRIAL OF INTEGRATED MOTIVATIONAL INTERVIEWING AND COGNITIVE BEHAVIOR THERAPY (MI-CBT) FOR PEOPLE WITH A SCHIZOPHRENIA DIAGNOSIS AND SUBSTANCE MISUSE - THE MIDAS TRIAL

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Background: The aim of the study was to evaluate the effectiveness of integrated MI-CBT in addition to standard care for patients with psychosis and a co-morbid substance use problem in a 2-center, open, rater-blind randomized controlled trial in UK Secondary Care setting. Methods: The psychological therapy consisted of "motivation building" and "action" phases, the latter phase supporting and facilitating the patient in making changes using CBT approaches drawn from both the psychosis and substance use evidence base. The primary outcome was death from any cause or admission to hospital in the 12 months after therapy. Secondary outcomes included substance use, readiness to change, perceived negative consequences of use, psychotic symptom ratings, number and duration of relapses, global assessment of functioning and deliberate self harm, at 12 and 24 months. Analysis was by intention-to-treat with robust treatment effect estimates. Results: 327 patients with clinical diagnoses of schizophrenia, schizophreniform or schizoaffective disorder and DSM-IV diagnoses of drug and/or alcohol dependence or abuse were randomly allocated to integrated MI-CBT or standard care. There was no beneficial treatment effect on hospital admissions/ death during follow-up. For secondary outcomes there was no treatment effect on frequency of substance use or perceived negative consequences, but a statistically significant effect of therapy on amount used per substance-using day. There was a statistically significant treatment effect on readiness to change use at 12 months not maintained at 24 months. There were no treatment effects on assessed clinical outcomes. There was a statistically significant treatment by subgroup interaction on the percentage of days abstinent for those using alcohol alone compared with other participants. Conclusion: We conclude that up to 26 sessions over 1 year of the therapy was successful in engaging patients in treatment and did improve patients' motivation to make changes in their substance use. Motivation for change waned after the treatment period finished, but there was an improvement in severity of substance use which was maintained over 2 years' assessment. There is some indication that the treatment may be more effective at reducing the substance use for those who use alcohol only. However, MI-CBT does not improve outcome in terms of hospitalization, symptom outcomes or functioning and thus it remains unclear how best to improve clinical outcomes for this client group.
ID: 979462

EFFECT OF A MOTIVATIONAL INTERVENTION ON EXERCISE BEHAVIOR IN PERSONS WITH SCHIZOPHRENIA SPECTRUM DISORDERS (SSDS)

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Background: Death rates from diabetes, respiratory/cardiovascular, and other obesity-related illnesses are significantly higher among the over 2 million Americans with schizophrenia, schizoaffective disorder and schizophreniform disorder (SSDs) than in the general population. Yet, despite the well-known benefits of exercise and the health dangers associated with obesity, persons with SSDs rarely exercise and few interventions to promote exercise have been tested. Although studies have demonstrated that exercise can improve health in this population, few studies have attempted to modify actual exercise behavior. Methods: Ninety seven outpatients with SSDs were randomly assigned to the Walk, Address Sensations, Learn About Exercise, Cue Exercise Behavior for SSDs (WALC-S), a motivational intervention designed to increase exercise behavior (n =48), or a time and attention control group (TAC, n =49). WALC-S and TAC groups met weekly for 4 weeks; then a 16 week walking program was offered to all subjects. We compared the exercise attendance, persistence and compliance of the groups during the walking program. Results: WALC-S recipients attended more walking groups, for more weeks and walked more minutes than those receiving TAC. Percent of WALC-S or TAC groups attended was significantly correlated with overall attendance (r = .38, P = .001), persistence (r = −.29, P = .01), and number of minutes walked during months 2–4 (r = .34, P = .01; r = .34, P = .01 and r = .30, P = .01 respectively). Conclusion: This study is among the first to examine interventions designed to enhance exercise motivation in SSDs, and is a critical first step toward our ultimate goal of developing practical, effective exercise interventions for widespread use.
ID: 927574

CELLULAR TELEPHONE USE IN SCHIZOPHRENIA SPECTRUM DISORDERS (SSDS)

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Background: Cellular telephones provide opportunities for increased communication with psychiatric clients. A handful of studies have documented increased appointment attendance and one study documented significantly increased psychiatric medication compliance in SSDs after land-line telephone intervention. The purpose of this pilot study was to determine the feasibility of using cellular telephone contact to communicate with research participants with schizophrenia spectrum disorders (SSDs = schizophrenia and schizoaffective disorder) in future studies. Methods: Ten outpatients with SSDs were provided cellular telephones for 5 months; trained nurses contacted participants weekly and recorded: numbers of calls to make contact, responses to telephone contacts, reasons for missed calls and problems reported. Nurses used a standardized telephone intervention protocol. Protocol items included treatment adherence, symptoms, interpersonal relationships, substance use/cravings, and an open ended query. Results: Eight persons with schizoaffective disorder and 2 with schizophrenia were enrolled; 5 men and 5 women with an average age of 45 years (range 28–55, SD = 8.3). Seven participants retained telephones until study completion: one lost interest, one sold the telephone and one telephone was stolen. Completers were spoken to an average of 12 times (SD = 4.7); an average of 4 attempts were needed to make contact. Calls ranged from 2–14 minutes in length. 75% of calls were completed during month 1; percentage of calls completed decreased over time. Reasons for missed calls were gathered at the next successful contact. The most common reasons given for missed calls were psychiatric hospitalization and psychotic symptoms. A total of only 6 problems were reported: difficulty retrieving messages, answering or charging the telephone, and problems associated with memory deficits, ie forgetting to take the telephone when leaving home. Conclusion: These preliminary findings indicate that persons with SSDs are willing and able to utilize cellular telephones, and most experienced few problems. Barriers to the use of cellular telephones in this group include lifestyle factors and poor decision making. Researchers and clinicians should consider the use of cellular telephones enhance communication and contribute to a sense of connectedness to others.
ID: 952510

COGNITIVE REMEDIATION WITH WORK THERAPY IN THE INITIAL PHASE OF SUBSTANCE ABUSE TREATMENT

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Background: This presentation will describe a new NIDA-funded study to pilot test a cognitive remediation therapy (CRT) combined with work therapy (WT) as an adjunct to the initial phase of outpatient substance abuse treatment. There is ample evidence of cognitive impairment in the early phase of substance abuse recovery. Cognitive impairment has been associated with poorer substance abuse treatment outcomes and may be remediated through training programs that target these impairments. We have previously reported on favorable outcomes for a model combining CRT with work therapy (WT) for outpatients with psychotic disorders. Our Specific Aims are: 1. Test the feasibility and tolerability of CRT & WT in the early phase of treatment. 2. Obtain effect size for CRT & WT compared with WT alone on a primary substance abuse outcome measure (Percent Days of Abstinenc, PDA) and for secondary outcomes (cognitive, psychosocial, vocational). 3. Examine moderators such as age, substance abuse type, and cognitive status and mediators such as neuropsychological change and adherence to understand mechanisms of treatment effects. Methods: 50 participants who wish to receive WT are randomized into 2 conditions: 25 are assigned to 15 hours of WT plus 5 hours of CRT weekly (CRT+WT) and 25 are assigned to an active control of 20 hours of WT. The active phase will be for 13 weeks. CRT is comprised of repetitive training on a hierarchy of visual and auditory exercises from Positscience. WT involves paid work activity in a placement of their choosing at the medical center. Participants are paid the same hourly rate (half federal minimum wage)for their time in CRT and WT. Comprehensive assessments are performed at intake, 3 months and 6 months. These include substance abuse, cognitive, and psychosocial outcomes as well as adherence to treatment. During the 3 month active phase, participants have weekly urine toxicology screens, breathalyzer tests and PDA assessments, as well as monthly work performance evaluations. Data analyses include random effects regression models, as well as models of moderator and mediator effects on the primary outcome of PDA. If meaningful effects are found, these results will guide a subsequent R01 submission. Results: Tolerability and feasibility of the intervention with the first 10 participants are described. Conclusion: Findings will inform future studies on cognitive remediation for substance abusers in the early phase of treatment.
ID: 979452

THE EFFECTS OF A GROUP BASED BEHAVIORAL APPROACH TO SUBSTANCE MISUSE AND SCHIZOPHRENIA

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Background: Individuals with schizophrenia and other serious mental illness (SMI) have high rates of substance use disorders (SUDs). The combination of SMI and SUD has a profound impact on the course and severity of both mental illness and SUDs, and SUDs stand as an important barrier to recovery for individuals with SMI. Behavioral Treatment for Substance Abuse in SMI (BTSAS) is a group program for treating SUDs that is adapted to meet the needs of individuals with schizophrenia and other SMI. BTSAS includes motivational interviewing, urinalysis contingency, goal-setting, drug refusal and coping skills training, education, and relapse prevention. Cognitive and social deficits are addressed via small group format, highly structured sessions, reducing skills to smaller steps, over-learning of a few basic skills, behavioral rehearsal via role-playing, soliciting input to enhance realism, and providing social pressure during role-plays. Data from a pilot study and a small-scale randomized trial (Bennett, Bellack, & Gearon, 2000; Bellack et al., 2006) suggest that BTSAS is associated with meaningful reductions in substance use and improvements in functioning. Methods: This talk will present findings from a recently completed randomized trial of BTSAS in which a large and diverse sample of individuals with SMI and substance dependence (n = 133) were recruited, assessed, and randomized to receive either BTSAS or a supportive comparison group. Results: While data are currently being readied for analysis, several important domains will be addressed. First, we will describe participants at their entry into the project, including data on background and substance use characteristics, motivation to change, and psychosocial functioning. This information will provide important context in which to understand the many challenges faced by individuals with SMI who attempt to change their substance use. Second, we will examine attendance and treatment retention over the course of the trial, and discuss factors associated with treatment engagement and drop out. Third, we will present outcomes including during-treatment substance use (based on in-session urinalysis data) and substance use and psychosocial functioning at post treatment and follow-up. Conclusion: We will discuss the implications of these findings for engaging individuals with substance dependence in treatment, providing treatment to individuals with SMI and SUDs, and supporting recovery in individuals with SMI.
ID: 979491

PARTIAL OCCUPANCY OF THE GLYCINE TRANSPORTER TYPE 1 IN MONKEY BY RG1678 LEADS TO EFFICACY IN A MODEL OF PREFRONTAL CORTICAL FUNCTION

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Background: Hypofunction of glutamatergic transmission via *N*-methyl-D-aspartic acid (NMDA) receptors has been implicated in the pathophysiology of schizophrenia. The reduced function of NMDA receptor-mediated neurotransmission may be normalized by increasing availability of the obligatory co-agonist glycine at its modulatory site on the receptor, through inhibition of glycine transporter type 1 (GlyT1). A novel and highly selective GlyT1 inhibitor, RG1678, recently demonstrated efficacy against negative symptoms of schizophrenia in a Phase II proof-of-concept trial. Deficient function of prefrontal networks may play an etiologic role in negative symptoms. The effects of RG1678 on performance of a task probing prefrontal functioning were evaluated and related to GlyT1 occupancy, measured by positron emission tomography (PET), in monkeys. Methods: Delayed-match-to-sample (DMTS) experiments were conducted in cynomolgus macaques (n = 7) that received graded doses of RG1678 (0.3–6 mg/kg p.o.) or vehicle. Animals were first presented with a sample stimulus on a touch screen. Following a variable delay of 1–100 seconds, choice stimuli were presented; the correct choice stimulus had to be matched to the sample stimulus. For PET experiments, baboons pre-treated with vehicle or RG1678 (2–12 mg/kg p.o.) received 18–20 mCi [^{11}C]RO5013853 i.v. followed by 90 minutes of scanning using a high-resolution research tomog-

raphy PET scanner. PET data were analyzed using a 2-tissue 5-parameter model, a 1-tissue 3-parameter model, and a graphic reference region method (Logan plot). Results: Acute administration of 1 mg/kg of RG1678 in the DMTS task significantly improved performance at long delays, suggesting that central blockade of GlyT1 by RG1678 enhanced prefrontal cortex function. PET experiments demonstrated high uptake of [^{11}C]RO5013853 in the brainstem, pons, thalamus, and cerebellum. Pre-treatment with RG1678 produced a plasma-concentration-dependent blockade of the tracer in most regions. Plasma concentrations at doses of RG1678 that improved performance in the DMTS task produced occupancy of GlyT1 in the thalamus of ~40%. Conclusion: The GlyT1 inhibitor RG1678 improves prefrontal cortical function in monkeys, as probed by DMTS. A relatively low GlyT1 inhibition seems sufficient to reach optimal effects. Improved prefrontal function may mediate some of the beneficial effects of RG1678 on negative symptoms in schizophrenia.
ID: 976869

ONSET AND PERSISTENCE OF TREATMENT RESPONSE IN SUBJECTS WITH SCHIZOAFFECTIVE DISORDER

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Background: Onset and persistence of a therapeutic response to interventions is an important clinical consideration in treatment selection. Reports on onset of effect with antipsychotics in patients with schizophrenia consistently demonstrate an early therapeutic effect within the first days to weeks of treatment. A report on the persistence of response suggests that active treatment is more likely than placebo to be associated with a persistent response that may occur early or late. To the best of our knowledge, this phenomenon has not been previously studied for schizoaffective disorder. Paliperidone ER is an antipsychotic effective for the psychotic and mood symptoms of schizoaffective disorder. We examined onset and persistence of response patterns with paliperidone ER in subjects with schizoaffective disorder. Methods: Pooled data were from 2 phase 3 international double-blind 6-week trials of subjects with schizoaffective disorder receiving paliperidone ER or placebo. Response was defined as $\geq$30% reduction in Positive and Negative Syndrome Scale total score from baseline (assessed at day 4, weeks 1, 2, 3, 4, 6, or endpoint). Response patterns were defined by persistence (persistent = response at every time point from first response to endpoint for $\geq$2 time points; nonpersistent = other patterns) and onset (early = first response at day 4 to week 2; late = week 3 to endpoint). Between-group differences were evaluated using chi-square tests. Results: A persistent response (early or late) occurred in 52.7% of subjects receiving paliperidone ER and 35.1% receiving placebo ($P < .001$). An early persistent response occurred in 39.1% and 23.9%, respectively ($P < .001$), while a late persistent response occurred in 13.6% and 12.2%, respectively ($P = .659$). A nonpersistent response (early or late) occurred in 16.7% and 14.9%, respectively ($P = .595$). No response occurred over this study period in 25.1% of subjects receiving paliperidone ER and in 40.4% receiving placebo ($P < .001$). Conclusion: These post hoc findings suggest that an early persistent response is more likely to be achieved with paliperidone ER than with placebo in subjects with schizoaffective disorder. Response rates for other patterns were similar between the 2 groups. This differs somewhat from a similarly designed analysis in subjects with schizophrenia where active treatment was more likely associated with a persistent response occurring early or late.
Supported by Ortho-McNeil Janssen Scientific Affairs, LLC
ID: 977793

CLOZAPINE VS. OTHER ANTIPSYCHOTICS FOR SCHIZOPHRENIA AND CO-OCCURRING CANNABIS USE DISORDER

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Background: Cannabis use disorder is common in patients with schizophrenia and is associated with poor outcomes. Data on the role of most atypical antipsychotics for reducing cannabis use in these patients are mixed or negative. However, preliminary reports have shown that the atypical antipsychotic clozapine appears to be associated with decreased cannabis and other substance use in these patients. To confirm previous reports, we conducted a randomized trial of the effects of clozapine compared with other antipsychotics on cannabis use in patients with schizophrenia and co-occurring cannabis use disorders. Methods: Thirty-one patients with a SCID diagnosis of schizophrenia or schizoaffective disorder and current cannabis use disorder were randomized to clozapine or to stay on their current dose of other oral antipsychotic. They were followed weekly for 3 months. Medications known to limit substance use (eg, naltrexone and others) were not allowed. At each visit, cannabis use was measured by blinded raters with the Timeline Followback instrument. Symptoms were measured monthly with the Brief Psychiatric Rating Scale (BPRS). The main outcome, amount of cannabis use per week, was analyzed using longitudinal mixed models. Results: Characteristics of study participants: Of the 31 participants, 24 (77.4%) were male and 26 (83.9%) were Caucasian. The mean age of the participants was 36 +/−10.3 years. The mean number of lifetime psychiatric hospitalizations was 5.9 +/−7.3. The mean total BPRS score was 25.3 +/−8.4. The mean number of cannabis joints smoked per week was 12.3+/−12. The group randomized to clozapine had fewer hospitalizations (2.5 +/−1.7 vs. 9.1+/−9.1). Main outcomes analyses: Data during hospitalization or imprisonment were censored. For the primary analysis only, data were censored for days of missed doses and discontinuation of study medication. Longitudinal models showed that the clozapine group used less cannabis than the other antipsychotic group during the study ($P = .09$). For the intent to treat analysis, similar results were found: patients in the clozapine group used less cannabis than patients in the other antipsychotic group during the study ($P = .10$). BPRS scores did not change over time. Conclusion: This study provides evidence from a randomized, controlled trial that clozapine may limit cannabis use more than continued treatment with other antipsychotics in patients with schizophrenia and co-occurring cannabis use disorders.
ID: 979673

A PILOT STUDY EVALUATING THE COGNITIVE EFFECTS OF RIMONABANT IN PEOPLE WITH SCHIZOPHRENIA

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Background: Rimonabant is a cannabinoid 1 (CB1) antagonist, which is effective in treating obesity in the general population. Human and animal studies suggest that rimonabant may also have significant effects on cognitive function. Methods: We conducted a 16-week, double-blind, placebo-controlled study of rimonabant (20 mg/day) in people with DSM-IV schizo-

phrenia or schizoaffective disorder, who were clinically stable on second generation antipsychotics. Participants had a BMI ≧ 27 kg/m^2 with hyperlipidemia or BMI ≧ 30 kg/m^2, in the absence of current substance abuse/dependence (except nicotine), more than weekly cannabis use, or recent depressive symptoms/suicidality. An exercise and dietary counseling group was offered weekly. We used the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Iowa Gambling Task (IGT), the N-Back task, and a probabilistic learning task (PL) to examine the effects of rimonabant on cognition. Target enrollment was 60; the trial was terminated early due to withdrawal of rimonabant from the European market. Results: Fifteen participants were randomized (7 rimonabant, 8 placebo). Fourteen participants had baseline and end of study neuropsychological data (7 in each group). There was a significant treatment effect for the RBANS total score, with the placebo group showing greater improvement than the rimonabant group (estimated difference [mean ± S.E.): −7.7 ± 3.5; P = .048; effect size = 0.63). There were no significant group differences for any of the RBANS scales, the IGT, or the N-Back task. On the PL task, the rimonabant group demonstrated a trend for improved performance in proportion of correct responses in the 70:30 reinforcement learning paradigm: estimated difference 18.4 ± 8.9 (P = .065, effect size = 1.07). On the same task, the rimonabant group also showed a robust effect on learning based on positive feedback: estimated difference 16.5 ± 5.1 (P = .009, effect size = 1.88). Conclusion: The study results suggest that rimonabant does not have a beneficial effect on generalized cognitive function, but may play an important role in feedback-based paradigms of learning in schizophrenia. Supported by the NIMH 1 R34 MH077839 (P.I.: Robert W. Buchanan), NIDA Contract N01DA59909 (P.I. Deanna L. Kelly), and the Intramural Research Program, NIH, NIDA.
ID: 975922

A RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, FLEXIBLE-DOSE STUDY EXPLORING THE NEUROCOGNITIVE EFFECT OF SERTINDOLE VS. QUETIAPINE IN PATIENTS WITH SCHIZOPHRENIA USING THE MATRICS CONSENSUS COGNITIVE BATTERY (MCCB)

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Background: The neurocognitive effect of 12 weeks treatment with sertindole or quetiapine in schizophrenia patients was explored using the overall composite MCCB™ T score. Methods: A multi-center, randomized, double-blind, parallel-group, active-comparator, flexible-dose study was conducted in 25 centers in the United States in stable schizophrenia outpatients aged 18–55. After a 16 day cross-titration period, patients entered a maintenance flexible dose phase (sertindole 12–20 mg/day; quetiapine 400–600 mg/day). Results: Of the 264 patients treated (sertindole: 131, quetiapine: 133), mean age = 42, 67% were men, 62% were Black, 36% were Caucasian. The MCCB composite T score improved in both treatment groups, changes from baseline were not significant. There were no statistically significant between treatment differences for any cognitive domains (speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, social cognition). There was no strong correlation between MCCB composite T score or domain T scores and Positive and Negative Syndrome Scale, Clinical Global Impression-Severity, Calgary Depression Scale for Schizophrenia, or Heinrich Quality of Life scores. There was no strong correlation between cognition and Global Assessment of Functioning score. There were significant correlations between UCSD Performance-based Skills Assessment total score and cognitive domains, speed of processing (r = .60, P < .05), working memory (r = .64, P < .05), and MCCB composite score (r = .69, P < .05). 66% sertindole patients and 76% quetiapine patients had treatment-emergent AEs. Incidence of treatment-emergent SAEs was low (sertindole 4%, quetiapine 1%). Primary reason for withdrawal was AEs, ~12% in both groups. There was no strong correlation between MCCB composite T score and domain T scores and any EPS scales. Dyskinesia, akathisia and parkinsonism were generally not observed. There were no clinically relevant changes in clinical laboratory values, vital signs or ECG parameters. Conclusion: There was no significant difference between sertindole and quetiapine on cognition (adjusted MCCB composite T score) or functional outcome (UPSA total score) after 12 weeks of treatment. Changes in cognition appear to be independent of improvement of psychopathology and extrapyramidal side effects, while there appears to be a positive correlation between cognition and functional outcome. No new safety concerns were observed with either sertindole or quetiapine
ID: 980789

USE OF DEPOT ANTIPSYCHOTICS IN NON-ADHERENT PATIENTS WITH SCHIZOPHRENIA: A 12-MONTH FOLLOW-UP OBSERVATIONAL STUDY

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Background: The use of depot antipsychotics is a frequent strategy to cope with non-adherence to oral antipsychotics in schizophrenia. The objective of this poster is to describe the patterns of use of depot antipsychotics in patients with schizophrenia who are at risk of non-adherence to oral antipsychotic medication. Methods: A cohort of 597 outpatients was followed for 12 months from the time point their treatment was modified. A full descriptive analysis of antipsychotic treatment was done in those who started a depot formulation. Depot and non-depot patients' baseline characteristics were compared by means of t or Chi-square tests. Results: Ninety-two patients (15.4%) started a depot formulation at baseline (79 risperidone, 7 zuclopenthixol, 6 flufenazine). With respect to the remaining 505 non-depot counterparts, these patients had suffered more prior psychotic episodes, had a worse functional status and a worse attitude towards medication. Other baseline characteristics were similar. After 12 months, 90 (15.1%) relapsed. Fifteen out of 90 who relapsed (16.7%) and 77 out of 507 who did not relapse (15.2%) had started depot antipsychotics. During follow-up, 22 further patients (only 8 following a relapse) started depot antipsychotics (14 risperidone, 5 zuclopenthixol, 3 flufenazine). At study end, 72.6%, 100% and 40.0% of patients who started risperidone, zuclopenthixol and flufenazine at baseline, respectively, were also on oral antipsychotics. Conclusion: Despite non-adherence risk, the use of depot antipsychotics, regardless of relapse during follow-up, was under 20%. The depot antipsychotics most frequently used were of second generation.
ID: 977522

TREATMENT OF EARLY-ONSET SCHIZOPHRENIA: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: We aimed to evaluate the randomized, controlled trial (RCT) data base for antipsychotics (APs) in early-onset schizophrenia (EOS). Methods: Systematic review and meta-analysis of all randomized, placebo and active controlled studies of APs in youth with EOS. Results: 14 RCTs ($n = 1155$) were found. 6 RCTs had a placebo comparator, evaluating haloperidol ($N = 2$, $n = 67$), loxapine ($N = 1$, $n = 51$), aripiprazole ($N = 1$, $n = 301$), quetiapine ($N = 1$, $n = 220$), risperidone ($N = 1$, $n = 160$, and olanzapine ($N = 1$, $n = 107$), and 1 ($n = 279$) used low dose risperidone (0.15–0.6 mg/day) as a pseudo-placebo comparator. 7 RCTs ($n = 275$) directly compared APs, ie, thiothixene vs. thioridazine ($N = 1$, $n = 21$), haloperidol vs. olanzapine vs. risperidone ($N = 1$, $n = 50$), molindone vs. olanzapine vs. risperidone ($N = 1$, $n = 119$), haloperidol vs. clozapine ($N = 1$, $n = 21$), clozapine vs. olanzapine ($N = 2$, $n = 64$), and olanzapine vs. quetiapine ($N = 1$, $n = 50$). While the 2 underpowered typical AP trials did not significantly separate from placebo, all atypical AP trials showed superiority on the primary, general psychopathology score outcome for all studied doses. The numbers-needed-to-treat (NNT) for response ranged from 4–10 for aripiprazole, olanzapine, quetiapine and risperidone. Across the 7 active-controlled trials, the only significant group differences were in favor of clozapine compared with haloperidol and compared with olanzapine. Response rates were lower in adolescents compared with adults, but youth were more sensitive to AP side effects, ie, sedation, EPS (except for akathisia), withdrawal dyskinesia, prolactin abnormalities, weight gain and metabolic abnormalities, with significant differences among the studied APs. Conversely, diabetes and tardive dyskinesia were less prevalent in pediatric samples, at least during the relatively short study periods and at lower doses than used in adults. Conclusion: Data from RCTs support a statistically significant superiority of all studied APs compared with placebo in EOS. Except for superiority of clozapine, efficacy differences among APs were small, like in adults, but response rates are lower than in adults. By contrast, acute side effects were greater in youth than adults, but differed significantly across APs, like in adults.
ID: 976741

CHALLENGES AND PITFALLS IN THE IMPLEMENTATION AND CONDUCT OF CLINICAL TRIALS

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Background: Over the last decades, there has been a marked shift in the design and conduct of clinical psychopharmacology studies. Trials have become more complex, regulatory requirements are more stringent, more studies are conducted concurrently in the same disease area, and trials are conducted increasingly involving multiple sites, countries and cultures. Partly as a result of these changes, clinical assessments have become more demanding, screening and consenting procedures require more involved patient participation, study management and oversight have been outsourced, the number of participants and drop outs has grown, effect sizes have decreased, and concerns about study integrity as well as internal and external trial validity has grown. Methods: Review of factors that are relevant to the successful conduct of antipsychotic trials designed to gain regulatory approval and of elements that can interfere with this success. Examples from recent studies with antipsychotics will be used to illustrate issues that are critical in ensuring valid and interpretable trial results. Results: Research on and attention to trial implementation and conduct has been neglected, as sponsors and academicians alike have relied more heavily on trial design and methodology. Factors that can have a profound impact on the sample size requirements and on the validity and interpretability of the results include the following: blinding or masking methods, functional unblinding opportunities, patient expectation, rater bias, rater drift, inter-rater reliability, type and degree of oversight and quality control, management of sites and CROs, and incentivisation methods that shift the focus from timelines and quantity to enhanced quality of included patients and obtained assessments. Conclusion: There is an increasing need to consider and control a number of factors when implementing and conducting clinical psychopharmacology trials. Different stakeholders and entities involved in the conduct of such studies need to collaborate efficiently, and appropriate checks and balances are required. In particular, the ''risk'' of a failed trial needs to be distributed across these constituencies to assure optimal overall performance.
ID: 980261

SIGNAL DETECTION IN CLINICAL TRIALS: A POST-STUDY SURVEY OF SCHIZOPHRENIA TRIAL SITES

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Background: Diminishing drug-placebo differences and increasing placebo responses have been observed in recent psychiatric trials. The objective of this survey based study was to evaluate the relationship between investigative site characteristics and signal detection in schizophrenia clinical trials. Methods: Principal investigators (PIs) at 42 US sites from 2 recently completed lurasidone, placebo-controlled schizophrenia trials received a questionnaire that covered questions regarding patient population and recruitment methods, rater consistency, and PI assessment of several factors potentially relevant to clinical trial outcome. Site-specific drug-placebo effect sizes of PANSS total scores and their associations with site and PI practices were examined using multiple stepwise regression analysis weighted by the inverse variance of PANSS change score. Analyses were adjusted for significant confounding covariates, including CRO quality and duration of illness. Results: Of the 42 US study sites, 32 (76%) completed the survey. The PI responses showed a majority of the sites recruited patients outside their practices. A larger lurasidone-placebo effect size was observed at sites where subjects were more likely to be research-naïve ($P < .05$) and had longer illness durations ($P < .05$). Sites with less revenue derived from pharma-sponsored studies ($P < .01$), fewer subjects recruited via advertisements ($P < .05$), and which were academic/non-profit were associated with larger effect sizes. Other relevant factors at the site level included patient selection (diagnostic accuracy), ability to identify a reliable informant, the importance given by investigators to the need for control of placebo response and for investigator and rater experience, plus specific patient characteristics (history of response to non-standard (high dose) treatment, and history of alcohol or substance abuse). The PI rated ''extremely important'' contributors to trial success were sponsor and CRO quality, responsiveness, and involvement. Illness duration from survey responses was verified against the lurasidone trial database source data and showed a correlation trend ($P < .10$), supporting the validity of survey responses. Conclusion: Our findings suggest certain site characteristics can affect the likelihood of detecting treatment efficacy signals in schizophrenia

trials. Further research is needed to confirm whether these findings are study-specific or generalizable to other clinical trials.
ID: 978964

INTERNAL CONSISTENCY OF RATINGS IMPROVE AND ERROR RATES DECREASE WITH ONGOING MONITORING AND FEEDBACK IN AN INTERNATIONAL SCHIZOPHRENIA CLINICAL TRIAL

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Background: Diminution of placebo drug separation in multi-site international clinical trials in schizophrenia and other CNS disorders is a matter of urgent concern. We report the apparent effects of a program of ratings data monitoring, feedback and remediation on error rates and internal consistency of PANSS ratings in an international clinical trial. Methods: Investigators were trained and certified in administration and scoring of the PANSS and CGI. Surveillance of clinician-rated outcomes data was enacted via a computer-driven system with daily clinical oversight. Predetermined PANSS, CGI and other data inconsistencies were flagged as proxies of potential rater error. Clinicians assessed each flag and, when indicated, contacted and remediated site raters. Internal consistency of the PANSS and the error rate for the PANSS and CGI ratings were tracked over 1 month measurement periods using an index score (number of flags corrected by number of possible flags given visits conducted and scales administered). Flag rates and internal consistency (Cronbach's alpha) were compared at a 1 month measurement period near the onset of the trial vs. a 1 month measurement period 6 months later. Results: The flag rate index score for the initial month measurement period (.062) was statistically significantly higher than for the sixth month measurement period (.037) (Pearson chi-square = 7.21, $P < .008$). In addition, Cronbach's alpha reliability for the PANSS was statistically significantly higher for the sixth month measurement period ($r = .90$) compared with the initial measurement period ($r = .74$) ($z = 3.78$, $P = .0001$). Conclusion: The error rate for the PANSS and CGI fell statistically significantly over a 6 month period, consistent with improvement in ratings technique. Cronbach's alpha for the PANSS improved statistically significantly over time consistent with more appropriate use of the scale. The current findings are consistent with previous reports of reduction in error rates involving the MADRS, HAM-D and YMRS (Busner, Daniel and Bartko, Kalali and Spear, 2007). In addition, we will report the initial results of an ongoing program in which external reviewers provided ongoing quality review and remediation of site diagnostic and ratings procedures utilizing videotaped patient interviews in global schizophrenia clinical trials.
ID: 978056

EFFECT SIZE IN CLINICAL TRAILS

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Background: Topics discussed included: what effect size is, how to calculate for continuous and discrete data, how to interpret it, how big is a big effect size, does it change over time, what it means for practice, what it means in cost effectiveness, what is the effect size for treatment of schizophrenia, how effect size in psychiatric drugs compare with those of internal medicine. Methods: A systematic meta-analysis of studies of schizophrenia, other psychiatric drugs, of drugs used in internal medicine plus a narrative discussion of concepts and meaning of effect size. Results: How meta-analysis calculates effect size and how these indices are interpreted will be presented for both acute and maintenance treatment. The effect sizes and their variability of drugs for schizophrenia, for efficacy, weight gain, eps, prolactin, and other outcomes, for drugs for other psychiatric disease entities and for drugs used for common medical diseases will be presented. The effect sizes in psychiatry are similar to those for medical drugs. Conclusion: The pitfall of various effect sizes indices will be presented, with their implication for comparing different outcomes, choosing medication in practice, and implication for cost-effectiveness studies. Effect sizes of psychiatric drugs will be compared with those in internal medicine.
ID: 979191

OPEN-LABEL COMPARISON OF OLANZAPINE LONG-ACTING INJECTION AND ORAL OLANZAPINE: A 2-YEAR, RANDOMIZED STUDY IN OUTPATIENTS WITH SCHIZOPHRENIA

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Background: To compare the long-term treatment effectiveness of monthly olanzapine long-acting injection (LAI) with that of oral olanzapine. Methods: Outpatients with ≥ 2 episodes of worsening of schizophrenia in the past 24 months and a PANSS total score <70 at baseline were randomized to receive 405 mg/4-weeks of olanzapine LAI ($N = 264$) or 10 mg/day oral olanzapine ($N = 260$) for up to 2 years of open-label treatment. After 4 weeks, dosing was flexible (150–405 mg/4-weeks olanzapine LAI [corresponding to approximately 5–15 mg/day] vs. 5–20 mg/day oral olanzapine). Investigators could, at their discretion, taper the previous oral antipsychotic (first 2 weeks only) and/or supplement with oral olanzapine 5 mg/day (subsequent 6 weeks only). The primary outcome measure was time to all-cause discontinuation. Results: There were no significant group differences in median time to all-cause discontinuation (645 days LAI, 678 days oral; $P = .61$), discontinuation rate (54.9% LAI, 52.3% oral; $P = .60$), or relapse rate (31.1% LAI, 29.2% oral; $P = .70$). Psychiatric hospitalization rates during the study were very low and similar for the 2 groups (7.6% LAI, 9.2% oral), but duration of hospitalization was significantly shorter for the LAI group (0.4 days vs. 1.8 days, $P = .020$). There were no incidents of post-injection syndrome and no clinically significant group differences in adverse events or other safety measures. Mean weight change (via MMRM) over the 2-year study did not significantly differ ($P = .866$) for the 2 groups (at 1 year., 2.3 kg LAI vs. 2.9 kg oral; at 2 years., 2.1 kg LAI vs. 2.3 kg oral). To control for the higher maximum allowed dose in the oral group, a post hoc analysis was conducted. When we treated dose increases to 20 mg/day after the initial 8 weeks of treatment as a sub-acute relapse, the LAI group had a lower relapse rate (31.1% LAI, 45.8% oral; $P < .001$) and a longer median time to relapse (379 days LAI, 213 days oral; $P < .001$) than the oral group, indicating that dose differences likely impacted the primary study findings. Conclusion: Olanzapine LAI and oral olanzapine were similarly effective and well tolerated for up to 2 years of treatment in patients with schizophrenia. The discontinuation rate for olanzapine LAI was similar to that of oral olanzapine, despite the 3-hour post-injection observation period and other precautionary procedures related to the risk of post-injection syndrome.
ID: 975820

A DOUBLE-BLIND TRIAL OF ARTEMISININ TO REDUCE THE SYMPTOMS OF SCHIZOPHRENIA

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Background: This clinical trial was undertaken to test the hypothesis that symptoms of schizophrenia may be reduced by the antimalarial compound artemisinin when used in addition to standard antipsychotic medications. Artemisinin has been widely used in many countries for the treatment of malaria with a low level of recorded side effects. Artemisinin has also been shown to inhibit the parasite *Toxoplasma gondii* in cell culture. Artemisinin was selected for this trial because of the hypothesized role of *Toxoplasma gondii* in schizophrenia pathogenesis. Methods: Participants were outpatients with schizophrenia with residual psychiatric symptoms of at least moderate severity. Participants were administered a 2-week placebo run-in and then randomized to receive artemisinin (100 mg twice per day) or placebo for 10 weeks in addition to their regular psychiatric medications. Results: A total of 66 patients were enrolled; 65 completed the run-in and were randomized and 57 (86%) completed the full 12 weeks of the trial. The mean age of participants was 47.3 years (±9.3); 33 (50%) were Caucasian and 33 (50%) African-American; 38 (58%) were male. The mean baseline PANSS total score was 68.9 (±10.3). There was not a significant difference between the 33 patients randomized to artemisinin and the 33 patients randomized to placebo on these characteristics (all $P > .1$). There was not any significant difference by treatment group in the change in PANSS total score between baseline and the end of week 12 for the completers. There was also not a significant difference between groups in PANSS total score by repeated measures ANOVA analysis. Looking only at individuals with elevated Toxoplasma antibody levels (defined as >=90th percentile of controls), the repeated measures ANOVA by group is significant ($F = 2.89$, $P = .0145$). That is, the 8 of 33 in the artemisinin group who were Toxo >90th %ile showed more improvement than the 14 of 33 who were Toxo >90 %ile in the placebo group. Individuals receiving artemisinin showed a decrease in antibodies to gliadin, a wheat protein antibodies to which we have shown to be increased in individuals with recent onset psychosis ($F = 4.42$, $P = .040$). Conclusion: Artemisinin and related compounds have promise to reduce symptoms in individuals with schizophrenia who have increased levels of antibodies to *Toxoplasma gondii*.
This study was funded by the Stanley Medical Research Institute.
ID: 979732

OPTIMIZATION OF TMS TREATMENT PARAMETERS FOR NEGATIVE SYMPTOMS IN SCHIZOPHRENIA: RESULTS OF A META-ANALYSIS AND SUGGESTIONS FOR FURTHER RESEARCH

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Background: The past decade several studies have been performed on the efficacy of repetitive Transcranial Magnetic Stimulation (rTMS) for negative symptoms in schizophrenia. A meta-analysis found a significant small-to-medium effect size for rTMS vs. sham (Dlabac-de Lange JJ et al 2010). The optimal parameters of rTMS in negative symptoms, including the position of TMS on the skull, duration and number of treatments, the frequency of the TMS stimulation, are still under investigation. By adding recent study data to the meta-analysis and by performing subanalyses on studies included in the meta-analysis variables contributing to the efficacy of rTMS are studied. Methods: The method of the meta-analysis is described in our previous study (Dlabac-de Lange JJ 2010). Effect sizes (Cohen's *d*) of each study were calculated and the overall standardized mean difference was calculated under a random effects model with 95% confidence intervals. A subgroup analyses compared the following published treatment parameters: stimulus frequency and treatment duration. Results: The updated meta-analysis ($N = 238$) showed a medium effect size ($d = 0.44$; 95% CI: 0.1–0.78). The studies using a frequency of 10 Hz had a larger mean effect size of 0.62 (95% CI: 0.18–1.06). Studies with a longer duration of treatment (> or = 3 weeks) showed a larger mean effect size ($d = 0.58$ (95% CI: 0.19–0.97)) compared with studies with a shorter treatment duration ($d = 0.36$ (95% CI: −0.17 to 0.89)). Conclusion: These results suggest a frequency of stimulation of at least 10 Hz and a duration of treatment of 3 weeks or longer may enhance treatment effects of rTMS in negative symptoms. Further studies of rTMS as a potential treatment of negative symptoms in schizophrenia are warranted. Future research may include other treatment parameters like position of the rTMS coil on the scalp (for instance using fMRI guidance), uni- or bilateral stimulation of the dorsolateral prefrontal cortex, and the combination of rTMS with psychosocial interventions may contribute to optimize the treatment of negative symptoms. A randomized trial investigating 3 weeks high frequency rTMS for negative symptoms is underway at the University of Groningen in The Netherlands. Preliminary results are expected March 2011.
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ID: 978298

A BROAD CORTICAL RESERVE ACCELERATES RESPONSE TO COGNITIVE ENHANCEMENT THERAPY IN EARLY COURSE SCHIZOPHRENIA

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Background: Cognitive rehabilitation has emerged as an effective method for improving cognition in many individuals with schizophrenia, and its early application may play a key role in preventing future disability. Significant heterogeneity does exist, however, in how patients respond to cognitive rehabilitation, which may reflect variability in underlying neurobiologic reserves and capacity to enhance cognition. Unfortunately, little is known about the biomarkers of response to cognitive rehabilitation, or whether those with a greater neurobiologic reserve will exhibit a particularly favorable response to treatment. This study investigated the effects of pre-treatment neurobiologic reserves on response to Cognitive Enhancement Therapy (CET) in early course schizophrenia. Methods: Outpatients in the early course of schizophrenia or schizoaffective disorder were randomly assigned to CET ($n = 29$) or an Enriched Supportive Therapy control ($n = 21$) and treated for 2 years. Cortical surface area and gray matter reserve data were collected prior to treatment using structural magnetic resonance imaging, and processed using SPM 5 and FreeSurfer. Comprehensive measures of neurocognition and social cognition were administered at study baseline, and after 1 and 2 years of treatment. Moderator analyses were conducted to examine the impact of greater pre-treatment cortical surface area and gray matter volume on differential neurocognitive and social-cognitive response to CET. Results: Greater whole brain cortical surface area and gray matter volume prior to initi-

ating treatment significantly moderated the effects of CET on social cognition, but not neurocognition. Patients with a greater neurobiologic reserve demonstrated a rapid social-cognitive response to CET in the first year of treatment ($d = .64$), whereas patients with less neurobiologic reserve improved little in the first year ($d = .09$), but achieved a comparable social-cognitive response ($d = .45$) by the second year of treatment. Region of interest analyses indicated that nearly every lobar and regional measurement significantly contributed to this accelerated treatment response. Conclusion: A broad cortical surface area and gray matter reserve is associated with an accelerated social-cognitive response to CET in early schizophrenia. The benefits of cognitive rehabilitation are still apparent after a longer duration of treatment in those with less initial neurobiologic resources.
ID: 977583

CHALLENGES IN DRUG DEVELOPMENT FOR COGNITIVE IMPAIRMENT IN ASSOCIATED WITH SCHIZOPHRENIA

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Background: The first wave of drug trials targeting Cognitive Impairment in Associated with Schizophrenia (CIAS) have been completed but have not shown efficacy. Reasons may be related to target selection, target validation, or trial execution. An analysis of these programs suggests specific avenues to increase the chance of success for future efforts. Methods: Results of publicly available clinical trials in CIAS were reviewed in terms of target validation, target engagement, and study design. Because many trials have not been published, 3 recent, unpublished trials were examined, including a potent H3 inverse agonist, an NPY5 antagonist, and an ORL1 antagonist, where doses were selected based on PET studies with specific ligands. Results: Problems with trials included questions about target engagement, dose selection, and power. None included an active comparator making it difficult to distinguish failed from negative trials. Practice effects in some suggest changes in cognition are detectable. Regarding 3 trials of novel compounds, execution appeared adequate but did not show efficacy ($P > .2$). These results highlight issues related to duration of treatment and effects of antipsychotics. Finally, if CIAS is heterogeneous, efficacy in subgroups could have been obscured. Several concerns could be addressed by further research. For example, regarding heterogeneity, a randomized withdrawal design could be evaluated, where only clear responders are randomized to active drug vs. placebo. Cognitive remediation (CR), hypothesized to enhance detection of efficacy, could also be evaluated. Given the ostensible failures, greater efforts at target validation may be required. Recent drug targets have been largely supported by preclinical results or a limited mix of data from patients. More substantial clinical evidence, using, for example, genetics and brain imaging, may be necessary to qualify new targets. Conclusion: Methodological issues have clouded the interpretation of results from clinical drug trials. Some could be addressed through additional research on methodology. In Alzheimer's disease, sustained public and industry funding of such trials have provided critical information on design, patient selection, and outcome measures, perhaps serving as a model for future efforts in CIAS. Given the paucity of well validated drug targets, more persuasive human data relating targets to the underlying biology of CIAS may be needed.
ID: 979720

THE EFFECT OF AEROBIC EXERCISE ON CORTICAL ARCHITECTURE IN PATIENTS WITH CHRONIC SCHIZOPHRENIA. A RANDOMIZED CONTROLLED TRIAL

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Background: Bilateral hippocampal volume reduction is a very well replicated finding in schizophrenia. Whether or not this represents a fixed deficit is uncertain. From animal studies it is known that aerobic exercise is a stimulus to hippocampal plasticity. Methods: A randomized controlled 3-armed study was performed to determine whether hippocampal volume would increase with exercise in humans and whether this effect would be related to improved aerobic fitness. Male patients with schizophrenia attending a day hospital program or an outpatient clinic were randomised to either aerobic exercise training (cycling) or playing table football (control group) for a period of 3 months. The 2 intervention arms were compared with a group of healthy subjects performing aerobic exercise training (cycling) for the same period of time. As primary outcome parameter magnetic resonance imaging of the cortex and as secondary outcome parameter magnetic resonance spectroscopy, neuropsychological (Rey Auditory Verbal Learning Test, Corsi block tapping test) and clinical features (Positive and Negative Syndrome Scale) were used. Results: Measuring surface expansion and surface contraction of cortical regions, schizophrenic patients overall revealed surface expansion in fronto-parietal regions, while control subjects more in parietal areas. Comparing schizophrenic patients performing aerobic exercise with those doing table football showed more pronounced surface expansion in frontal areas. Conclusion: There is increasing evidence that aerobic exercise has an effect on brain structure and function in humans. This link is better established for people with dementia or mild cognitive impairment, but recently found some support for patients with schizophrenia (Pajonk et al. 2010). We could show using a region of interest approach that following exercise training, relative hippocampal volume increased significantly in patients (12%) and healthy subjects (16%), with no change in the non-exercise group of patients (−1%). Based on a broader analysis of our structural MRI data, we have now demonstrated here that aerobic exercise has an additional effect on cortical regions in schizophrenia. Further studies are needed to show whether these effects are lasting and whether they could be used to improve cognitive dysfunction in schizophrenia.
ID: 979514

PALIPERIDONE PALMITATE VS. ORAL ANTIPSYCHOTICS FOR PEOPLE WITH SCHIZOPHRENIA RECENTLY RELEASED FROM JAIL: RATIONALE AND METHODOLOGY

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Background: Overrepresentation of people with serious mental illness (SMI) in US jails and prisons is an important public health problem. After release from incarceration, successful community reentry is challenged by barriers to obtaining essential healthcare, social services, and financial resources, perpetuating a revolving door of incarceration followed by failed

community reentry. Although untreated psychotic illness may be an important variable, no studies have compared the effectiveness of psychopharmacologic treatments in individuals with schizophrenia following release from jail. A recently initiated clinical study compares a monthly long-acting injectable antipsychotic with daily oral antipsychotics in delaying time to community reentry failure in patients with schizophrenia. We report on the nature of the problem, study rationale, and methodological challenges encountered in designing a psychopharmacology intervention trial to address public health and clinical dimensions of a problem frequently encountered by people with schizophrenia. Methods: This 15-month randomized, open-label, multicenter, effectiveness study was designed to compare paliperidone palmitate with oral antipsychotics in subjects with schizophrenia recently released from jail. The primary endpoint is time to a treatment failure event, defined as arrest; reincarceration; hospitalization; suicide; discontinuation of antipsychotic because of inadequate efficacy, safety, or tolerability; supplementation with another antipsychotic because of inadequate efficacy; or increase in level of services to prevent imminent psychiatric hospitalization. Results: There is extensive site variation due to regional differences in mental health systems and services for this population among the study site locations. This reflects the real-world nature of the study and poses methodological challenges for the study design and analysis. Conclusion: This is a comparative effectiveness study to determine whether time to treatment failure for people with schizophrenia recently released from jail differs between treatments with paliperidone palmitate, a long-acting atypical injectable antipsychotic, and commonly prescribed oral antipsychotics. Endpoints were chosen to address meaningful clinical and public health outcomes. Methodological approaches addressed here may aid future studies at the intersection of clinical research and mental health policy.

Supported by Ortho-McNeil Janssen Scientific Affairs, LLC
ID: 977811

EXAMINATION OF SWITCHING FROM MANIA TO DEPRESSION IN SCHIZOAFFECTIVE DISORDER

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Background: A mood switch, or transition from a mood episode of one polarity to another, is a core feature of bipolar disorder. It may be triggered by stress, sleep deprivation, and various medications, or it may be spontaneous without identifiable precipitating etiology. Schizoaffective disorder is a distinct diagnostic entity characterized by symptoms of mania and/or depression plus psychotic symptoms of schizophrenia. Few studies focus on these patients, and the prevalence and impact of mood switching in schizoaffective disorder is not well understood. Recently, paliperidone ER became the first treatment to be approved in the US for the acute treatment of schizoaffective disorder, effective for both psychotic and affective symptoms. This analysis examines mood switches using the paliperidone ER phase 3 trial database with an initial focus on switching from mania to depression. Methods: Data were pooled from 2 international double-blind placebo-controlled 6-week studies of paliperidone ER in subjects with schizoaffective disorder. For this post hoc analysis, subjects with prominent manic symptoms at baseline were included (HAMD-17 <16 plus YMRS ≥ 16). Mood switch was defined as (1) $\geq$4-point increase in HAMD-17 at $\geq$2 consecutive visits or at endpoint or (2) HAMD-17 ≥ 16 at $\geq$2 consecutive visits or at endpoint. Depression-related AE rates were summarized. Between-group differences were assessed by the Cochran-Mantel-Haenszel test or Fisher exact test for categorical measures and by ANCOVA models for continuous measures. Results: 269 subjects met inclusion criteria: 175 paliperidone ER; 94 placebo. YMRS and HAMD-17 scores improved with paliperidone ER compared with placebo (LS mean difference [SE] vs. placebo: -5.6 [1.4], $P < .001$, and -2.4 [0.6], $P < .001$, respectively). Mood switch defined by criteria 1 occurred in 8.0% of the paliperidone ER group and 17.0% of the placebo group ($P = .019$). Rates for mood switch defined by criteria 2 were 4.0% and 12.8%, respectively ($P = .015$). Depression-related AEs were reported by 1 subject (0.6%) with paliperidone ER and by 2 (2.1%) with placebo. Conclusion: To our knowledge, this is the largest patient-level prospective meta-analysis of pharmacologic treatments for schizoaffective disorder. This analysis of subjects with prominent manic symptoms showed that, compared with placebo, paliperidone ER reduced manic symptoms and decreased switching from mania to depression.

Supported by Ortho-McNeil Janssen Scientific Affairs, LLC
ID: 977771

PREDICTORS OF ATTRITION IN NEUROPLASTICITY-BASED AUDITORY TRAINING IN SCHIZOPHRENIA

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Background: Recent studies investigating the effects of cognitive remediation in schizophrenia have shown promising results. While effective, attrition rates are a concern, and the characteristics of subjects who complete training vs. those who drop out are unknown. Here we report the attrition rates and characteristics of individuals with chronic schizophrenia and recent-onset schizophrenia who participated in 2 RCT's of neuroscience-guided cognitive remediation. Methods: Individuals with chronic schizophrenia (N = 84) and recent-onset schizophrenia (N = 74) were randomized to an experimental condition where they completed 40 hours of cognitive training exercises or a control condition of 40 hours of computer games. All subjects were assessed with MATRICS-recommended measures of cognition and the PANSS. Adults with chronic schizophrenia were assessed with an abbreviated version of the Quality of Life Scale and recent-onset subjects were assessed with the Global Role and Social Functioning Scales. Chi-Square and Independent Samples T tests and were used to compare attrition rates and group characteristics. Results: Adults with chronic schizophrenia showed a significantly lower attrition rate (12%) compared with recent-onset subjects (32%), $P < .01$. In the total sample, participants who withdrew from training were significantly younger ($P = .004$), with less impairment in baseline cognition (Global Cognition $P < .01$), and lower PANSS total symptom ratings (trend level), compared with completers. Participants who withdrew were not significantly different from completers in gender, education, or IQ. Adults with chronic schizophrenia who withdrew from training showed greater anhedonia and less environmental engagement, while individuals with recent-onset schizophrenia who withdrew showed higher social functioning. Conclusion: These findings indicate that participants who withdraw from training are younger, with more preserved cognitive functioning, and less symptom severity. These subjects may feel that the training is not necessary relative to more severely impaired subjects. In chronic schizophrenia, symptoms of anhedonia may cause a lack of motivation to complete cognitive training, while in recent-onset schizophrenia, better social functioning appears to play a role. Future research is needed to determine additional characteristics of individuals who will benefit from cognitive training and ways to increase interest and motivation to complete training.

ID: 979816

PRELIMINARY 1-YEAR RESULTS OF THE RENEW PROGRAM FOR WEIGHT LOSS

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Background: People with serious mental illness are at greater risk for obesity due to poverty, limited access to health care, poor health behaviors and side effects of antipsychotic medications (Allison et al, 1999; Dixon et al, 2000; Holmberg & Kane, 1999). Until recently, behavioral weight reduction programs for people with psychiatric disabilities have largely focused on inpatients and show modest weight loss with dietary reduction and behavior modification (reviewed by Faulkner, 2003). Few studies target community-based individuals with psychiatric disabilities where investigators have less control of the environment. Methods: The Recovering Energy through Nutrition and Exercise for Weight Loss program (RENEW) is a randomized controlled trial specifically designed for people with psychiatric disabilities in community-based settings. The primary aim of the program is weight loss and this is targeted through education and skills training aimed at improving nutrition and physical activity status. Participants were stratified by psychiatric medication risk for weight gain (low, medium, and high risk) and then randomly assigned to either the intervention or control group. The program includes a 12 week intensive intervention with 3 hour weekly meetings followed by a 12 week maintenance phase with monthly meetings and phone supports and ends with 6 months of intermittent supports. Results: 89 individuals completed the program (47 intervention, 42 control; 54 female, 35 male; mean age 44.6 ±10.9). Diagnoses included 50% schizophrenia, 26% bipolar and 24% major depression. Individuals in the intervention group lost 5.3 pounds at the end of the 3 month intensive phase and maintained this weight loss at 6 months, while the weight of those in the control group remained stable. Weight loss was highly variable between individuals (−34.5 pounds to +24.6 pounds). Data are being analyzed to assess characteristics between those who were successful and unsuccessful at weight loss during the 1-year program. There was no significant difference in weight loss based on medication risk ($F = .603$, $df = 4,164$, $P = .66$). Conclusion: Weight loss is challenging but achievable in individuals with serious mental illness. Our findings suggest that results are highly variable, but many individuals do respond well to a program utilizing evidenced based practices paired with psychiatric rehabilitation strategies. No differences in the efficacy of the program were found based on medication risk.
ID: 979923

RANDOMIZED CLINICAL TRIAL OF COGNITIVE BEHAVIORAL SOCIAL SKILLS TRAINING (CBSST) FOR OLDER PEOPLE WITH SCHIZOPHRENIA: REPLICATION AND ROLE OF DEFEATIST ATTITUDES

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Background: There is an increasing need for empirically validated psychotherapy interventions that improve functioning in older people with schizophrenia. We developed a group therapy intervention called Cognitive Behavioral Social Skills Training (CBSST), which combined cognitive behavior therapy with social skills and problem solving training to improve functioning. In a previous trial, we found significantly greater improvement in functioning in CBSST relative to treatment as usual in older people with schizophrenia. In this study, CBSST is compared with an active goal-focused supportive contact condition, and examined whether defeatist attitudes ("why bother, I'll just fail") were related to functional outcome. Methods: Participants with schizophrenia or schizoaffective disorder ($n = 63$) age 50 or older were randomly assigned to either CBSST or a goal-focused supportive contact (GFSC) group therapy intervention that focused on setting and discussing functioning goals. The primary outcome measure was the Independent Living Skills Survey (ILSS) and defeatist attitudes were assessed using the Defeatist Performance Attitude Scale (DPAS), which were obtained at baseline, end of treatment (9 months) and 9-month follow-up. Results: Patients in CBSST showed significantly greater improvement in self-reported functioning on the ILSS relative to GFSC. In addition, more severe defeatist attitudes were associated with poorer functioning trajectories on the ILSS in GFSC but not in CBSST, suggesting CBSST reduced the impact of defeatist attitudes on outcome. Conclusion: CBSST can improve functional outcome in older people with schizophrenia. The modification of defeatist attitudes may be an important treatment target in cognitive-behavioral interventions, whereby reduction in defeatist performance beliefs may contribute to improved effort devoted to goal-directed functioning tasks.
ID: 979988

FUNCTIONAL CAPACITY MEASURES IN CLINICAL TRIALS AND MODELS OF FUNCTIONAL OUTCOME

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Background: One obstacle for development of cognition-enhancing drugs in schizophrenia is the need to identify co-primary measures. The Food and Drug Administration has taken the position that, in addition to improvement on cognitive performance tests, improvement needs to be demonstrated on a functionally meaningful co-primary measure. Interest on co-primary measures has focused largely on functional capacity measures that involve simulations of daily activities. This presentation will address 2 questions: 1) How do functional capacity measures perform in clinical trials? and 2) Where do functional capacity measures fit in models of outcome in schizophrenia? Methods: Data will be presented from 3 different studies. Two are NIMH- sponsored evaluations of the psychometrics, validity and practicality / tolerability of several functional capacity tasks and interview-based measures of cognition (the Psychometric and Standardization Study (PASS) and Validation of Intermediate Measures (VIM) Study). Both studies involved large samples of schizophrenia patients evaluated at baseline and at 4-week retest. The third data set is from an ongoing study of perception, functional capacity, and outcome in schizophrenia. Structural equation modeling was used to determine the relationships among constructs. Results: Both the PASS and VIM studies demonstrated that all potential co-primary measures included showed acceptable test-retest reliability and good utility as a repeated measure. Functional capacity measures showed significantly stronger associations with cognitive performance than interview-based measures of cognition. None of the measures showed strong correlations with self-report assessments of community functioning. The modeling analyses suggest that functional capacity is closely related to cognitive performance, but that several intervening variables are needed to explain its relationship to community outcome. Conclusion: The psychometric studies indicate that functional capacity measures have good psychometrics and are practical and tolerable. They show strong correlations with cognitive performance and weaker associations with community outcome. The modeling analyses suggest that both cognitive performance and functional capacity are indicators of competence, but that community functioning depends on post-competence factors, such as social support, negative symptoms and dysfunctional beliefs.
ID: 976776

RESULTS FROM A 15-WEEK PILOT STUDY OF A CLINIC- AND HOME-BASED HEALTHY LIFESTYLE PROGRAM FOR RECENT-ONSET SCHIZOPHRENIA PATIENTS

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Background: The role of physical inactivity and poor diet as independent risk factors for cardiovascular disease in schizophrenia highlights the need for lifestyle-based interventions with this population. Methods: This study reports results from a 15-week healthy lifestyle training (HLT) pilot program for recent-onset schizophrenia patients ($n = 8$) consisting of 1 hour of exercise and 2 hours didactic instruction in nutrition and stress management at the clinic plus 1 hour of exercise and 1 hour of combined nutrition self-monitoring and motivation counseling at home. Patients in a concurrent 15-week feasibility study of clinic- and home-based cognitive training (CT) ($n = 7$) served as a comparison group. Assessments were completed at baseline, 5 weeks, and 15 weeks. Results: The attendance rate for the in-clinic HLT group sessions was high (86%). Self-monitoring homework assignment completion rates were in an acceptable range (60%). The at-home exercise completion rate was 66%, and the combined in-clinic and at-home exercise rate was 75%. In other words, the schizophrenia patients in our program exercised over twice as much as adults of similar age without the disorder.[1] At 5 weeks, HLT participants perceived significantly ($P < .05$) more benefits and fewer barriers to engaging in healthy behaviors (Cohen's $d = .64$ and -1.15, respectively) and also significantly increased their self-efficacy for nutrition ($d = .72$) and exercise ($d = 1.07$). The HLT intervention also appeared to prevent a significant decline in muscular strength and endurance experienced by patients in the CT comparison group (HLT $d = .02$, CT $d = -.90$), as measured by the YMCA 1-minute modified sit-up test. At 15 weeks, self-efficacy for nutrition and exercise remained significantly improved over baseline levels ($d = .68$ and .45, respectively). Perceived stress levels significantly decreased from baseline levels ($d = -.43$) and BMI also significantly decreased ($d = -.49$) in the HLT patients. Conclusion: Results from the pilot study indicate that a combined outpatient clinic- and home- based healthy lifestyle program is feasible with recent-onset schizophrenia patients. Furthermore, these results encourage examination of this intensive HLT program in a fully-powered, randomized clinical trial. This research is supported by NIMH research grants MH037705, MH066286, and MH014584.

[1]Schoenborn CA, Adams PF. Health behaviors of adults: United States, 2005–2007. National Center for Health Statistics. Vital Health Statistics,10(245). 2010.

ID: 977139

LIFETIME ANTIPSYCHOTIC TREATMENT FOR ALL SCHIZOPHRENIA PATIENTS?: A 26-YEAR EVIDENCE-BASED APPROACH

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Background: The reports of the PORT, which is based on a review of over 400 recent treatment articles, are that continuous antipsychotic medications is the standard of care for schizophrenia patents (SZ). Almost all of the major reports in this area are based on short-term (0–3 years) evaluations. The data from the current longitudinal research suggests modifications of the view that all schizophrenia patients (SZ) need to be treated with antipsychotics throughout their lifetime. Methods: Early young patients ($n = 97$) with psychotic disorders from the Chicago Followup Study, including 60 with schizophrenia (SZ), were assessed during the acute phase and then followed-up 7 times over the next 26 years. Patients were assessed with standardized research instruments at each follow-up for positive symptoms, negative symptoms, cognitive impairment, affective syndromes, work disability, social activity level and treatment, including first and second generation antipsychotics. Results: 1) At the acute phase of hospitalization antipsychotic medications were extremely helpful in reducing and/or eliminating flagrant psychosis. 2) However, 4–5 years later, those schizophrenia patients not on antipsychotics for a prolonged period were significantly more likely to be experiencing periods of recovery. 3) By the 4.5 year follow-ups and continuing until the 26-year period, 25%–45% of the SZ had removed themselves, or been taken off antipsychotics, for prolonged periods. 4) The SZ who were no longer on antipsychotic medications for a prolonged periods showed significantly less work disability by the 4.5 year follow-ups. 5 Over a prolonged period the SZ who were not taking antipsychotic medications tended to have less neurocognitive impairment. Conclusion: A) the 26-year longitudinal data raise questions about the assumption that all SZ need to be treated with antipsychotic medications throughout their lifetime and suggest the role of non-treatment factors which may influence both psychosis and periods of recovery. B) Work disability in SZ may be increased by antipsychotics, which block dopamine receptors and reduce motivational salience. C) Those SZ with greater neurocognitive impairment and those with more vulnerability to anxiety are more likely to be treated over a prolonged period with antipsychotic medications and less likely to be experiencing periods of recovery.

ID: 977997

A PROSPECTIVE, 1-YEAR, OPEN-LABEL, FLEXIBLE DOSE STUDY OF LURASIDONE IN THE TREATMENT OF SCHIZOPHRENIA: SAFETY, TOLERABILITY, AND EFFECTIVENESS

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Background: Lurasidone is a new atypical antipsychotic in development for the treatment of schizophrenia and bipolar disorder. The objective of this study was to assess the long-term safety, tolerability, and effectiveness of once-daily 40–120 mg/day lurasidone in a 1-year, open-label study. Methods: Patients with schizophrenia (ICD-10 with or without acute exacerbation) were enrolled in this study which was conducted in Japan. Lurasidone dosing was initiated at 40 mg/day, and adjusted up to a maximum of 120 mg/day over a 16-week period, and then held fixed from Week 16 to Week 52. The key effectiveness measure was discontinuation of treatment for any cause. Other safety and tolerability outcomes included adverse events (AEs) and laboratory evaluations. Kaplan-Meier and Growth Mixture Model (GMM) analyses were applied. Results: A total of 182 patients, aged 20–64 years, were treated with a mean dose of 71 mg/day lurasidone. There was an increase in dosage from Week 1 to Week 8 within the mean dose range of 41–77 mg/day, while dosages at Week 9 and thereafter were stable (within the mean dose range of 80–85 mg/day). One hundred and fourteen (63%) patients completed 16 weeks of treatment, and 80 (44%) completed the 1-year study. Eighteen (10%) discontinued due to AEs before 16 weeks, while 35 (19%) discontinued due to lack of efficacy. Kaplan-Meier analysis showed 17% cumulative discontinuation rate for AE at 6 months and 23% at 12 months. Likewise, K-M discontinuation rate due to lack of efficacy was 25% at 6 months and 28.5% at 12 months. Mean weight change at 1

year was −1.5 (SD 4.8) kg. Long term mean changes (SD) from baseline were: total cholesterol −7.5 (25.8) mg/dl, triglycerides −7.9 (56.9) mg/dl, fasting glucose 0.5 (9.8) mg/dl, and prolactin −12.7 (54.0) (ng/ml). Most of the adverse events were mild or moderate, and only 4.4% were rated severe. The trajectory patterns for the primary outcomes (BPRS and PANSS scores) were consistent, showing greatest improvement in the subgroup with higher baseline severity (GMM mean BPRS −9.9 from baseline 61, $n = 27$), compared with the lower baseline severity groups (mean BPRS −6.8 from baseline 49, $n = 59$; and −3.5 from the baseline 34, $n = 96$). Conclusion: Lurasidone was well tolerated with no adverse mean changes in weight, lipids and prolactin in this 1-year open-label study in subjects with schizophrenia. In addition, lurasidone was associated with a gradual and sustained improvement in total PANSS and BPRS scores.
ID: 979564

GLYCINE TRANSPORTER TYPE 1 (GLYT1) INHIBITOR RG1678: PROOF OF MECHANISM OF ACTION IN HEALTHY VOLUNTEERS

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Background: Hypofunction of glutamatergic transmission via *N*-methyl-D-aspartate (NMDA) receptors has been implicated in the pathophysiology of schizophrenia. An approach to normalizing NMDA receptor neurotransmission is to increase availability of the obligatory co-agonist glycine at its modulatory site on the receptor by inhibiting glycine transporter type 1 (GlyT1). The potent and noncompetitive GlyT1 inhibitor RG1678 has recently demonstrated efficacy in a proof-of-concept study in schizophrenia. In this study, the relationship of glycine cerebrospinal fluid (CSF) concentration to RG1678 dose was assessed in order to provide proof of mechanism in humans. Methods: RG1678 pharmacodynamics, safety, and tolerability were investigated in a single-center, open-label study in healthy male volunteers. Subjects received 10 days of treatment at 1 of 4 sequential dose levels (3, 10, 30, or 60 mg) once daily under fasting conditions. On study days −2 and 10, a 12-hour indwelling lumbar CSF catheter was inserted and samples collected until 12 hours post-dose. For each subject, glycine area under the curve (AUC_{0-12}) was calculated at baseline (day −2) and at end of treatment on day 10. Plasma and CSF pharmacokinetics of RG1678 were also characterized. Results: 22 subjects aged 18–45 were enrolled, 20 completed the study. Plasma C_{max} and $AUC_{0\text{-}12}$ of RG1678 increased dose-proportionally. Similarly, CSF AUC_{0-12} increased linearly with dose. The CSF concentration-time profiles were flat, without an evident peak concentration over the 12-hour sampling period of day 10. CSF glycine concentrations showed a dose-dependent increase from baseline to day 10. The geometric mean (coefficient of variation, %) ratios of AUC_{0-12} on day 10 over AUC_{0-12} at baseline were 1.3 (17), 1.3 (49), 1.7 (18), and 2.3 (14) after 3, 10, 30, and 60 mg RG1678 respectively. In contrast, plasma glycine concentrations remained relatively constant from baseline to day 10, with no apparent increasing trend. RG1678 was generally well tolerated. Intensity of adverse events was similar between doses and in general was rated as mild or moderate. Conclusion: A dose-dependent increase of glycine in CSF after 10 days of treatment was observed, confirming the mechanism of action of RG1678 as a GlyT1 inhibitor in humans. These data support the utility of this approach for clinical studies of RG1678 in patients with schizophrenia.
ID: 976889

METACOGNITION IN COGNITIVE REMEDIATION THERAPY FOR SCHIZOPHRENIA: PRELIMINARY DATA FROM A NEW COMPUTERIZED INTERVENTION

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Background: Cognitive remediation therapy aims to improve cognition because this is known to be a barrier to functioning in the community. Metacognition may play a key role in ensuring that cognitive change leads to benefits on community functioning. A new computerized cognitive remediation therapy - CIRCUITS - will be introduced that targets metacognition. For the first time this therapy incorporates detailed process measurement so its action on metacognition can be elucidated to a greater extent. This therapy is based on a previous evidenced based intervention (Wykes and Reeder, 2007) where the particular approach to metacognition was formulated. Methods: Twenty people with a diagnosis of schizophrenia took part in a feasibility study of CIRCUITS. They attended regular - 3 times a week - cognitive remediation therapy sessions lasting up to an hour, using a variety of tasks. The therapy tasks were designed to be engaging, attractive and age appropriate. Participants rated task difficulty, timing and strategy usefulness before and after all therapy tasks. Neuropsychological performance, client rated outcomes and therapy acceptability data were also gathered before and after therapy. Results: Therapy adherence was good; participants also rated CIRCUITS as acceptable, enjoyable and attractive. Neuropsychological test performance showed post therapy improvements. Within therapy measures of metacognition indicated that more consistent use of strategy was associated with performance improvements, such as increased correct responses, lower self rating of task difficulty and briefer task duration. Conclusion: This feasibility trial of CIRCUITS demonstrated that this form of cognitive remediation, which explicitly targets metacognition, can successfully be computerized in a way that is acceptable to service users. Furthermore, CIRCUITS shows promise as means of gathering process data on how this type of therapy acts to benefit metacognition in this client group.
ID: 979168

THE FREQUENCY OF ANTIPSYCHOTIC POLYPHARMACY IN "HIGH-UTILIZING" PATIENTS WITH SCHIZOPHRENIA IN GERMANY

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Background: Since negative side-effects emerge with the use of multiple antipsychotics (AP), guidelines usually recommend pharmacologic monotherapy (except for combinations of clozapin and amisulpride). However, in clinical practice, antipsychotic polypharmacy is common especially for chronically ill patients. The purpose of this study was to assess the current practice of antipsychotic polypharmacy and its conformance with current treatment guidelines in "high-utilizing" patients with schizophrenia in inpatient mental healthcare services in Germany. Methods: Antipsychotic medication was assessed using data of patients with schizophrenia from 2 independent multi-center studies conducted at psychiatric university hospitals ($n = 219$) and non-academic psychiatric hospitals ($n = 449$). Information on antipsychotic drug use was obtained from medical records or collected via the Client Socio-Demografic and Service Receipt Inventory (CSSRI). Socio-demographic characteristics, illness severity (CGI), functioning (GAF) and number of antipsychotic agents (APs) were compared

between both samples using *T* and chi-tests. Results: Antipsychotic combination treatment was administered to 43.2% of the patients (2 APs: 34.4%, 3 APs: 7.9%, 4 APs: 0.8% and 6 APs 0.1%). Combination treatment not including clozapine was apparent in 35 % (2 APs: 28.6%, 3 APs: 5.8%, 4 APs: 0.5% and 6 APs 0.1%). Patients treated at the non-academic hospitals had a significantly higher amount of non-clozapine combination treatment than those treated at the university hospital. Sociodemographic characteristics or severity of illness and functioning did not influence the extent of combination treatment. Conclusion: We found antipsychotic polypharmacy including combination treatment with clozapine very frequently in the treatment of patients with schizophrenia showing high utilization of mental healthcare in-patient services use. This indicates considerable deviation from recommendations of national treatment guidelines in Germany. Research should focus on elucidating factors contributing to wide-spread polypharmacy, especially in non-university treatment settings with high non-clozapin combination.
ID: 979199

VAPTANS: A POTENTIAL NEW APPROACH FOR TREATING CHRONIC HYPONATREMIA IN PSYCHOTIC PATIENTS

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Background: Hyponatremia (serum sodium concentration [Na+] <136 mEq/l) is a potentially life-threatening condition often presenting chronically in patients with psychotic disorders. Vasopressin antagonists have recently shown in short-term studies to correct hyponatremia in diverse patient populations, including individuals with both psychosis and idiopathic hyponatremia. However, the safety and efficacy of long-term administration of vaptans is only beginning to be investigated. The objective of this study was to assess whether one of the vaptans, specifically tolvaptan, maintained its safety and efficacy over a prolonged period in patients with psychosis and chronic idiopathic hyponatremia. Methods: SALTWATER was a multicenter, open-label extension of the Study of Ascending Levels of Tolvaptan in Hyponatremia. Of the 111 subjects enrolled in SALTWATER, 8 were male patients with both psychosis and idiopathic hyponatremia who received oral tolvaptan. All had evidence of impaired water excretion demonstrated either by persistent hyponatremia (<135 mEq/l) despite fluid-restriction or standard evidence of SIADH (ie, urine osmolality >100 mOsmoles/kg with [Na+] <130 mEq/l). Study assessments occurred on Day 1 (baseline and 8 hours after first dose), Days 2 through 14 (to end of titration), and Day 31; every 8 weeks from Weeks 10 through 58; every 12 weeks from Weeks 70 through 214; and a follow-up visit 7 days after the last dose of tolvaptan. Safety was assessed at all visits. Results: These subjects provided a total of 7406 patient-days of exposure to tolvaptan. Mean serum [Na+] for the 8 psychotic patients increased from 131.6 mEq/l at baseline to >135 mEq/l throughout the observation period ($P < 0.05$ vs. baseline at most points). No drug-related adverse events led to study discontinuation. Conclusion: Chronic hyponatremia is known to have deleterious effects on the quality of life for many patient groups. These preliminary results suggest that oral tolvaptan provides rapid, effective, and safe treatment of chronic hyponatremia in patients with psychotic disorders and that the effect is safely sustained over long periods of time. This represents an important step forward in treating this significant unmet need in psychotic populations.
ID: 988260

ADJUNCTIVE TREATMENT WITH ARIPIPRAZOLE FOR RISPERIDONE-INDUCED AMENRRHEA

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Background: Hyperprolactinemia and associated side effect, amenorrhea, often occur with risperidone treatment. We investigated the effect of adjunctive treatment with aripiprazole on risperidone induced amenorrhea in female patients with schizophrenia. Methods: A retrospective chart review of 38 female patients with adjunctive aripiprazole treatment for risperidone induced amenorrhea between August 2008 and July 2009 was conducted. The inclusion criteria included: female subjects, aged 18–45, a confirmed DSM-IV diagnosis of schizophrenia, clinically stable, who had been treated with ripsperidone monotherapy and taking the same dosage of risperidone for at least 3 months after adjunctive aripirpazole treatment. The information collected include age, menstrual cycle, duration of amenorrhea, prolactin level (before aripiprazole treatment and after regaining menstruation), dose of risperidone and aripiprzole, time from starting aripiprazole adjunctive treatment to regaing menstruation. The Student's *T* test, Pearson's Chi-square test were used for data analysis. Results: 36 patients with adjunctive aripiprazole treatment for improving risperidone induced amenorrhea were screened. Finally 24 patients were satisfied with inclusion criteria. Percent decreased prolactin levels from baseline to endpoint was 71.4 ± 8.6% in all patients (96.6 ± 25.2 ng/ml, 28.1 ± 9.4 ng/ml)($t = 11.73$, $df = 20$, $P < .0001$). 75.0% (18/24) of patients resumed menstruation, while 12.5% (3/24) did not regain menstruation after 3 month's aripiprazole treatment and 12.5% (3/24) were withdrawn due to aggravated symptoms, insomnia and nausea. Prolactin levels at end point in 3 patients who didn't regain menstruation were 28.6ng/ml, 42.2 ng/ml and 52.7ng/ml. In patients with regaining menstruation, mean duration from taking aripiprazole to resume menstruation was 6.6 ± 2.4 weeks, mean dose of aripiprazole was 12.2 ± 3.9mg/day (with dose range from 5mg to 20 mg/day). Aripiprazole dose for regaining menstruation was not significantly correlated with baseline prolactin level. CGI score was not significantly changed after aripiprazole treatment. Conclusion: Adjunctive aripiprazole treatment is very effective to treat risperidone induced amenorrhea in female patients with schizophrenia.
ID: 981730

ADJUNCTIVE ARMODAFINIL FOR NEGATIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA: A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Background: The purpose of this 24-week, double-blind, placebo-controlled, parallel-group study was to evaluate the efficacy and safety of adjunctive armodafinil for negative symptoms in adult patients with schizophrenia treated with antipsychotic medication. An earlier 4-week, proof-of-concept study had suggested that adjunctive armodafinil 200

mg/day would decrease negative symptoms in patients with schizophrenia. Methods: Adult patients with schizophrenia were eligible for the study only if they were being treated with olanzapine, risperidone, or paliperidone and had been clinically stable for at least 8 weeks. 285 patients were randomized 1:1:1:1 to once daily armodafinil 150 mg ($n = 71$), 200 mg ($n = 70$), or 250 mg ($n = 72$), or placebo ($n = 72$). The primary efficacy outcome measure was the negative scale score of the Positive and Negative Syndrome Scale (PANSS). Tolerability was assessed. Results: There was no evidence of benefit of armodafinil for negative symptoms of schizophrenia. The mean change from baseline (SD) of the PANSS negative scale score was −1.9 (3.8) for the armodafinil 150 mg group, −2.3 (3.6) for the 200 mg group, −2.0 (3.3) for the 250 mg group, and −2.2 (4.1) for the placebo group (all not significant, armodafinil vs. placebo). No significant changes in the PANSS total score were detected (armodafinil vs. placebo). Armodafinil was generally well tolerated. The most frequently occurring adverse events among patients in the armodafinil group and occurring with greater frequency than in patients in the placebo group, were headache (15% vs. 9% in placebo group), initial insomnia (9% vs. 1%), dry mouth (5% vs. 4%), nausea (7% vs. 4%), and cough (5% vs. 1%). There was no indication of any increase in positive symptoms of schizophrenia, as measured by the PANSS positive scale score, in patients in the armodafinil group. There were no new safety concerns identified by the results of laboratory tests (serum chemistry, hematology, and urinalysis), vital signs measurements, ECG findings, physical examination findings, or concomitant medication usage throughout the study. Conclusion: This study found no advantage of adjunctive armodafinil in negative symptoms in adult patients with stable schizophrenia being treated with olanzapine, risperidone, or paliperidone. Armodafinil was generally well tolerated in these patients. Sponsored by Cephalon, Inc., Frazer, PA.
ID: 978804

EFFICACY OF ILOPERIDONE IN EARLY-STAGE SCHIZOPHRENIA: RESULTS FROM A POOLED ANALYSIS OF 4 PHASE III CLINICAL TRIALS

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Background: Iloperidone (ILO), a mixed D2/5-HT2 antagonist, is indicated for the treatment of schizophrenia. This analysis evaluated the treatment effects of ILO in patients with early-stage schizophrenia in short-term trials. Methods: Data were pooled from 4 double-blind, placebo (PBO)-controlled trials (4 or 6 weeks' duration) that enrolled adult patients with schizophrenia/schizoaffective disorder (schizoaffective patients were excluded from this analysis). This analysis compared efficacy in patients with early stage (≤25 years of age or ≤5 years since onset at baseline) vs. non-early stage schizophrenia. Brief Psychiatric Rating Scale-derived (BPRSd) and Positive and Negative Syndrome Scale Total (PANSS-T) scores were analyzed. To calculate reductions from baseline, the last observation before Week 4 (1 study) or 6 (3 studies) was carried forward until Week 4 or 6, respectively, in the intent-to-treat population. To compare reductions between treatments, least squared mean (LSM) change ± standard error (SE) was derived from an analysis of covariance model with treatment, study, early stage, and treatment by early stage as factors; baseline as a covariate. Results: 1498 Patients were included in this analysis (410 with early stage and 1088 with non-early stage schizophrenia). At Week 4/Week 6, LSM ± SE mean changes (* = $P < .05$ vs. PBO) in PANSS-T scores among early patients were −8.0 ± 2.2/−8.9 ± 2.3 with ILO 4–8 mg/day, −13.4 ± 1.9*/−14.0 ± 2.1* with ILO 10–16 mg/day, −12.2 ± 1.9/−18.0 ± 3.2* with ILO 20–24 mg/day, and −7.4 ± 1.8/−5.3 ± 2.3 with PBO. Significant reductions vs. PBO were observed in BPRSd (ILO 10–16 mg/day at Weeks 4 and 6, and ILO 20–24 mg/day at Week 6). Corresponding changes in PANSS-T among non-early stage patients were −7.5 ± 1.5/−7.8 ± 1.6, −9.6 ± 1.2*/−9.7 ± 1.3*, −9.8 ± 1.4*/−9.4 ± 2.8, and −5.0 ± 1.0/−5.8 ± 1.4, respectively. Significant reductions vs. PBO in non-early stage patients were also observed in BPRSd (ILO 10–16 mg/day at Weeks 4 and 6, and ILO 20–24 mg/day at Week 4). Early stage patients responded numerically better than non-early stage patients, with significance seen with ILO 20–24 mg/day at Week 6 (PANSS-T and BPRSd, $P < .05$). Conclusion: These results suggest that ILO is effective for symptom improvement in schizophrenia patients regardless of duration of illness, and that patients with early stage schizophrenia respond well. Early stage patients responded numerically better than non-early stage patients, with significance seen with ILO 20–24 mg/day at Week 6. Support: Novartis Pharmaceuticals Corporation.
ID: 984088

HOW DOES METHODOLOGY AND TRIAL DESIGN AFFECT STUDY OUTCOMES AND INTERPRETATION?

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Background: In the recent past several major pharmaceutical companies have reduced or abandoned their commitment to the development of new CNS compounds. There are a number of factors which have contributed to these decisions. Methods: It is increasingly difficult to market a "me too" compound which places increasing emphasis on comparative superiority, either in efficacy or tolerability. These requirements call for different types of trials than have generally been conducted in the past. In addition, signal detection in CNS clinical trials, even in schizophrenia, has become more and more inconsistent and unpredictable. A review of a large selection of failed or inconclusive clinical trials was undertaken to identify common themes. Results: Patient selection processes as well as the appropriateness and operational execution of inclusion/exclusion criteria are a constant theme in failed trials. Inordinately high placebo response or disappointingly low response to the "active comparator" has become all too frequent. At the same time there is increasing need for targeting specific domains within schizophrenia such as cognition, negative symptoms and inadequately responsive positive symptoms. These targets require studies carefully designed and implemented to specifically address them rather relying on attempts to study multiple domains in the same patients simultaneously. The availability of potential biomarkers and increasing emphasis on "personalized" medicine will also influence the design and interpretation of clinical trials. Specific examples of failed or uninformative trials will be reviewed and discussed in order to highlight existing problems and novel designs to address some of these issues will also be presented. Conclusion: A new emphasis on rigorous study design with innovative elements will be necessary in the current and future environments. Everyone with a true interest in schizophrenia should contribute to advancing the field in this context.
ID: 977473

A TELEHEALTH INTERVENTION FOR SUICIDAL PATIENTS WITH SCHIZOPHRENIA

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Background: Suicide is a leading cause of premature death in patients with schizophrenia. We describe a telehealth intervention using the Health Buddy device, designed to reduce post-discharge suicide risk among indi-

viduals with schizophrenia. Our hypothesis is: Telehealth monitoring will lead to a more rapid improvement in suicidal and depressive symptoms in recently discharged patients with schizophrenia admitted for suicidal behavior. Methods: Participants had a DSM-IV diagnosis of schizophrenia/schizoaffective disorder; age >17 years; scores >0 on items 4 or 5 of the Scale for Suicidal Ideation (SSI); and 17 item Hamilton Depression Rating Scale scores >7. After discharge from the hospital for suicidal behavior, subjects entered a 6-month intensive case management program consisting of 2x weekly phone calls with SSI and Patient Health Questionnaire 9 (PHQ9) monitoring and weekly visits with a clinician. Half were also randomized to telehealth monitoring wherein the patient responds to daily electronic queries regarding depressive and suicidal symptoms. Patient responses were sent to the hospital and checked by nurses every 4 hours to provide 24/7 monitoring. Safety concerns were discussed and acted on if necessary, with the on-call staff. Face to face assessments included the SSI and Calgary Depression Rating Scale. Results: Thirty eight participants were randomized to both groups. Fifteen of 19 telehealth participants used the device regularly and 10 were still in daily monitoring by month 3; in addition, 10 control participants were active by month 3. Average daily telehealth adherence rates for months 1–3 were 81%, 80% and 84%, respectively. Over 3 months, there were no differences in Calgary Depression Rating Scale scores between the 2 groups when analyzed with a rank sum transformation repeated measures model. However, based on an intent to treat analysis, the telehealth group was more likely to reach an SSI score of 0 over the 3 months; a logistic regression analysis yielded a significant treatment x time interaction [$F(11,267) = 4.87$; $P < .001$]. Conclusion: The telehealth system provided a reliable and user-friendly means of monitoring post-discharge suicide risk in patients with schizophrenia/schizoaffective disorder. The majority of participants were able to use the telehealth monitoring system to provide daily symptom reporting. Importantly, our findings also suggest that telehealth monitoring is associated with a more rapid remission of symptoms of suicidal ideation.
ID: 950659

TIME TO RESPONSE TO ANTIPSYCHOTICS IN PATIENTS WITH RECENT ONSET SCHIZOPHRENIA

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Background: Recent reviews have led to the hypothesis of early-onset of action of antipsychotics in the treatment of schizophrenia, within the first 2 weeks of treatment. However, such data come mainly from randomized controlled trials in chronic schizophrenia. We assessed time to response to antipsychotics in subjects with recent onset schizophrenia in an outpatient setting. Methods: We conducted an open trial with patients with exacerbation of recent onset schizophrenia. Subjects were randomized to first generation antipsychotic (FGA) or second generation antipsychotic (SGA) and then assessed with PANSS at baseline and weeks 2, 4, 6, 8 and 12. We followed the IPAP algorithm (International Psychopharmacology Algorithm Project): monotherapy with an antipsychotic for 4–6 weeks, and in case of non response, patients should undergo another trial with a second antipsychotic for 4–6 weeks. If a patient does not respond to 2 antipsychotic trials, he/she is considered refractory and candidate to clozapine. Response was defined as 30% improvement of PANSS score in comparison with baseline. Remission was defined according to Andreasen's et al criteria. Results: Twenty-two patients were included (SGA = 12; FGA = 10); 17 completed the 12-week period of study. Baseline PANSS was 94,16 (±21,98). Mean age was 30,33 years (±7,9) and mean time since schizophrenia diagnosis was 1,5 year (±1,92). Mean duration os untreated disease was 1,6 year (±2,60). Completer analyses showed an initial improvement of at least 20% of the PANSS in 50% of the subjects; 41.2% responded in the first 4–6 weeks and 58.8% did not respond in the first 6 weeks. At 8–12 weeks, 76.5% have responded to the treatment and 23.5% have not. Nine patients achieved remission; 12 did not respond to the first antipsychotic and switched to a second one; 9 (75%) responded to the second antipsychotic. A regression analysis using the general linear model with time as a factor, showed a significant improvement at PANSS only at week 8. No differences were observed between FGA and SGA. Initial improvement of at least 20% at PANSS in the first 2 weeks was not related with response or remission rates at week 12. Conclusion: In this small open pilot trial we did not observe a rapid response to antipsychotic but a cumulative higher response rate over time. Initial improvement did not predict better response.
ID: 979218

A MODEL OF COGNITIVE OUTCOME MEASURE CHOICE IN EARLY TO LATE PHASE SCHIZOPHRENIA TRIALS

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Background: Two of the major aims of the MATRICS initiative were to provide recommendations about 1. A battery of cognitive tests to be used as primary outcomes in schizophrenia cognition trials, and 2. Guidelines for the design of these trials. These aims have been achieved via published guidelines and the MATRICS Consensus Cognitive Battery (MCCB). FDA representatives have accepted these recommendations for regulatory studies. However, the neurobiology and pharmacology of cognition in humans suggests that more specific cognitive neuroscience measures may yield a more sensitive cognitive signal in early phase drug development. At what point should researchers use cognitive neuroscience measures? If the ultimate goal is benefit to measures of cognition with functional relevance as reflected by the MCCB, how can early work on healthy humans and patients with schizophrenia yield results with relevance to later phase clinical trials? Methods: This presentation will review data from all available phase 2 and 3 clinical trials of cognition in schizophrenia, including 2 large-scale industry trials not previously presented or published. This presentation will also review unpublished data from schizophrenia cognitive enhancement clinical trials that have used cognitive neuroscience measures. Results: Several yet-unpublished large-scale industry studies indicate that the MCCB demonstrates excellent reliability (ICC > 0.88), minimal practice and placebo effects ($d < 0.22$), and large correlations with functional capacity measures ($r > 0.56$). Further, international versions of the MCCB in non-English languages used in these trials have produced data that are clearly comparable to data collected with the English version, with similar means, standard deviations, and distributions using US norms. Unpublished results of the Treatment Units for Research on Neurocognition in Schizophrenia (TURNS) network suggested that cognitive neuroscience tasks could be utilized in a 6-site trial, and that adequate reliability could be achieved with the N-back (1-back ICC = 0.68; 2-back ICC = 0.62) and AX-CPT (ICC = 0.72) in a clinical trials context. Conclusion: Standard cognitive outcomes and cognitive neuroscience measures have a profile of strengths and limitations that can guide cognitive outcome staging in schizophrenia trials.
ID: 977255

EFFECTS OF THE CANNABINOID-1 RECEPTOR ANTAGONIST RIMONABANT ON PSYCHIATRIC SYMPTOMS IN OVERWEIGHT PEOPLE WITH SCHIZOPHRENIA: A RANDOMIZED, DOUBLE-BLIND PILOT STUDY

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Background: Weight gain is a major side-effect of several second-generation antipsychotic (SGA) medications. Rimonabant is a cannabinoid-1 (CB1) receptor antagonist that promotes weight loss in the general population. Methods: We conducted a 16-week, double-blind, placebo-controlled pilot study of rimonabant (20 mg/day) in people with DSM-IV schizophrenia or schizoaffective disorder, who were clinically stable on SGAs. Participants had a BMI $\geq$ 27 kg/m^2 with hyperlipidemia or BMI $\geq$ 30 kg/m^2, in the absence of current substance abuse/dependence (except nicotine), more than weekly cannabis use, or recent depressive symptoms/suicidality. An exercise and dietary counseling group was offered weekly. Primary Assessments for Psychiatric Symptoms included the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS) and the Calgary Depression Rating Scale (CDS). Metabolic measurements included BMI, waist circumference, blood pressure, fasting lipids, insulin and glucose, HbA1C, and adiponectin. Target enrollment was 60; the trial was terminated early due to withdrawal of rimonabant from the European market. Results: Fifteen participants were randomized (7 rimonabant, 8 placebo); 5 completed in each group. Rimonabant was associated with a greater reduction in BPRS total score vs. placebo (mean $\pm$ S.E. difference -1.9 ± 0.8, $P = .02$), driven by differences in the BPRS anxiety/depression (-1.4 ± 0.35, $P = .0004$) and hostility (-0.7 ± 0.3, $P = .02$) factors. Group differences were not significant for the CDS total score ($P = .24$), SANS total score ($P = .13$), BMI, blood pressure, fasting lipids, glucose or other metabolic measures. Side effects did not differ between groups. Conclusion: Rimonabant was well tolerated with no significant adverse events. No significant weight loss, metabolic effects, or adverse psychiatric effects were associated with the CB1 receptor antagonist rimonabant in this small sample of people with schizophrenia. The endocannabinoid system remains a promising target for pharmacotherapy of schizophrenia and obesity.
ID: 975797

TOLERABILITY AND EFFICACY OF PALIPERIDONE PALMITATE VS. RISPERIDONE LONG-ACTING THERAPY IN SUBJECTS WITH RECENTLY DIAGNOSED SCHIZOPHRENIA

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Background: Patients with schizophrenia respond well to treatment early in the course of their illness but may be more susceptible to adverse events (AEs), contributing to partial adherence or nonadherence and to treatment discontinuation. Long-acting injectable atypical antipsychotics may be a useful option for these patients. This analysis compared the tolerability and efficacy of paliperidone palmitate (PP), administered once monthly, with that of risperidone long-acting therapy (RLAT), administered bi-weekly, in patients recently diagnosed with schizophrenia. Methods: This was a post hoc analysis of a 13-week, randomized, double-blind, double-dummy, comparative study of PP and RLAT in adults with schizophrenia (NCT00589914). This subgroup analysis included subjects diagnosed $\leq$5 years before study entry. Safety assessments included AEs, Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS), weight, and prolactin levels. Efficacy assessments included the Positive and Negative Syndrome Scale (PANSS). Between-group differences were evaluated using ANCOVA models. No adjustments were made for multiplicity. Results: 134 PP subjects and 142 RLAT subjects were included; 89.6% and 88.7% completed the study, respectively. 0.8% of PP subjects and 2.1% of RLAT subjects discontinued because of AEs. Most common ($\geq$5%) AEs (PP vs. RLAT) were injection site pain (5.2% vs. 0.7%), headache (6.7% vs. 7.0%), somnolence (3.7% vs. 5.6%), anxiety (5.2% vs. 1.4%), insomnia (6.0% vs. 6.3%), and schizophrenia symptom worsening (2.2% vs. 6.3%). Mean SAS, BARS, and AIMS scores were <1 for both groups throughout the study, with no significant between-group difference in change scores at endpoint. LS mean (SE) change in weight (kg) from baseline to endpoint was 1.7 (0.4) in both PP and RLAT groups ($P = .981$). LS mean (SE) change in prolactin (ng/ml) from baseline to endpoint was 7.8 (5.3) for PP and 14.2 (5.3) for RLAT ($P = .166$). Mean (SD) baseline PANSS total scores were 83.8 (10.0) and 81.6 (10.3) in PP and RLAT groups, respectively. LS mean (SE) improvements in PANSS total score from baseline to endpoint were similar between the PP and RLAT groups (-21.1 [2.1] vs. -20.1 [2.1]; $P = .589$). Conclusion: In patients with recently diagnosed schizophrenia, the tolerability and efficacy of PP and of RLAT were generally similar both to each other and to the overall study population.
ID: 977704

BRAIN STRUCTURE AND COGNITION IN SCHIZOPHRENIA AND THE EFFECTS OF TREATMENT

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Background: Schizophrenia is highly disabling, and much of the disability is related to cognitive impairments. Cognitive remediation is effective in improving cognition in patients with schizophrenia but the underlying neurobiologic changes that occur during these treatments and support cognitive improvement are not well known. Methods: We examined differential changes in brain morphology in early course schizophrenia patients during cognitive enhancement therapy vs. supportive therapy. In a randomized controlled trial involving 53 symptomatically stable but cognitively disabled outpatients in the early course of schizophrenia or schizoaffective disorder. Results: Patients who received cognitive enhancement therapy demonstrated significantly greater preservation of gray matter volume over 2 years in the left hippocampus, parahippocampal gyrus, and fusiform gyrus, and significantly greater gray matter increases in the left amygdala compared with those who received enriched supportive therapy. Less gray matter loss in the left parahippocampal and fusiform gyrus and greater gray matter increases in the left amygdala were significantly related to improved cognition and mediated the beneficial cognitive effects of cognitive enhancement therapy. Conclusion: Cognitive enhancement therapy may offer neuroprotective effects in early schizophrenia that are associated with improved long-term cognitive outcomes.
ID: 978580

USE OF NON-PARAMETRIC ITEM RESPONSE THEORY TO DEVELOP A SHORTENED VERSION OF THE POSITIVE AND NEGATIVE SYNDROME SCALE(PANSS) FOR PATIENTS WITH SCHIZOPHRENIA

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Background: One of the most widely used measures of psychopathology of Schizophrenia is the Positive and Negative Syndrome Scale (PANSS).Despite extensive psychometric research, it was unclear how individual PANSS items differ in their usefulness in assessing the severity. The present study(-a)examined and charactered the performance of individual items from the PANSS at both the option(severity)and item(symptom) levels,(b)examined the ability of the 3 PANSS subscales to discriminate among individual difference in illness severity, and(c)constructed scoring algorithms using a summed score linking technique while still being able to directly compare results obtained with the shortened scale to those of the original scale. Methods: Nonparametric item response theory (IRT) was used to examine (a)the performance of individual PANSS items and their options,(b)the effectiveness of various subscales to discriminate among individual differences in symptom severity, and (c)the development of an abbreviated PANSS (Mini-PANSS) linking scores on the original PANSS. Option characteristic curves(OCCs)and Item Characteristic Curves(ICCs) were estimated to examine the probability of rating each of 7 options within each of 30 PANSS items as a function of subscale severity, and summed-score linking was applied to items selected for the Mini-PANSS. Data were baseline PANSS scores from 7187 patients with Schizophrenia enrolled in clinical trials. Results: Results show the majority of items forming the Positive and Negative subscales perform very well and better discriminate along symptoms severity compared with the General Psychopathology subscale. 6 of the 7 Positive Symptom items, 6 of the 7 Negative Symptom items, and 7 out of the 16 General Psychopathology items were selected for the Mini-PANSS. Summed score linking and linear interpolation were able to produce a translation table for comparing total subscale scores on the Mini-PANSS to total subscale scores on the original PANSS. Scores on the subscales of the Mini-PANSS can be linked to scores on the original PANSS subscales with very little bias. Conclusion: The Mini-PANSS is a better indicator of the psychopathology severity. One of the implications is that the study of different dimensions of Schizophrenia may help to improve symptom-specific treatments. Also, defining subtypes of symptoms from a standardized measure instead of clinical criteria could benefit symptom dimension identification of patients.
ID: 977907

A LONG-TERM, PHASE 2, SAFETY STUDY OF LY2140023 MONOHYDRATE VS. ATYPICAL ANTIPSYCHOTIC STANDARD OF CARE IN SCHIZOPHRENIA

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Background: To compare the time to discontinuation due to lack of tolerability over 24 weeks in patients suffering from schizophrenia treated with LY2140023 monohydrate (the prodrug of a metabotropic glutamate 2/3 (mGlu2/3) receptor agonist, LY404039) or standard of care (SOC). Methods: Study HBBR is a multicenter, randomized, open-label study comparing the long-term safety and tolerability of LY2140023 monohydrate with SOC (investigator's choice of atypical antipsychotics: olanzapine, risperidone, or aripiprazole) for schizophrenia. Patients were to have moderate symptomatology, with prominent negative symptoms and evidence of functional impairment. Those who met entry criteria were randomized to open-label treatment with either LY2140023 monohydrate (target dose: 40 mg BID; $n = 130$) or SOC ($n = 131$). Results: Analysis of the primary objective showed LY2140023 monohydrate to be comparable to SOC in time to discontinuation due to lack of tolerability (ie, adverse events) ($P = .184$). The incidence of serious adverse events was comparable between groups. LY2140023 monohydrate-treated patients were significantly more likely to experience the treatment-emergent adverse events of insomnia, vomiting, agitation, and dyspepsia, while SOC-treated patients reported significantly more akathisia and weight gain. SOC was associated with greater increases in Parkinsonism, akathisia, and prolactin. One patient had a seizure during the placebo lead-in phase of the study before receiving any study medication. A second patient had 2 seizures 1 day after discontinuing 3 weeks of LY2140023 monohydrate treatment and initiating treatment with a conventional antipsychotic. The patient spontaneously recovered without any residual effects. All-cause discontinuation and discontinuation due to lack of efficacy were significantly greater in the LY2140023 monohydrate group compared with SOC. Initial improvement on PANSS total and positive scores over the 6–8 weeks of acute treatment did not differ between treatments. Improvement at the 24-week endpoint was significantly greater in the SOC group. LY2140023 monohydrate and SOC had comparable negative symptom improvement over the 24 weeks. Conclusion: These data provide further evidence that the potential antipsychotic LY2140023 monohydrate, with a glutamatergic mechanism of action, may have a unique tolerability profile characterized by a low association with adverse events that characterize currently available dopaminergic antipsychotics.
ID: 978489

NEUROCOGNITIVE IMPAIRMENT LIMITS THE RESPONSE TO TREATMENT OF AGGRESSION WITH ANTIPSYCHOTIC AGENTS

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Background: Neurocognitive impairment plays an important role in various outcome studies. The purpose of this study was to understand better its role in determining treatment response in schizophrenic patients. We investigated its role in modulating decrease in aggressive behavior in violent schizophrenic patients randomized to clozapine (CLO), olanzapine (OLZ) and haloperidol (HAL). We investigated also the interaction between treatment group and cognitive impairment to see if the latter plays a different role in each medication group. Methods: 106 physically aggressive schizophrenic inpatients were assigned to a randomized, double-blind, parallel-group, 12-week treatment. There were 34, 37 and 35 subjects in the CLO, OLZ, and HAL groups, respectively. They were administered a battery of tests assessing psychomotor, executive, and visuospatial functions, as well as visual and verbal memory prior to randomization. A general cognitive index (GCI) was derived from this battery. The Modified Overt Aggression Scale (MOAS) was used to measure the number and severity of all aggressive events, including physical, verbal and property. The overall score on the MOAS and the MOAS physical aggression score were used as the main independent variables. Psychiatric symptoms were assessed with the PANSS; side effects were also measured. Results: The 106 patients were dichotomized on the basis of GCI score into high ($N = 49$) and low ($N = 57$) cognitive impairment groups. The patients with high GCI scores were significantly more aggressive during the 12 weeks of treatment

than the low GCI patients, as determined by the Total MOAS score (F = 8.95 df = 2,105 P = .003) and the Physical Aggression score (F = 6.26, df = 2,105; P = .01). There was also a significant effect of medication treatment on aggression, CLO being superior to OLZ ($P < .01$) and OLZ superior to HAL ($P < .01$). However, there was no interaction between treatment group and cognitive impairment. In each group, the high GCI patients were more aggressive than the low GCI ones. Conclusion: In violent schizophrenic patients, cognitive functioning predicts aggression regardless of the medication used. It is important to consider the level of cognitive impairment when determining response to antipsychotic treatment.
ID: 984442

ESTROGEN TREATMENT FOR WOMEN WITH SCHIZOPHRENIA: RESULTS FROM 2 PLACEBO CONTROLLED TRIALS

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Background: Accumulating evidence suggests estrogens may have therapeutic effects in schizophrenia, via neuromodulatory and neuroprotective activity. Two studies trialling adjunctive estrogen in women with schizophrenia will be presented. The first study compared the effectiveness of adjunctive 100 mcg, and 200 mcg transdermal estradiol to adjunctive placebo in the treatment of acute psychotic symptoms in child bearing age women with schizophrenia. The second study examined the impact of adjunctive Selective Estrogen Receptor Modulator (SERM) (120 mg oral Raloxifene daily) treatment compared with placebo on the psychopathology and cognitive functioning of postmenopausal women with schizophrenia. Methods: Study One: 124 women of childbearing age with schizophrenia consented to take part in this 8-week 3-arm RCT. Participants were randomly assigned to receive either 100 mcg/day or 200 mcg/day adjunctive transdermal estradiol or adjunctive transdermal placebo. Psychopathology symptoms were assessed fortnightly using standardized assessments (eg PANSS, MADRS). Cognition assessments were conducted at baseline and at trial completion. Hormonal levels were assessed monthly. Study Two: 26 postmenopausal women with a diagnosis of schizophrenia were invited to participate in a 12-week double-blind RCT to receive either daily adjunctive Raloxifene HCl (120mg) or oral placebo. Psychopathology and cognitive assessments were as for Study One. Results: Study One: Preliminary results revealed a significant Group x Time interaction for the PANSS Positive scores, F(6,333) = 2.18, P = .045, whereby patients on estrogen (100mcg & 200mcg) showed a greater reduction in PANSS Positive symptoms, compared with the placebo group. There were no other significant differences between the 3 groups for other psychopathology measures. Study Two: One-way ANOVA found there was a significant reduction in total PANSS from baseline only with raloxifene ($P < .0005$) but not placebo ($P = .25$). A significant group interaction was also evident for General PANSS scores, with a reduction in general symptoms with raloxifene ($P < .0005$) but not placebo ($P = .42$). There was a significant decrease in depressive symptoms across the trial in both groups. Conclusion: Preliminary findings suggest that adjunctive estradiol and SERM produces greater than placebo improvements in psychotic symptoms. Estrogen is a promising new adjunctive treatment for schizophrenia.
ID: 981727

THE USE OF SELECTIVE ESTROGEN RECEPTOR MODULATORS IN THE TREATMENT OF WOMEN WITH SCHIZOPHRENIA

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Background: Several recent studies have reported prospective findings using adjunctive hormones in the treatment of psychosis and depressive symptoms, as well as the prevention of cognitive decline. The aim of this trial is to examine the impact of adjunctive SERM (120mg oral Raloxifene daily) treatment on the psychopathology and cognitive functioning of postmenopausal women with schizophrenia. Methods: Postmenopausal women with a diagnosis of schizophrenia or schizoaffective disorder were invited to participate in 12-week double-blind RCT to receive either daily oral Raloxifene HCl (120mg) or oral placebo while continuing with their previous antipsychotic treatment. Psychopathology was measured fortnightly, hormone assays monthly and cognitive function at baseline and study endpoint. Results: Preliminary analysis of the first 26 patients was conducted with mean change from baseline total PANSS scores. A two-way ANOVA found a significant time-by-group interaction for total PANSS scores, F(6,144) = 3.80, P = .002). Separate post-hoc one-way ANOVAs found there was a significant reduction in total PANSS from baseline only with raloxifene ($P < .0005$) but not placebo ($P = .25$). A significant time-by-group interaction was also evident for General PANSS scores, F(6,144) = 3.40, P = .004), with again post-hoc one-way ANOVA finding a reduction in general symptoms with raloxifene ($P < .0005$) but not placebo ($P = .42$). There was a significant decrease in depressive symptoms across the trial in both groups. Conclusion: These preliminary results have shown great promise in demonstrating the benefit of adjunctive treatment with 120 mg RLX and offers support for the potential role of this SERM in treating postmenopausal women with schizophrenia. Acknowledgements: This study is supported by National Health and Medical Research Council (NHMRC).
ID: 981689

DESIGNING A BENEFIT-RISK ASSESSMENT OF MAINTENANCE THERAPY WITH AN ORAL VS. A LONG-ACTING INJECTABLE AGENT IN SCHIZOPHRENIA

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Background: Maintenance therapy in schizophrenia is an important clinical and public health concern requiring careful balance between benefit and risk. The Benefit-Risk Action Team (BRAT) framework, developed by the Pharmaceutical Research and Manufacturer's Association, is a structured approach to benefit-risk assessment. This work describes our solutions to key schizophrenia maintenance-specific challenges when applying the BRAT framework. Methods: Initial steps in the BRAT framework focus on identification/definition of outcomes and identification/extraction of data. Clinical outcomes were identified from the literature and consultation with clinical experts. Efficacy outcomes included relapse and CGI, PSP, and PANSS scores. Safety outcomes included EPS, QT prolongation, syncope, weight gain, lipid abnormalities, and hyperprolactine-

mia. Outcome rates were developed from patient-level data in 2 double-blind placebo-controlled relapse studies with comparable (1) endpoint definitions; (2) study designs (run-in/transition, stabilization, double-blind maintenance, open-label extension); and (3) inclusion/exclusion criteria. One study used an oral formulation; the other used a long-acting injectable formulation. Results: Three issues proved challenging: (1) The stabilization and relapse criteria differed slightly between the 2 studies. To allow for fair comparison, the study populations were adjusted to match stabilization criteria. (2) Many events occurred more frequently at the start of the maintenance period. To avoid bias due to an assumption of constant risk and to study benefit-risk evolution with time, assessments were defined at multiple time points. (3) Maintenance response in the placebo arm of the injectable study was markedly higher than in the oral study, possibly because the injectable formulation from the previous stabilization period remained detectable in the plasma for several months, whereas the oral formulation cleared in days. Also, a higher placebo effect may have resulted from injection vs oral formulation. For these reasons, placebo correction of the active arm response would be misleading. Instead, the benefit-risk assessment is based on differences between the active arms for each formulation directly. Conclusion: With this work, we address the methodological challenges posed by benefit-risk analyses comparing oral antipsychotics with long-acting injectable maintenance therapy.
Supported by Ortho-McNeil Janssen Scientific Affairs, LLC
ID: 978534

THE EFFICACY OF CANNABIDIOL IN THE TREATMENT OF SCHIZOPHRENIA - A TRANSLATIONAL APPROACH

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Background: In search of new mechanisms for antipsychotic drugs translational approaches are of increasing relevance. We recently discovered that increasing of anandamide levels is accompanied by significantly less pronounced psychopathology in acute schizophrenic patients. We therefore tested the hypothesis that cannabidiol (CBD) modulated ananamide levels in humans and may thereby counterbalance psychotic symptoms in acute schizophrenia. Methods: We performed 2 randomized, double-blind, controlled, clinical trials in acute, paranoid schizophrenia patients, fulfilling diagnostic criteria of DSM-IV. First, we performed a 4-week double-blind, 2-armed, randomized, active-controlled clinical trial of CBD vs. the dopamine D2/D3-receptor antagonist amisulpride in 42 schizophrenic patients. In a second clinical trial, 29 antipsychotic-naïve, first-break schizophrenic patients were treated with either CBD or placebo for 14 days and than switched to the corresponding cross-over condition. Drop-out patients were replaced per protocol to gain a total of 18 patients treated. Endocannabinoids were measured by HPLC/MS in cerebrospinal fluid and serum from patients at certain timepoints during the trials. Results: Well comparable to amisulpride, treatment with CBD was safe and significantly improved psychotic symptoms compared with baseline. CBD displayed, however, a side-effect profile that was markedly superior to amisulpride's. It did not induce prolactin elevation, extrapyramidal symptoms or weight gain. CBD induced a significant increase in serum anandamide concentration. A linear regression slope analysis of psychotic symptom progression vs. anandamide changes in serum revealed a significant association between both. In our second, placebo-controlled trial, CBD again significantly improved psychotic symptoms during the first 14 days of treatment when compared with baseline. A MMRM analysis of all randomized patients yielded a favorable albeit not significant improvement on PANSS total for CBD vs. placebo. Ten patients terminated on placebo while only 1 patient did so early on CBD. Conclusion: Based on our findings, we suggest that the endocannabinoid system plays a significant pathophysiological role in schizophrenia and that modulation its functioning may yield antipsychotic effects in this devasting disease. Thus, modulation of anandamide levels by CBD represents a promising new approach to the treatment of acute schizophrenia.
ID: 979719

LURASIDONE IN THE TREATMENT OF ACUTE SCHIZOPHRENIA: RESULTS OF THE DOUBLE-BLIND, PLACEBO-CONTROLLED, 6-WEEK, PEARL 3 TRIAL

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Background: The aim of this study was to evaluate the efficacy and safety of lurasidone (80 mg/day and 160 mg/day) in patients with an acute exacerbation of schizophrenia. Methods: Hospitalized patients who met DSM-IV criteria for schizophrenia with a PANSS total score ≥80 were randomized to 6-weeks of double-blind treatment with lurasidone 80 mg ($N = 125$), lurasidone 160 mg ($N = 121$), quetiapine XR 600 mg (QXR; $N = 120$; included to confirm assay sensitivity), or placebo ($N = 122$), administered once-daily in the evening. A mixed model repeated measures (MMRM) analysis was performed for the primary measure, the Positive and Negative Symptoms of Schizophrenia Scale (PANSS) total score, and the key secondary measure, the Clinical Global Impression-Severity scale (CGI-S). Safety and tolerability measures included adverse events, weight, and lipids. Results: Treatment with lurasidone was associated with significantly greater endpoint improvement on the PANSS total score vs. placebo (−10.3) among patients in the 80 mg (−22.2; $P < .001$) and 160 mg (−26.5; $P < .001$) dosage groups. On the CGI-S, significant improvement was observed vs. placebo (−0.9), during treatment with both the 80 mg (−1.5; $P < .001$) and 160 mg (−1.7; $P < .001$) doses of lurasidone. Significant separation from placebo occurred by Day 4 for both lurasidone doses on the PANSS total score, and for the 160 mg dose on the CGI-S. QXR produced significantly greater improvements than placebo on the PANSS total score (−27.8 vs. −10.3; $P < .001$) and the CGI-S (−1.7 vs. −0.9; $P < .001$). The following adverse events occurred with an incidence ≥5% and ≥2-times placebo: akathisia (L80; L160), nausea (L80; L160), parkinsonism (L80; L160), dizziness (L80; L160), somnolence (QXR), constipation (QXR), dry mouth (QXR), increased weight (QXR), arthralgias (QXR). Treatment with lurasidone 80 mg and 160 mg, respectively, was associated with a mean increase in weight that was not significantly different from placebo (+0.6 kg and +0.6 kg vs. +0.1 kg) while the mean increase in weight was significantly higher with quetiapine XR (+2.1 kg; $P < .001$). Total cholesterol and triglycerides were decreased at endpoint on both doses of lurasidone, but were increased on quetiapine XR. Conclusion: In this study, lurasidone, in doses of 80 mg and 160 mg, was effective for the treatment of patients with an acute exacerbation of schizophrenia. Treatment with lurasidone was not associated with clinically meaningful effects on weight or lipids.
ID: 979705

A BOTTOM-UP BIOFEEDBACK REMEDIATION IMPROVES EMOTION RECOGNITION IN SCHIZO-

PHRENIA: EVIDENCE FROM A VISUAL SCAN PATH PILOT STUDY

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Background: Cognitive deficits in schizophrenia are now widely accepted as both a core feature of schizophrenia and an area lacking effective treatment regimes. Their resistance to the effects of antipsychotic mediations, association with functioning and apparent separateness from positive symptoms demonstrates the need for efficacious treatments targeting cognition. To date, remediation strategies have adopted a largely top-down remediation approach. This is despite extensive evidence for bottom-up sensory training resulting in downstream, higher order improvements. However, this has largely been ignored in the schizophrenia remediation literature. The rationale for the present study was that in order for the brain to assign meaning to face emotion stimuli it must first generate reliable neurological responses relating to the location and sampling of sensory information. Utilizing a novel remediation strategy derived from the neurosciences, we predicted that visual scanpath performance would be altered (with patients recording a less restricted viewing strategy and increased fixations) with a downstream improvement in emotion recognition. Methods: Twenty five participants with schizophrenia were randomly allocated to a emotion recognition treatment program (METT/SETT) or a biofeedback based treatment. Participants completed training weekly for 6 weeks. At baseline, post treatment and 6 weeks follow-up participants completed a battery of tasks assessing face emotion and complex stimuli recognition and SPEM tasks while their eye movements were recorded. Results: Post treatment improvement was observed (P = .001) with both remediation groups showing improvement in emotion recognition. Further, paired sample t test revealed a significant increase in raw scanpath length for the biofeedback group only post treatment ($P < .05$). No pre/post change in SPEM performance was reported for either treatment group. Conclusion: Training targeting low level visual processes results in gains in emotion recognition, a process highly relevant to psychosocial functioning in schizophrenia. Further, these gains were observed at a psychophysiological level via the normalization of some visual scanpath parameters for the bottom-up based remediation alone suggesting that treatments targeted at low level functions have significant downstream effects.
ID: 977447

PREDICTORS OF OUTPATIENT ADDICTION TREATMENT DROPOUT IN ADULTS WITH CO-OCCURRING SERIOUS MENTAL ILLNESS

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Background: Adults who suffer from co-occurring drug use disorders and schizophrenia and other forms of serious mental illness (SMI) are at heightened risk of dropping out of outpatient addiction and mental health treatment prematurely. Outpatient treatment dropout is associated with a variety of negative outcomes. Predictors of outpatient addiction treatment dropout in individuals with co-occurring SMI are not well understood. The aim of this study was to determine if demographic variables, measures of cognitive functioning, and/or measures of substance use and psychiatric severity predicted treatment dropout. Methods: We investigated predictors of addiction treatment dropout in 94 adults diagnosed with SMI who received 12 weeks of contingency management (in addition to treatment as usual) for stimulant dependence as part of a larger RCT. Treatment dropout was defined as 3 consecutive weeks of not attending contingency management treatment appointments. Predictors of treatment dropout included baseline demographic variables, measures of cognitive functioning, as well as measures of substance use and psychiatric severity. Logistic regression was used to identify independent predictors of treatment dropout. Results: Treatment dropout occurred in 58% (n = 55) of participants. In the logistic regression analysis measures of recent drug use severity (positive urinalysis, high levels of >9 days of drug use in the last 30 days), and higher levels of self-reported paranoia independently predicted treatment dropout. Participants who presented to treatment with predominately positive (vs. negative) symptoms were also more likely to dropout of treatment. Conclusion: Accounting for demographic and cognitive variables, measures of recent drug use and positive symptoms predicted dropout in a sample of SMI adults receiving evidence based addiction treatment.
ID: 980087

A RANDOMIZED CLINICAL TRIAL OF FAMILY-AIDED ASSERTIVE COMMUNITY TREATMENT FOR YOUNG PERSONS AT HIGH RISK FOR ONSET OF AN INITIAL PSYCHOSIS

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Background: This report describes a randomized clinical trial that compared (a) family-aided assertive community treatment (FACT) and psychotropic medication to (b) medication, family education and family crisis intervention (Comparison)in reducing symptom levels, improving functioning, and preventing the onset of psychosis in young people at clinical high risk (CHR) for psychosis. Methods: CHR subjects were identified via community education about attenuated psychotic symptoms, targeting school counselors, pediatricians, and mental health professionals in a catchment of 340 000 people. Community-referred young people aged 12–35 were assessed using the Structured Interview for Prodromal Syndrome (McGlashan, et al., 2002). The test treatment was a comprehensive, prodrome-specific combination of psychoeducational multifamily group (PMFG), supported education/employment and assertive community treatment. Psychotropic medication was prescribed by symptom indication. Patients received independent assessments at baseline and 24 months, blinded to experimental condition. The outcomes were conversion to psychosis, clinical symptoms and psychosocial functioning. Results: 100 CHR young people (53 males, 47 females, mean age 16.3 years) were identified and randomly assigned to FACT vs. Comparison conditions. By 24 months, conversion to psychosis occurred in 8% of the FACT cohort and 16% in the comparison condition; however, the difference was not statistically significant (P = .22). Positive, negative, disorganized and general symptoms all improved significantly but equally, as did functioning. Mean GAF was 40.2 and 36.4 at baseline and 55.5 and 52.7 at 24 months, respectively, (pre-post, $P < .01$), but treatment differences were non-significant. 94% and 90% were functioning in expected roles (n.s.). Post-hoc deconstruction analysis found that, controlling for other significant treatment components, PMFG intervention accounted for functional outcomes (B = 0.417, t(56.85)=3.29, P = .002), while antipsychotic and antidepressant medication did not. Conclusion: Outcomes for psychosis onset, symptoms and functioning were equally positive in the 2 test conditions. The PMFG component was individually associated with functional benefit. Less intensive interventions may be effective in the treatment of some CHR youth.
This study was supported by NIMH and Robert Wood Johnson Foundation.
ID: 978730

DOES EXTENDED SPECIALIZED INTERVENTION FOR PATIENTS WITH FIRST EPISODE PSYCHOSIS IMPROVE OUTCOME IN THE CRITICAL PERIOD? THE OPUS II TRIAL

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Background: The Danish OPUS trial succeeded in randomizing 547 patients with first-episode psychosis to a 2-year specialized intensive assertive treatment program (OPUS) or standard treatment. The results clearly favored OPUS treatment, and psychotic and negative symptoms, substance abuse, adherence to treatment, use of antipsychotic medication, user satisfaction, and use of bed days were better in OPUS compared with standard treatment. However, the 5-year follow-up, 3 years after patients from OPUS were transferred to standard treatment, showed that the positive clinical effects were not sustained, when the intensive treatment was terminated, except from OPUS-patients being less likely to stay in institutions than patients who received standard care. The results at 5-year follow-up clearly indicate the need for investigating how long time the intensive treatment should last to ensure long lasting clinical effects. It has been hypothesized that there is a critical period up to 5 years after onset of illness, which represents a window of opportunity where a long-term course can be influenced. It is possible that extending the specialized assertive intervention service up to 5 years will allow the beneficial effects to continue beyond this high-risk period? Methods: The trial is a randomised clinical trial. Inclusions criteria: Patients, aged 19–37 years, with first episode psychosis in the schizophrenia spectrum, received OPUS treatment for 2 years. 400 patients treated in OPUS will after 2 years of treatment be randomised to 3 years further OPUS treatment vs. transfer to standard treatment. The integrated OPUS treatment consisted of 3 core elements; Assertive Community Treatment, family treatment and social skills training. Primary outcome measure: Negative symptoms. Secondary outcome: Simultaneous remission of psychotic and negative symptoms, substance abuse, user satisfaction, adherence to treatment, compliance with medication, suicidal behavior, working alliance, self- efficacy, use of bed days, ability to live independently, and labor market affiliation. Results: Inclusions of patients started July 2009 and expected to be complied in the fall 2011. Conclusion: The results will guide the implementation of specialized early intervention services in Denmark and other countries.
ID: 977549

LURASIDONE IN THE TREATMENT OF ACUTE SCHIZOPHRENIA: RESULTS OF THE DOUBLE-BLIND, PLACEBO-CONTROLLED PEARL 2 TRIAL

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Background: The aim of this study was to evaluate the short-term efficacy and safety of lurasidone in patient with acute schizophrenia. Methods: Hospitalized patients who met DSM-IV criteria for schizophrenia were randomized to 6-weeks of double-blind treatment with lurasidone 40 mg (n = 119), lurasidone 120 mg (n = 118), olanzapine 15 mg (n = 122; included to test for assay sensitivity) or placebo (n = 114), dosed once-daily. After 3 weeks, patients were eligible for discharge. A mixed model repeated measurements (MMRM) analysis was performed for the Week 6 change from baseline in PANSS total (primary efficacy measure) and CGI-S (key secondary efficacy measure) to evaluate the efficacy of lurasidone. Results: Treatment with lurasidone was associated with significantly greater Week 6 improvement on the PANSS total score vs. placebo (−16.0) among patient in the 40 mg (−25.7; adjusted P = .002) and 120 mg (−23.6; adjusted P = .022) dosage groups, as well as on the PANSS positive and negative subscales. Treatment with lurasidone was also associated with significantly greater improvement on the CGI-S vs. placebo (−1.1) in both the 40 mg (−1.5; adjusted P = .011) and 120 mg (−1.4; adjusted P = .040) dosage groups. No dose-response relationship was observed on the PANSS total or subscale scores, or the CGI-S scores, for the 40 mg vs. 120 mg doses of lurasidone. Olanzapine 15 mg/day produced significantly greater improvement than placebo on the PANSS total score, CGI-S, and PANSS positive and negative subscales. The proportion of patient experiencing ≥7% weight gain was 5.9% for combined lurasidone doses, 34.4% for olanzapine and 6.9% for placebo. Median change in triglycerides at LOCF endpoint was similar for lurasidone and placebo (+1.0 vs. −1.0 mg/dl) compared with an increase of +24.0 mg/dl for olanzapine. Lurasidone 40 mg was associated with a lower adverse event rate, and lower discontinuation due to adverse events, compared with lurasidone 120 mg. Conclusion: In this multicenter, double-blind, placebo-controlled, Phase 3 trial, lurasidone, at fixed daily doses of 40 and 120 mg, was a safe and effective treatment for patients with an acute exacerbation of chronic schizophrenia. Changes in weight, lipids, and glucose among patient treated with lurasidone were comparable to placebo. Treatment with olanzapine was associated with marked effects on weight and selected metabolic parameters compared with placebo.
ID: 979604

A FEASIBILITY STUDY OF A MULTI-SITE TRIAL OF NEUROPSYCHOLOGICAL EDUCATIONAL APPROACH TO COGNITIVE REMEDIATION

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Background: The field of cognitive remediation has rapidly developed to address cognitive dysfunctions of schizophrenia. While a number of methods have been tested in lab settings, the field is ready to examine their feasibility outside the lab into community settings. The current study reports findings on feasibility of Neuropsychological Educational Approach to Cognitive Remediation (NEAR) from a multi-site trial at 5 community hospitals. Methods: Sixty-nine patients with schizophrenia and 4 patients with schizoaffective disorder participated in the study. There was no significant difference between treatment group (N = 51) and control group (N = 22) in terms of their age, gender ratio, illness duration, age of illness onset, and symptom severity. Treatment group showed higher baseline cognitive test scores compared with control group. Treatment group participated in 2 weekly computerized remediation sessions and a weekly verbal bridging session for 6 months, while control group received treatment as usual. Session attendance rate was 90.1%. Brief Assessment of Cognition for Schizophrenia (BACS) was administered to all participants; Social Functioning Scale (SFS), MOS-SF36 ver2 (Medical Outcomes Study 36-item Short-Form scale), PANSS (Positive and Negative Syndrome Scale) were administered to treatment group at pre- and post-intervention. Control group was administered BACS with 6-months intervals. The study protocol was ap-

proved by the relevant IRBs and all participants provided informed consent. Core clinicians at respective sites underwent training and received supervision. Treatment fidelity was confirmed by independent raters. Results: Results of ANCOVAs with baseline cognition as covariates indicated significant interaction effects (time × group); treatment group demonstrated larger increase in verbal memory and learning ($P < .001$, effect-size = .176), working memory ($P < .001$, effect-size = .180), verbal fluency ($P < .033$, effect-size = .064), executive function (effect-size = .098), and overall cognition ($P = .001$, effect-size = .155). Among MOS-SF36 subscales, physical functioning ($P = .002$) and social functioning ($P = .012$) showed significant increase at post-intervention. There was no significant difference for SFS and PANSS scores. Conclusion: The present study suggests that a multi-site trial of NEAR is feasible and produces some modest but positive outcomes in areas of cognition and QOL. This study was financially supported by Grant-in-Aid for Scientific Research C 20530630.
ID: 978246

INTEGRATED NEUROCOGNITIVE THERAPY (INT): FINAL RESULTS OF AN INTERNATIONAL RCT INCLUDING A 1-YEAR FOLLOW-UP

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Background: Nowadays the treatment of cognition is one of the main topics in the therapy of schizophrenia patients. The NIMH MATRICS initiative established a consensus on separate neurocognitive and social cognitive domains that are relevant for the treatment of schizophrenia. Therefore, we expanded the well evaluated and implemented Integrated Therapy Program (IPT) and we developed the Integrated Neurocognitive Therapy (INT) designed for schizophrenia outpatients. This new cognitive-behavioral group therapy approach covers all cognitive MATRICS domains. INT is partly computer based and intends to restitute and compensate neurocognitive and social cognitive (dys-) functions. This ''bottom up'' and ''top down'' approach puts a strong focus on the patients' daily life context to promote transfer and generalization. INT additionally intends to facilitate intrinsic motivation and resources. Methods: During the last 5 years, INT was evaluated in an international randomized multi-cite study in Switzerland, Germany and Austria, which was supported by the Swiss National Science Foundation. INT was compared with treatment as usual (TAU). INT patients received 30 therapy sessions twice a week, lasting 90 minutes each. A comprehensive assessment battery comprising proximal and distal measures was applied before and after therapy and at a 1-year follow-up. Expert ratings were administered blindly. Finally, 169 outpatients from 8 centers could be included in the study. Results: INT patients obtained significantly stronger effects in proximal outcome as composite scores in neurocognition and social cognition indicated it. In detail, the superiority of INT reached significance level in speed of processing, attention, reasoning and problem solving, emotion perception, and partly in attribution and schema. Effects could be maintained at follow-up of 1 year. Additionally, INT patients showed significantly reduced negative symptoms, increased social functioning and coping (distal outcome measures). Furthermore, the improved motivation and insight into illness during therapy supports the didactic strength of INT technology. Finally, the low drop-out rate of 10.3% of the INT patients during the study represents a high acceptance by the patients. Conclusion: Results support evidence that INT is an efficient, economic, easy to handle and well accepted new group therapy approach for schizophrenia outpatients.
ID: 979312

IMPACT OF LURASIDONE AND OLANZAPINE ON FRAMINGHAM 10-YEAR CORONARY HEART DISEASE RISK ESTIMATE IN SCHIZOPHRENIA

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Background: Patients with severe mental illness are at increased risk for coronary heart disease (CHD)-related mortality. We conducted a post-hoc analysis to test the significance of treatment effects on Framingham Risk Score (FRS). Estimates of 10-year CHD risk and their changes from baseline to Week 6 endpoint were compared in a double-blind, placebo-controlled study of lurasidone and olanzapine in acute schizophrenia patients. Methods: At screening, demographics and medical history were measured. Vital sign and fasting lab measures were evaluated at baseline and over the 6-week study. Subjects were randomized to fixed doses of lurasidone 40 or 120 mg/day (LUR), olanzapine 15 mg/day (OLZ), or placebo (PBO). An analysis of covariance model, with terms for treatment, gender, treatment-by-gender interaction, and baseline value was applied. Results: The FRS analysis sample included 315 subjects aged >30 years. The CHD risk factor prevalence rates in the baseline sample were: diabetes 12%, hypertension 22%, low HDL 45%, and high total cholesterol 17%. Baseline smoking prevalence was overall 68% but significantly higher in males (75%) vs. females (47%)($P < .001$). The baseline mean 10-year CHD risk was higher in males (9%) vs. females (5%), per Wilson et al. (1998). Average risk ratio (10-year CHD absolute risk relative to normal reference risk) was 2.3 for males and 1.4 for females. At Week 6, changes from baseline in overall 10-year CHD risk were: for LUR, baseline 8.4% to endpoint 8.3%, for PBO, baseline 6.6% to 7.2%, and for OLZ, 8.5% to 10.3%. Changes were significantly higher in men treated with OLZ (9.4%–12%) vs. LUR (9.4%–9.3%) ($P < .001$) and vs. PBO (7.6%–8.3%) ($P < .001$). In contrast, no female group showed significant Week 6 differences (treatment-by-gender interaction effect, $P < .01$). Changes in CHD risk factors included 23 new diabetes cases (LUR 3.8%, OLZ 14%, and PBO 6.8%) ($P > .05$). There were elevations of hypertension risk in men receiving OLZ vs. PBO ($P < .05$). Fasting total cholesterol levels significantly increased among males treated with OLZ (+6.8 mg/dl) vs. LUR (−9.2 mg/dl) and PBO (−10.6 mg/dl) ($P < .05$). Conclusion: These 6-week study results indicate LUR and PBO had similar acute effects on 10-year CHD risk in patients with schizophrenia, while OLZ was associated with higher risks in male patients vs. placebo. Further research involving long-term treatment is merited to verify these findings.
ID: 978910

ANTIPSYCHOTIC MONOTHERAPY TREATMENT WITH ATYPICALS IN OUTPATIENTS WITH SCHIZOPHRENIA: RESULTS FROM A NATURALISTIC OBSERVATIONAL STUDY

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Background: Antipsychotic monotherapy is recognized as the treatment of choice for patients with schizophrenia. This study assessed the annual rate and duration of antipsychotic monotherapy among patients with schizophrenia initiating treatment with olanzapine, risperidone, quetiapine or amisulpride in the Schizophrenia Outpatient Health Outcomes (SOHO) Study. Methods: The SOHO study was an observational, 3-year prospec-

tive study which enrolled 10 972 patients from 10 European countries. This post-hoc analysis focused on patients ($N = 6866$) who were evaluated at all time points during the first year of the study, and initiated with olanzapine, risperidone, quetiapine, or amisulpride at baseline, either in monotherapy or with another antipsychotic. The percentage of patients with monotherapy at baseline, taking monotherapy after 1 year post initiation, and the cumulative number of days on monotherapy were calculated for all patients and for each of the 4 atypical antipsychotic treatment groups. Analyses employed repeated measures generalized linear models and non-parametric bootstrap re-sampling, controlling for patient baseline characteristics. Results: Approximately two thirds of the patients (68.8% or 4724/6866) were on baseline antipsychotic monotherapy after 1 year post-initiation. The percentage was higher for olanzapine (72.9%) than risperidone (67.8%), quetiapine (48.1%) and amisulpride (57.8%) ($P < .05$ for all pair-wise comparisons). The multivariate model also showed that olanzapine-initiated patients were significantly more likely to be on monotherapy with the initiating antipsychotic at the end of the 1-year period, compared with risperidone (OR = 0.64; 95% CI: 0.54–0.75), quetiapine (OR = 0.29; 95% CI: 0.23–0.36) and amisulpride (OR = 0.42; 95% CI: 0.30–0.60). In addition, the bootstrapping results demonstrated that the mean cumulative number of days on baseline monotherapy was also significantly greater for olanzapine (272) compared with risperidone (261), quetiapine (210) and amisulpride (233). Conclusion: The proportion of patients on monotherapy and the duration of monotherapy treatment appear to vary by antipsychotic medication. Olanzapine was the medication with the highest monotherapy rate and the longest duration of maintained monotherapy, followed by risperidone, amisulpride and quetiapine. Limitation: Results should be interpreted conservatively due to the observational study design.
ID: 979129

OLANZAPINE PLASMA LEVELS AND DOSE: FINDINGS FROM A 10 YEAR REVIEW OF A THERAPEUTIC DRUG MONITORING SERVICE

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Background: Olanzapine therapeutic drug monitoring (TDM) is the measurement of plasma olanzapine concentrations in an appropriate blood sample, which may be helpful in guiding dosage. We aimed to investigate the relationship between olanzapine dose and plasma levels based on TDM use in routine clinical practice. Methods: We audited data from blood samples submitted for routine plasma olanzapine analysis to a therapeutic monitoring laboratory in King's College Hospital (1999–2009, London, UK). Samples taken post-mortem or submitted for suspected self-poisoning were excluded. Plasma olanzapine was measured by high-pressure liquid chromatography with UV detector and more recently with mass spectrometry, conforming to FDA/CDER standards. Descriptive analyses and multi-linear regression analysis were conducted to investigate predictors factors for olanzapine plasma levels. Dose (mg/day) groups were 2.5–5, 7.5–10, 12.5–15, 17.5–20, 22.5–25, 27.5–30, 32.5–40, >40. Results: In all 5856 samples from 3207 patients were analysed. 77% of males and 62% of females were smokers at the time of sampling. Prescribed dose information was available for 3371 (58%) samples. Daily doses ranged from 2.5 mg to 95 mg. For every dose a wide range of plasma levels was detected. For doses up to 20 mg/day, only 22.1%–34.2% were within the target range of 20–39 μg/l. As dose increased, plasma levels were more likely to be reported in the potentially toxic range of >60 μg/l (up to 20 mg: 1.5%–21.5%; >20 mg: 29.8%–59.1%). For dose range 17.5–20 mg/day: the proportion of samples in the plasma concentration rangers were <2 μg/l: 3.7%, 2–19 μg/l: 18.4%, 20–39 μg/l: 34.2%, 40–59 μg/l: 22.2%, 60+ μg/l: 21.5%. Ninety-two samples were from patients aged <18 years and the same patterns were detected but with higher mean levels per dose. The multivariate linear regression model for adults aged 18 and over included dose, smoking status, sex, age, and body weight and predicted 24% of the variance for olanzapine plasma concentration levels with females and non-smokers having higher levels for a given dose than males and smokers. Conclusion: For each dose of olanzapine, plasma levels varied considerably. The biovariability seen is in part explained by increasing dose, smoking, male gender and weight. However, degree of adherence, timing of sample post-dose, and interaction with concomitant medication may also contribute. Olanzapine TDM may have a useful role in routine clinical practice for patients of all ages and particularly so for doses above 20 mg/day.
ID: 986680

EFFECT OF LURASIDONE ON WEIGHT AND METABOLIC PARAMETERS: RESULTS FROM POOLED SHORT-TERM PLACEBO-CONTROLLED AND LONG-TERM EXTENSION TRIALS IN SCHIZOPHRENIA

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Background: The aim of this analysis was to evaluate the safety of lurasidone treatment of schizophrenia on weight and metabolic parameters. Methods: Data were pooled from 5 double-blind, placebo-controlled, short-term (6-week) treatment studies of patients who met DSM-IV criteria for schizophrenia with an acute exacerbation. The short-term safety analysis sample consisted of patients treated with lurasidone (dose range, 20–120 mg, total $N = 1004$); olanzapine 15 mg ($N = 122$) and haloperidol 10 mg ($N = 72$)—both drugs included for assay sensitivity; and placebo ($N = 455$). Long-term (3-, 6-, 9-, and 12-month) open-label treatment data were also available on a combined lurasidone sample of 238 patients. Results: In the short-term (6 week) treatment sample, mean LOCF endpoint weight gain was +0.75 kg for the combined lurasidone dosage group, +4.15 kg for olanzapine, +0.02 kg for haloperidol, and +0.26 kg for placebo. The proportion experiencing ≥7% weight gain was 5.6% for combined lurasidone, 34.4% for olanzapine, 4.2% for haloperidol, and 4.0% for placebo. Median endpoint change in lipids were as follows: triglycerides (mg/dl), −5.0 for combined lurasidone, +25.0 for olanzapine, −3.0 for haloperidol, and −7.0 for placebo; total cholesterol (mg/dl), −8.0 for lurasidone, +9.0 for olanzapine, −8.0 for haloperidol, and −10.0 for placebo; similar trends existed for changes in LDL, HDL. Mean LOCF-endpoint change in glucose (mg/dl) and HbA1c (%), respectively, were similar for combined lurasidone (+1.3; +0.02), haloperidol (+1.5; −0.02), and placebo (−0.7; −0.02), but was higher for olanzapine (+10.4; +0.18). In the long-term (12-month) treatment sample, mean change in weight at Month 12 was −0.71 kg for the combined lurasidone treatment group; and Month 12 changes in metabolic parameters were: +0.2 mg/dl for glucose (mean), −3.0 mg/dl for total cholesterol (median), and −4.0 mg/dl for triglycerides (median). Similar trends existed for changes in LDL and HDL. Conclusion: In a pooled analysis of short-term treatment studies, treatment with lurasidone, in doses up to 120 mg/day, was associated with changes in metabolic parameters that were comparable to placebo. Short-term olanzapine therapy was associated with clinically significant increases in weight and metabolic parameters compared with placebo. Long-term treatment (up to 12 months) with lurasidone was not associated with clinically significant effects on weight or metabolic parameters.
ID: 979871

A SCOPING REVIEW OF CULTURALLY ADAPTED PSYCHOSOCIAL INTERVENTIONS FOR SCHIZOPHRENIA

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Background: An increased incidence of schizophrenia has been established in migrant populations. There is also concern provision of psychosocial interventions to minority communities is poor. Several Randomised Controlled Trials (RCTs) of culturally adapted interventions have shown significant improvements in clinical outcomes for non-anglophone psychosis sufferers. A scoping review was undertaken to examine the range and nature of existing culturally adapted psychological interventions for schizophrenia and to determine the feasibility of undertaking a full systematic review. Methods: Studies culturally adapting a psychosocial intervention for schizophrenia were identified via searching electronic databases, reviewing citations and contacting authors. Inclusion criteria required participants to suffer schizophrenia and schizophrenia like disorders; and to be from an ethnic minority and/or culturally distinct population. Study design or outcome measures were not exclusion criteria. Results: 41 studies were identified that met inclusion criteria. A narrative synthesis explored the diversity of the studies in terms of study design, setting, psychological intervention, cultural adaptation, outcome, outcome measures and quality assessment. 30 RCTs were identified all with 95% or more participants diagnosed with schizophrenia spectrum psychoses. A scale was developed to measure the extent to which cultural adaptations were made to RCTs. Adaptations ranged from simple translation to multiple adaptations including therapist-client ethnic matching, use of culturally familiar content, culturally sensitive negotiation of treatment goals and discussion of illness beliefs, recognizing family hierarchy and structure, addressing community stigma and acculturative stress. Conclusion: There is a considerable body of international research evidence concerning cultural adaptation of psychosocial interventions for schizophrenia. A full systematic review will be undertaken to evaluate the quality and effectiveness of trials.
ID: 977817

D-SERINE FACILITATION OF COGNITIVE RETRAINING IN PATIENTS WITH SCHIZOPHRENIA

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Background: There is a need to develop more effective treatments for the cognitive deficits of schizophrenia. The purpose of the study was to evaluate the feasibility and efficacy of the combination of D-Serine, an agonist of the NMDA glycine site, and Computerized Cognitive Retraining (CRT) in improving cognitive deficits of schizophrenia. Methods: In a double-blind, placebo-controlled design, antipsychotic-treated patients with schizophrenia ($n = 82$) were randomized to 1 of 4 arms: a) D-Serine (30 mg/kg) plus CRT (5 hours/week), b) placebo D-Serine plus CRT, c) D-Serine plus control CRT (video viewing), d) placebo D-Serine plus control CRT for 12 weeks. After completion of active treatment, subjects were followed up for 6 months to determine if any effects persisted beyond the active treatment phase. Of 82 subjects who were randomized, 64 completed the 12-week active phase and 43 completed the 6-month follow-up. Raw data was converted to scaled-scores and analyzed using mixed models. Results are reported as ''change from baseline scaled-scores'' unless specified. Results: At the 12 week end-point, D-Serine alone improved (trend) performance on measures of attention and working memory. CRT alone resulted in a significant improvement on sustained attention. The combination of D-Serine and CRT resulted in a significant improvement in the Cognitive factor of the PANSS, attention and a measure of Social Skills (scaled-scores). At the 6 month time-point, the combination of D-Serine and CRT significantly improved PANSS Negative Symptoms and trended to improve attention. There was no worsening of motor side-effects or depression. Conclusion: The findings of this study demonstrate the feasibility of combining a psychopharmacological and cognitive remediation approach in schizophrenia patients. Furthermore, the combination of D-Serine and CRT is well-tolerated though its effects on cognition are neither robust nor sustained.
ID: 978564

THE INTERACTIONS OF CBD AND THC IN THE LABORATORY AND THE EFFECTS OF ADJUNCTIVE CBD ON THE SYMPTOMS, SIDE EFFECTS AND METABOLIC FUNCTION IN SCHIZOPHRENIA

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Background: Cannabis contains a number of compounds including delta-9-Tetrahydrocannabinol (THC) and cannabidiol (CBD). THC, believed to be responsible for the psychotic effects of cannabis, produces a wide range of psychotomimetic, cognitive and psycho-physiological effects (such as P300 deficits) in healthy humans that are relevant to schizophrenia. CBD, on the other hand, does not have any propsychotic effects and instead appears to reduce the overall psychotic effects of cannabis. Data from preclinical studies support the antipsychotic potential of CBD in a number of animal models of psychosis. Further, CBD appears to attenuate some THC-induced effects, whether this extends to THC-induced psychotomimetic effects is unclear. Finally, limited data from small numbers of patients suggest that CBD has antipsychotic effects in schizophrenia. Methods: We currently have a 2-prolonged approach to characterize the safety and antipsychotic potential of CBD: 1) Pilot study in patients with schizophrenia: examining the safety, tolerability and efficacy of CBD augmentation on psychotic symptoms, cognitive deficits and metabolic profiles in antipsychotic treated patients with schizophrenia; and 2) A proof of concept, phase I study in healthy subjects in a laboratory model of THC induced psychotomimetic effects: The effects of CBD pretreatment in attenuating a on a wide range of THC- induced behavioral, cognitive, psycho-physiological and endocrine measures relevant to schizophrenia are being assessed. Results: Results from the ongoing clinical trial suggest that CBD is well tolerated in stable but symptomatic patients with schizophrenia and produces improvements in psychotic symptoms, verbal learning as well as a wide range of metabolic parameters including abdominal circumference, fasting labs and insulin resistance. These data will be presented along with the results from the phase I study. Conclusion: CBD may have potential as a novel antipsychotic with impact on the cognitive and metabolic dysfunction associated with schizophrenia.
ID: 980030

PANSS ITEM RELIABILITY: CAN STANDARDIZED RATER TRAINING IMPROVE NEGATIVE SUBSCALE ITEM RELIABILITY?

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Background: Paloa et al. (1994) identify the assessment of negative symptoms as important in the assessment of change in overall psychopathology

in schizophrenia. The accurate assessment of negative symptoms is also critical in the development of treatment for this debilitating, often under treated and recalcitrant feature of schizophrenia. However the assessment of these symptoms is difficult and numerous studies (eg, Möller, 2007; Betsen et al., 1996; Norman et al, 1996) have found that Negative Subscale items in the PANSS are somewhat less reliable than those in the Positive and General Subscales. Rater error, the subtlety of these symptoms, and the subjective nature of many of these items have been identified as probable culprits. Standardized rater training has been identified as one way to improve overall PANSS reliability. Here we asked if this applied equally to the Negative Subscale and if these results were durable. Methods: Results from several large standardized rater training events were analyzed. Training included both applied and didactic components. Raters were asked to rate the PANSS from a video-taped assessment before and after training. The inter-rater reliability was determined using intra-class correlation coefficient (ICC) for pre and post training scores on the Negative Subscale of the PANSS. Results: There appeared to be an improvement in the reliable assessment of Negative Subscale items after training in all cases examined. The ICC range for the PANSS Negative Subscale before training ranged from 0.358 (n = 11, $P < .001$) to 0.615 ($n = 30$, $P < .001$). The range of post training ICCs were 0.764 ($n = 9$, $P < .001$) to 0.945 ($n = 30$, $P < .001$). Conclusion: Based on the improvement in inter-rater reliability it appears that standardized rater training has a significant impact on the assessment of negative symptoms. It is posited that this effect is related to the framework to discuss and engage with the instrument as well as the exposure to clinical examples. Although every rater has unique clinical experience with the target population, the goal of standardized rater training is to encourage the consistent conceptualization of subscale items in the PANSS instrument.
ID: 983083

WEB-BASED HOME DELIVERY OF MULTI-FAMILY PSYCHOEDUCATIONAL THERAPY TO PERSONS WITH SCHIZOPHRENIA AND THEIR FAMILY MEMBERS: 1-YEAR OUTCOMES AND COGNITIVE DESIGN

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Background: This presentation will discuss the findings from a study that used a website and home computers to deliver on-line multi-family psychoeducational therapy to persons with schizophrenia and their family/support persons. The website was specifically designed to be accessible to those with cognitive impairments and severe mental illness. The website design model included the following principles: 1) limit the need to think abstractly (eg, via explicit vs. inferential labeling, and memory aids such as pop-up menus); 2) limit the need to rely on executive functions (eg, via reduced functional separation between navigation and content, providing relatively more links on navigation pages, and employing a shallow website hierarchy that placed all content just one-page/''click'' from the homepage); 3) reduce distractions (eg, via minimal superfluous content, images, designs); 4) reduce the need to scan and search (eg, via a simplified page lay-out design). Evaluation of this design found that persons with schizophrenia (n = 32) were able to complete a higher proportion of tasks ($P \leq .0002$) in less time ($P \leq .000007$), using this website than standard websites. Methods: Thirty-one persons with schizophrenia or schizoaffective disorder and 24 support persons were randomly assigned to the telehealth or usual care condition. 1 (3%) patient and 4 (17%) family members dropped out of the study. Results: The persons with schizophrenia in the treatment group showed: 1) significant and large ($d = -0.88$, $P = .042$) differential reductions in positive symptoms during the treatment, with 94% of intervention patients experiencing reduced positive symptoms; 2) a reduction in perceived stress ($F(1,27) = 4.47$, $P = .044$), and; 3) greater improvements in knowledge of illness ($t(24) = -2.34$ $d = 0.88$, $P = .028$). Patients with more severe positive symptoms tended to spend more time on ($r = .65$, $P = .005$) and access the website more frequently ($r = .62$, $P = .009$), indicating that those most in need of treatment sought and obtained a greater dose of therapy. Families showed a significant and large improvement in knowledge ($t(14) = 2.32$, $P = .036$, $d = 1.94$). Conclusion: These findings suggest that telehealth delivery of treatments to the homes of persons with severe mental illness, and their family members, has considerable potential to improve well being. This work was supported by a grant from the National Institute of Mental Health (R01 MH63484).
ID: 977585

COGNITIVE ENHANCING DRUGS IN PRECLINICAL MODELS OF SCHIZOPHRENIA AND IMPROVEMENTS IN COGNITION BY MODAFINIL IN PATIENTS WITH CHRONIC AND FIRST EPISODE SCHIZOPHRENIA

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Background: Cognitive impairments are common in psychotic disorders, often appearing before the onset of the psychotic syndrome, and contribute to poor functional outcome. People with schizophrenia are impaired in a wide range of cognitive functions, including learning, working memory, cognitive control and cognitive flexibility. Our preclinical studies have suggested new prospects for cognitive enhancement in schizophrenia and here we discuss these and provide new data from clinical studies. Methods: We conducted double-blind, randomised, placebo controlled studies of the effects of modafinil (200 mg) on cognitive impairments in patients with chronic schizophrenia ($n = 20$) and in patients in their first episode of the disorder ($n = 40$). Patients were tested using a comprehensive neuropsychological battery including tests from the CANTAB, using parallel versions to limit practice effects. Results: Modafinil was found to improve certain ''cold'' cognitive tasks such as cognitive flexibility. In particular patients showed a significant improvement in performance with modafinil on digit span (forwards score: $P = .018$; backwards score $P = .006$), and the IDED attentional set-shifting task (35% increase in completion rate, $P < .025$). Scores also significantly improved on numeric working memory, as well as on spatial working memory between errors and strategy use. In addition, modafinil improves ''hot'' cognitive tasks such as recognition of emotional faces. Notably modafinil improved sad face recognition, one of the most complicated emotions to distinguish from neutral faces (Scoriels et al. 2010a). There were no effects of modafinil on physiological indices (including blood pressure) or subjective reports. Conclusion: These new findings indicate that modafinil may be more effective in remediating cognitive impairment in first episode psychosis, which may be more tractable than those longstanding ones seen in chronic schizophrenia. Furthermore, it may be that improvements with modafinil in chronic schizophrenia are more likely in those who show a relatively higher level of functioning.
ID: 949462

LONG-ACTING INJECTABLE MEDICATION MAINTENANCE TREATMENT OF ''FIRST-EPISODE'' SCHIZOPHRENIA - A RANDOMIZED EFFECTIVENESS STUDY

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Background: Nonadherence to maintenance antipsychotic therapy is almost universal for ''first-episode'' patients. Because long-acting injectable (LAI) tends to be reserved for persistently ill, chronic patients, little is known about the effectiveness of this approach in recently diagnosed ''first-episode'' schizophrenia patients. Methods: A prospective RCT conducted from December 2004-March 2007 enrolled ''first-episode'' patients defined by appropriate SCID diagnosis and up to 16 weeks lifetime antipsychotic exposure. Participants were randomized (2:1 ratio) to recommendation of risperidone long-acting injectable (RLAI) or continuing on oral therapy (ORAL). Nonadherence behavior was defined as a medication gap (GAP) for at least 14 days. Adherence attitudes were ascertained blindly with the Rating of Medication Influences (ROMI) at 12, 36, 52, 78, 104 weeks. Analysis defined treatment groups by ''Intent-to-Treat'' (ITT) and ''As-Actually-Treated'' (AAT). Kaplan-Meir (K-M) survival until 1st medication GAP was the primary outcome for adherence behavior. For adherence attitudes, a generalized mixed linear model was constructed to predict impact of group status on 5 defined ROMI adherence attitude clusters (Denial of Illness, Influence of Others, Life Goals, Relapse Prevention, Medication Affinity, and Stigma); fixed factors were treatment assignment and ROMI assessment time (12, 36, & 52 weeks). Results: Medication nonadherence was common. By 12 weeks, 24% of subjects met GAP criteria and 74% did so by 52 weeks. Adherence behavior at 12 weeks favored RLAI patients who accepted RLAI (AAT analysis) but these adherence benefits of RLAI were not sustained at the 36, 52, 74 or 104 week follow-up (both ITT and AAT). Overall adherence attitudes on the ROMI 5 factors did not differ between groups at any of the 3 time points (12, 36 and 52 weeks) except for greater (better adherence attitude) Relapse Prevention scores among the RLAI acceptors at week 12 only. Conclusion: First episode patients who accept a recommendation of RLAI have an early benefit in adherence behavior but that benefit is not sustained over time. There were no differences between the RLAI and ORAL groups in adherence attitude measures, including stigma, coercion or therapeutic relationship suggesting that recommending or accepting injections does not have a negative effect on adherence attitudes.
ID: 979893

THE ADDITION OF TIAGABINE TO ANTIPSYCHOTIC MEDICATION IN THE TREATMENT OF RECENT-ONSET SCHIZOPHRENIA BY MODIFICATION OF DEVELOPMENTAL REORGANIZATION OF PREFRONTAL CIRCUITRY

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Background: Developmental disturbances of inhibitory interneurons that contain the calcium buffer protein parvalbumin (PV) may disturb the developmental synaptic pruning process in the prefrontal cortex during the period of late adolescence and early adulthood and contribute to the onset and the functional deterioration that is characteristic of the early course of schizophrenia (SZ). We report preliminary data on the possible efficacy of tiagabine (Gabitril), a selective uptake inhibitor of the GABA (gamma-aminobutryic acid) transporter GAT-1, in the treatment of the early course of SZ, presumably by preferentially enhancing inhibitory neurotransmission furnished by PV-containing interneurons. Methods: We conducted a pilot trial of 18-week treatment with tiagabine added onto the antipsychotic regimen in 2 male, young adult (ages 21 and 22) subjects diagnosed with SZ within 1.3 years prior to joining the study. Symptomatic improvement was measured throughout treatment using the Brief Psychiatric Rating Scale and the Scale for the Assessment of Negative Symptoms. Results: Both subjects showed improvement of negative symptoms, and the subject who began the trial exhibiting significant psychosis also showed some improvement in psychotic symptoms. In addition, functional magnetic resonance imaging (fMRI) used during 2-back working memory tasks completed before and after the 4-month course of treatment found significantly reduced prefrontal cortical activation, though performance in the tasks remained unchanged. These results are consistent with the idea that cortical circuits may have been more efficiently restructured as a result of tiagabine treatment. Conclusion: Our data suggest that treatment with tiagabine during the early course of SZ can modulate PFC activation, as demonstrated by fMRI during working memory, and improve negative symptoms. A double-blind placebo-controlled clinical trial, funded by the NIH, is currently ongoing in order to systematically test our hypothesis. The proposed treatment strategy represents an effort to aggressively translate preclinical findings in SZ research into clinically testable hypotheses. This kind of translational approach, we believe, will ultimately lead to breakthrough in the treatment of SZ.
ID: 979272

VARENICLINE TREATMENT FOR SMOKING CESSATION IN PEOPLE WITH SCHIZOPHRENIA: A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

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Background: It is well-known that that smoking in people with schizophrenia is more common than in general population. Varenicline, a partial agonist at the $\alpha4\beta2$ and full agonist at the $\alpha7$ nicotine acetylcholine receptor, has been shown to be an effective anti-smoking treatment. This study was performed to examine the effects of varenicline treatment on anti-smoking in people with schizophrenia. Methods: This study was a randomized, double blind, parallel group, placebo controlled 8 weeks trial. 60 smokers with schizophrenia, who were clinically stable, were recruited. Participants were randomized to either varenicline or placebo. The dose of antipsychotic drug remained fixed throughout the study. Smoking behavior was assessed using by the Minnesota Nicotine Withdrawal Scale, the Brief Questionnaire of Smoking Urge and the Modified Cigarette Evaluation Questionnaire and exhaled carbon monoxide measurement also were used to assess smoking dependency and status. 2-tailed student's *t* test, chi-square test, and Repeated measures ANOVA were used to data analysis. Results: During the 8-week study, amounts of smoking in the varenicline group, as compared with placebo group, were significantly decreased demonstrating a significant

treatment effect ($F = 6.12$, $df = 1,41$, $P = .018$) and time effect ($F = 8.54$, $df = 1.164$, $P < .001$). Expired CO levels in varenicline group significantly decreased showing significant time effect ($F = 14.72$, $df = 4.156$, $P = .0071$) and time X treatment interaction ($F = 3.66$, $df = 4.156$, $P = .007$). The mCEQ total scores in varenicline, compared with placebo, significantly reduced demonstrating significant treatment X time interaction ($F = 4.32$, $df = 4,160$, $P = .002$). The QSU-brief demonstrated significant time effect ($F = 10.94$, $df = 4,168$, $P < .001$), while not significant treatment X time interaction. Varenicline adjunctive treatment with antipsychotics was generally well tolerated and safe. Conclusion: Varenicline showed significant antismoking efficacy in peoples with schizophrenia, however, further study is needed to confirm whether its efficacy for smoking behavior is similar to those found in control smokers.
ID: 977337

EFFECT OF SHORT-TERM TREATMENT WITH LURASIDONE ON QUALITY OF LIFE IN SCHIZOPHRENIA: RESULTS FROM THE PEARL 3 TRIAL

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Background: The objective of this study was to evaluate the effect of lurasidone (80 mg/day and 160 mg/day) on well-being in patients with an acute exacerbation of schizophrenia. Methods: Patients who met DSM-IV criteria for schizophrenia were randomized to 6-weeks of double-blind treatment with lurasidone 80 mg ($n = 125$) or 160 mg ($n = 121$), quetiapine XR 600 mg ($n = 119$; included for assay sensitivity) or placebo ($n = 121$). The outcome measures included the Positive and Negative Symptoms of Schizophrenia Scale (PANSS) total and positive subscale scores, the Negative Symptom Assessment Scale score (NSA-16), and the Montgomery-Asberg Depression Rating Scale (MADRS). Quality of life was measured using the Quality of Well-being (QWB-SA) scale. The QWB-SA is a preference-weighted questionnaire with a combined score ranging from 0 to 1.0 (death to optimal functioning). Results: At baseline, QWB-SA scores were similar for patients randomized to lurasidone 80 mg (0.572), lurasidone 160 mg (0.562), quetiapine XR (0.583), and placebo (0.581). On an endpoint ANCOVA analysis, there was significant improvement in the ls mean QWB-SA score compared with placebo (0.631) in the lurasidone 80 mg group (0.672; $P = .049$), the lurasidone 160 mg group (0.710; $P < .001$), and the quetiapine XR group (0.711; $P < .001$). Endpoint improvement on the QWB-SA score exhibited the following correlations with endpoint improvement in the PANSS total score for lurasidone 80 mg ($r = -.176$; $P = .068$), 160 mg ($r = -.353$; $P < .001$) and quetiapine XR ($r = -.348$; $P < .001$). Endpoint improvement on the QWB-SA score also exhibited the following correlations, for lurasidone 80 mg, 160 mg and quetiapine XR, respectively, with endpoint improvement on the PANSS positive subscale score ($r = -.049$; $P = .615$; $r = -.280$; $P = .004$; $r = -.294$; $P = .003$), the NSA-16 ($r = -.021$, $P = .827$; $r = -.200$, $P = .046$; $r = -.148$, $P = .142$) and the MADRS ($r = -.059$, $P = .541$; $r = -.433$, $P < .001$; $r = -.277$, $P = .005$). In the placebo group, significant correlations were also observed between endpoint change in the QWB-SA and endpoint change in the PANSS total ($r = -.387$, $P < .001$) and positive subscale scores ($r = -.386$, $P < .001$), the NSA16 ($r = -.301$, $P = .002$), and the MADRS ($r = -.391$, $P < .001$). Conclusion: In this study, treatment with lurasidone, in once-daily doses of 80 mg and 160 mg, was associated with improvements in health-related quality of life in patients with an acute exacerbation of schizophrenia.
ID: 979733

OPTIMIZATION OF TREATMENT AND MANAGEMENT OF SCHIZOPHRENIA IN EUROPE: THE OPTIMISE TRIAL

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Background: This study will focus on 2 goals: optimizing current treatments and explore novel therapeutic options for schizophrenia. The study intends to both address basic but so far unanswered questions in the treatment of schizophrenia and develop new interventions. The project is expected to lead to evidence directly applicable to treatment guidelines and identify potential mechanisms for new drug development. To achieve these goals we will pursue the following objectives: I To test amisulpride as the first step in a treatment algorithm. II To test if non-responders to an antipsychotic drug benefit from switching to a drug with a different receptor binding profile. III To provide the acceptability and outcome data on the application of clozapine in non-responders within the first 10 weeks of treatment. IV To test if an IT-enabled psychosocial intervention can improve treatment adherence and global functional outcome in symptomatically remitted first-episode patients. V To test if glutamatergic markers predict response to first and second line treatments. VI To test if pharmacogenetic, proteomics- and metabolomic markers can provide predictive value. VII To define the nature and prevalence of ''organic'' pathology in patients with first episode psychosis. VIII To determine the extent to which MRI measures can predict response to antipsychotic treatment. Methods: 350 first episode schizophrenia patients, aged 18–40 years, that have used <2 weeks of antipsychotic medication prior to inclusion and/or 6 weeks lifetime, will be included at multiple (18–30) sites. A baseline MRI scan will screen for neurological pathology. Venous blood will be obtained for genetic and metabolic analyses. Baseline MRI and blood values will be used to predict treatment response. All patients will be provided open-label amisulpride for 4 weeks (phase I). Non-responders will enter the double blind phase of the study (phase II) and will be randomized to either continue on amisulpride or switch to olanzapine for 6 weeks. Remaining non-responders will be prescribed clozapine open-label for 12 weeks (phase III). All responders, after any phase, will be randomized to a psychosocial intervention (12 weeks) or to treatment as usual. The psychosocial intervention consists of psychoeducation, motivational interviewing and SMS warnings. Results: A European Consortium of 18 partners has been established to perform the study. Enrollment of subjects will start fall 2010. Conclusion: This study is supported by a EU FP7 Grant.
ID: 977532

CLOZAPINE VS. OLANZAPINE IN TREATMENT RESISTANT SCHIZOPHRENIA: SYSTEMATIC REVIEW AND METANALYSIS

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Background: Clozapine is considered as the gold standard for the treatment of patients with treatment-resistant schizophrenia (TRS), based upon its established superior efficacy against first generation antipsychotics. Nevertheless, data on other second generation antipsychotics (SGA) are scarce or divergent for this population. Methods: We conducted a systematic review of randomized, controlled trials (RCT) comparing clozapine to other SGA in patients with TRS. Response to treatment was measured by the percent-

age of responders or by mean change or endpoints values of psychotic symptoms scales. Effect sizes are shown as relative risks (RR), or weighted or standardized mean differences, with 95% confidence intervals. The fixed or random models were used when appropriate. Results: Seven RCT were included, comprising 648 patients. No differences between clozapine and olanzapine were identified, except a marginally significant higher effect size favoring olanzapine for negative symptoms, using pooled PANSS negative subscale endpoint scores (DM= −1,43, 95% CI: −2,56, −0,30). Studies had relatively higher olanzapine doses than usual, which might have influenced the results. Conclusion: High dose olanzapine might represent a therapeutic alternative for patients with TRS.
ID: 979009

LONG-TERM SAFETY AND TOLERABILITY OF LURASIDONE IN PATIENTS WITH SCHIZOPHRENIA: RESULTS OF A 6-MONTH, OPEN-LABEL STUDY

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Background: The aim of this study was to evaluate the safety and tolerability of lurasidone in the long-term treatment of schizophrenia, and to determine if improvement during the acute double-blind (DB) phase of treatment was sustained. Methods: Patients who successfully completed a 6-week, DB, placebo-controlled trial evaluating the efficacy of lurasidone 40 mg and 120 mg, and olanzapine 15 mg (included to confirm assay sensitivity), were eligible to continue in a 6-month open-label extension (OLE) phase in which patients received flexible doses of lurasidone in the range of 40–120 mg/day. Safety and tolerability measures included adverse events (AEs), body weight, lipid parameters, prolactin, and ECGs. Efficacy assessments included the Positive and Negative Symptoms of Schizophrenia Scale (PANSS) total score. Results: The mean PANSS total score, for all patients (N = 246) in the OLE phase, decreased from 96.6 at DB baseline to 66.6 at OLE baseline. During OLE treatment, patients showed further improvement in the PANSS total score, with a mean score of 54.9 at OLE endpoint. Two AEs occurred with an incidence ≥10%: akathisia (13.0%) and insomnia (11.0%); an AE was rated as "severe" by 7.3% of patients; and a total of 12.2% of patients discontinued due to an AE during OLE treatment. There were no clinically meaningful changes in vital signs, or laboratory and ECG parameters; one subject (0.4%) reported ≥60 ms increase in QTcF, and no subject had a QTcF interval >500 ms. Body weight and BMI remained relatively stable during the open-label extension, except for patients who had been randomized in the initial DB phase to olanzapine 15 mg: after the switch to open-label lurasidone, there was a mean (SD) reduction of −1.8 (4.9) kg in weight. There were no clinically meaningful changes, from open-label baseline to endpoint, in cholesterol (−7.1 mg/dl), LDL (−2.6 mg/dl), triglycerides (−18.3 mg/dl), insulin (−2.4 mU/l), or whole blood HbA1c (−0.06%). Prolactin, which had increased during the DB phase (+3.2 ng/ml on combined lurasidone; +3.4 ng/ml on olanzapine), showed an overall median decrease (−1.3 ng/ml) during the open-label extension. Conclusion: During this 6-month, open-label extension study, flexibly dosed lurasidone (40–120 mg, daily) was well-tolerated in patients with schizophrenia. Up to 8 months of treatment with lurasidone (acute and extension phase treatment, combined) was associated with a low potential for weight gain and dyslipidemia.
ID: 979652

RURAL AND URBAN YOUTH AT ULTRA HIGH RISK FOR PSYCHOSIS: BASELINE CHARACTERISTICS FROM THE DEPTH RANDOMISED CONTROLLED TRIAL OF COGNITIVE BEHAVIOR THERAPY

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Background: Recent longitudinal research into early intervention for youth at ultra high risk (UHR) for psychosis have shown beneficial outcomes such as better treatment compliance and higher rates of participation in education and the workforce [1]. The Detection, Evaluation and Psychological Therapy (DEPTh) project is a single blind randomised controlled trial to compare the effectiveness of cognitive behaviour therapy (CBT) and non-directive reflective listening (NDRL), in ameliorating "at risk mental states" for psychosis and delaying or preventing transition to psychosis among UHR youth. Methods: Youth aged 12–25 years, living in either the urban area of Newcastle or the rural area of Orange and identified as UHR by the CAARMS were randomly assigned to 6 months of CBT or NDRL. Assessment occurred at baseline through until 12 months and included clinical profiles, social functioning, drug and alcohol use. Results: The sample of 57 youth (mean age 16.5 years, 56% female) were mostly still attending school (56%) and a further 20% reported being unemployed. Nearly 79% met CAARMS criteria for the attenuated symptom group. Compared with the urban youth, rural youth (N = 32) were more likely to be taking antidepressants at baseline (44% compared with 16%), and had significantly more impaired functioning across a number of domains. Rural youth were more likely to be in crisis housing compared with urban youth. Conclusion: Baseline results indicate significant functional decline and therefore a high level of need for early intervention for rural youth experiencing compromised mental states akin to the pre psychotic phase of psychosis.
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ID: 980667

CAN EARLY-ONSET ANTIPSYCHOTIC EFFECT PREDICT LATER CLINICAL EFFECT OF ANTIPSYCHOTIC MEDICATION IN CHILDREN AND ADOLESCENTS?

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Background: The hypothesis of early-onset action of antipsychotics proposes no notable delay in onset of action and a gradual improvement towards a plateau. The hypothesis has not been tested in children and adolescents.

There is no consensus on the definition and the predictive value of early response of antipsychotic drugs. Also no consensus has been reached on when a non-responding patient should be switched to a potentially more effective treatment. Early onset effects of antipsychotics have shown to be a stable predictor of clinical response in adults with schizophrenia. A meta-analysis of double-masked studies including 7450 patients have shown greater improvement in the first 2 treatment weeks than in the next 2 weeks measured as reductions in total scores on the BPRS and PANSS. A multicenter study including 299 schizophrenic patients showed that both 4- and 6-week-measures significantly improved the prediction of remission after 12 months compared with baseline and 2-week-assessments. This study aims to 1)identify and define early predictors of clinical response of an antipsychotic drug in children and adolescents aged 12–17 years with psychosis 2)compare the early effects of quetiapine and aripiprazole and 3)describe the predictive value of early effects on response and remission after 12 weeks. Methods: The study is a randomized, double-blinded trial with aripiprazole vs. quetiapine for patients aged 12–17 years with first-episode psychosis. Early effects are measured as improvement after 2 and 4 weeks on the PANSS positive and total score. Response and remission after 12 weeks is defined according to recommendations for schizophrenia. The discriminative and predictive value of early effect is evaluated with a ROC curve, where the AUC expresses the balance between the true positive and the true negative cases. The best discriminative definition of early effect is identified by calculating AUC, sensitivity, specificity and positive and negative predictive values for all possible early improvement cut-offs of a percentage PANSS total score improvement. Results: Inclusion of patients in the trial started in May 2010. 200 patients will be included by 6 Child- and Adolescent Psychiatric Centers in Denmark. Conclusion: Evidence on early indicators of later sustained clinical effects of antipsychotics is of great clinical relevance. ClinicalTrials.gov Identifier: NCT01119014
ID: 998197

EFFECTIVENESS OF RISPERIDONE LONG-ACTING INJECTION IN THE EARLY PHASE OF SCHIZOPHRENIA: RELAPSE PREVENTION AND SYMPTOM REDUCTION

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Background: Short acting oral antipsychotic medication is more commonly used than long-acting injectable forms, but the effectiveness of oral medications is hampered by poor adherence. Methods: We are comparing the clinical efficacy of the long-acting injectable formulation of risperidone (RLAI) to the oral form in a 12-month randomized controlled trial in recent-onset schizophrenia patients. This is a preliminary report from a sample of first-episode schizophrenia patients (Sample 4) of the Developmental Processes in Schizophrenic Disorders Project (PI: Keith Nuechterlein, Ph.D.), conducted at the UCLA Aftercare Research Program. The enrollment target is 110. Interim analyses were conducted with 61 recent-onset schizophrenia patients who were randomized to injectable vs. oral risperidone. Results: To date, only 1 patient has refused to continue treatment at the time of randomization to RLAI, and 1 other discontinued after only 2 injections. There were notable clinical advantages of risperidone long-acting injectable (RLAI). The rate of psychotic relapse was lower (7% vs. 31%), time without relapse was longer (means of 350 vs. 300 days, $P = .013$), and the rate of early discontinuation of treatment for any reason was significantly lower (17% vs. 41%, $P = .04$) for the RLAI group compared with the oral risperidone group. Over the initial 6 months of treatment for 49 patients who completed 6 months or longer of the protocol, the RLAI group had reductions in Brief Psychiatric Rating Scale (BPRS) symptoms of Unusual Thought Content ($P = .03$), Conceptual Disorganization ($P=.05$), Hostility ($P =. 02$), and Emotional Withdrawal ($P = .04$), and increased Motor Retardation ($P = .03$), relative to the oral risperidone patient group. Each patient's adherence was rated on a 1–5 scale based on timeliness of injections for RLAI, and pill counts, patient reports, plasma levels, and psychiatrist judgments for oral medication. Adherence with oral risperidone did not differ prior to randomization, but adherence was much better for injectable compared with oral medication during the randomized treatment ($P < .001$). Medication adherence significantly predicted psychotic relapse ($P = .017$). Medication adherence was significantly associated with improvement on a number of symptoms on the BPRS over the initial 6 months. Conclusion: If these findings are confirmed in the full sample, they will support the use of RLAI in the early course of schizophrenia.
ID: 979090

TRANSLATIONAL COGNITIVE OUTCOMES FOR PROOF OF CONCEPT DRUG TRIALS

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Background: Efforts to develop interventions to reduce cognitive deficits in schizophrenia face numerous challenges. One is how to select the most useful outcome measures for clinical trials at different stages along the drug discovery/registration pathway. The clinical neuropsychological approach (eg, MATRICS or BACS) provides useful measures of global cognitive impairment that is related to functional disability, but may have significant limitations for Phase II POC (proof of concept) studies: 1) it provides highly intercorrelated measures of global deficit rather than measures of the specific cognitive abilities one might predict to be influenced by drugs targeting a specific neurochemical mechanism; 2) its measures have proven remarkably resistant to change, and thus may be more linked to trait-like intellectual abilities than is ideal when detecting cognitive change is the primary interest; 3) it fails to directly measure drug effect on the target organ - specifically the functional brain systems that support specific aspects of cognition targeted by a drug; and 4) it has only modest linkage to preclinical platforms. These limitations may contribute to the high rate of negative early phase trials across a range of targeted mechanisms. Methods: This presentation will compare neuropsychological, cognitive neuroscience, neurophysiological and fMRI measures in untreated first episode schizophrenia patients before and following risperidone therapy. New data from our Chicago first episode study will be emphasized. Results: The data will be used to show that as one moves closer to specific measures of cognition and to direct measures of brain function, the effect size of treatment outcomes, the ability to detect adverse as well as beneficial treatment outcomes, and the link to translational platforms all increase. Conclusion: These findings will be discussed in 2 contexts. First, the complex effects of antipsychotics on functional brain systems and cognition will be highlighted, as it is crucial knowledge for planning trials with adjunctive procognitive drugs used to supplement ongoing antipsychotic treatment. Second, the enhanced specificity and sensitivity of cognitive and systems neuroscience tools for evaluating drug effects in POC trials will be discussed as such studies need tools able to detect a signal in small sample studies.
ID: 979602

CHALLENGES FOR PRECLINICAL PHARMACOLOGY TO CRITICALLY CONTRIBUTE TO THE DEVELOPMENT OF NEW AND NOVEL DRUGS FOR SCHIZOPHRENIA

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Background: The development of experimental therapeutics for schizophrenia is perhaps the most challenging there is for any illness because the cellular, systems and molecular disease mechanisms are not known. Dopamine receptor (DAR) blockade was discovered serendipitously as an antipsychotic strategy. The use of preclinical models to build on this discovery has been straight forward because of its simplicity. What will be the useful preclinical models for new and novel drug development in the future? Methods: This talk will review the models used in early preclinical development of several new and novel drugs for schizophrenia which (1) add other pharmacological properties to dopamine receptor antagonism, (2) use novel antidopaminergic strategies, and (3) develop entirely novel molecular targets, possibly focused on dimensions of schizophrenia, like cognition enhancement. Results: The strategy of adding enhancing pharmacological properties to DAR blockade does not require new preclinical models only modified combinations of models. The development of novel anti-DA approaches requires classical preclinical models; these are feasible, given the firm knowledge that opposing DA-mediated transmission will have antipsychotic outcomes. It is the novel targets and models that are most vulnerable to failure. Those clinical constructs that have animal analogues (like, working memory or attention) should be the most amenable to drug development. It has not been the case that success has accrued yet in the development of drugs for cognition, but the application of preclinical models is more rational. Nonetheless, factors like asking drugs to inhibit vs. to enhance behaviors, augmenting drug treatment with psychological training, and finding the correct dose and dose sequence may be important to outcome. Human models may be useful. Conclusion: Short of discovering the mechanism(s) for schizophrenia, we can use previous experience to inform our current preclinical approaches to drug development.
ID: 988209

COMPENSATORY COGNITIVE TRAINING FOR PSYCHOSIS: RESULTS FROM A RANDOMIZED CONTROLLED TRIAL

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Background: Cognitive remediation therapy for schizophrenia is defined as "a behavioral training based intervention that aims to improve cognitive processes with the goal of durability and generalization" to functional outcomes. In the latest meta-analysis (McGurk et al., 2007), the mean effect sizes of cognitive remediation were $d = .41$ for cognition, $d = .28$ for symptoms, and $d = .36$ for functional outcomes. We investigated a manualized, 12-week, group-based compensatory cognitive training (CT) intervention targeting prospective memory, attention, learning/memory, and executive functioning. Methods: Sixty-nine participants with schizophrenia (54%), schizoaffective disorder (44%) or psychosis NOS (2%) were randomized to standard pharmacotherapy alone (SP; $n = 31$) or CT ($n = 38$). Assessments at baseline, post treatment, and 3 month follow-up included a comprehensive neuropsychological battery, the UCSD Performance-Based Skills Assessment (UPSA), the Positive and Negative Syndrome Scale, and the Quality of Life Interview (QOLI). Results: CT completers attended 82% of sessions. Compared with the SP group, those receiving CT showed improvement on measures of attention ($P = .022$), memory ($P = .045$), functional capacity (6-month, $P = .014$), negative symptoms ($P = .003$), and subjective quality of life ($P = .008$; all P-values derived from hierarchical linear modeling of group by time effects). Effect sizes for these domains ranged from .6 to .9. At 3-month follow-up, 73% of the CT group scored in the normal range on the neuropsychological battery, compared with 35% of the SP group ($P = .008$). Conclusion: Compensatory CT has the potential to improve aspects of cognition, psychiatric symptoms, functional capacity, and subjective quality of life. Effect sizes in these domains exceeded prior benchmarks established by meta-analyses of cognitive remediation studies.
ID: 976740

GLYCINE TRANSPORTER TYPE 1 (GLYT1) INHIBITOR RG1678: RESULTS OF THE PROOF-OF-CONCEPT STUDY FOR THE TREATMENT OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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Background: A Phase IIb proof-of-concept study investigated the effects of RG1678, a potent, noncompetitive inhibitor of glycine transporter type 1 (GlyT1), on negative symptoms of schizophrenia. Concurrently a positron emission tomography (PET) occupancy study was conducted with a novel PET ligand for GlyT1 in healthy volunteers. Methods: Clinically stable patients with predominant negative symptoms were randomized to 8 weeks of treatment with 3 doses of RG1678 (10 mg, 30 mg, 60 mg) or placebo once daily as adjunct to second-generation antipsychotics. Efficacy parameters included: change from baseline in Positive and Negative Syndrome Scale (PANSS) negative symptom factor score (NSFS); proportion of responders (defined as $\geq$20% improvement in NSFS); Clinical Global Impression-Improvement (CGI-I) in Negative Symptoms; and Personal and Social Performance (PSP) scale. Populations analyzed included intent-to-treat (ITT) and per protocol (PP; patients who completed 8 weeks of treatment without any major protocol violations). GlyT1 occupancy was measured at steady state after daily doses of 5–175 mg RG1678 in 15 healthy volunteers. Estimates of the exposure/occupancy relationship were applied to pharmacokinetic data obtained in the patient study. Results: 323 patients were randomized (mean age, 39.9 ± 10.1 [SD] years; PANSS NSFS, 26.1 ± 3.9; PANSS positive symptom factor score, 17.7 ± 3.6). The NSFS showed a significantly greater decrease from baseline ($\Delta = 25\%$) in the 10 mg and 30 mg groups vs. placebo ($\Delta = 19\%$) in the PP population (10 mg, $P = .049$; 30 mg, $P = .034$). The percentage of responders in the PP population was significantly higher in the 10 mg group vs. placebo (65% vs. 43%, Pp = .013). Differences in CGI-I in Negative Symptoms were significant for the 10 mg group vs. placebo in both populations (ITT, $P = .021$; PP, $P = .025$). Compared with placebo, there was a trend towards functional improvement as assessed by increase in PSP scale from baseline to week 8 in the 10 mg group in the PP population. RG1678 was well tolerated. Estimates of GlyT1 occupancy in patients indicated that occupancies below 50%–60% were associated with the best efficacy. At higher occupancies the clinical effects were lost. Conclusion: RG1678 is the first compound in clinical development to demonstrate a consistent and clinically meaningful reduction in negative symptoms associated with a positive effect on functionality. Low to medium target occupancy seems sufficient to achieve the strongest clinical effects.
ID: 979350

EFFECTS OF ZIPRASIDONE ON THE QTC INTERVAL: A POOLED DATA ANALYSIS

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Background: Second generation antipsychotics have been associated with QTc interval prolongation [1]. Previously clinical studies for ziprasidone have reported a dose-dependent modest increase in the mean QTc interval over the range of 40–320 mg/day [2]. All Pfizer-sponsored, controlled randomized trials for schizophrenia or bipolar disorder have evaluated the effects of ziprasidone on the QTc interval [3]. We present pooled analyses of these trials. Methods: Studies were pooled into group 1: placebo and active-comparator controlled oral adult trials, group 2: active-comparator controlled intramuscular (IM) adult trials, and group 3: placebo-controlled pediatric trials. We report the change from baseline to last available QTc measurement (mean, SD and range), categorical QTc prolongation (increase of $\geq$ 30, 60, and 75 ms), and highest measured QTc (threshold of $\geq$450, 480, and 500 ms). All reported QTc interval data used the Fridericia correction formula. Serious adverse events (AEs) and discontinuations related to QTc prolongation are also outcomes of interest. Results: In total, 3787 adult subjects received oral ziprasidone in the group 1 studies. Amongst these subjects there were no reports of QTc $\geq$ 480 ms; 20 subjects (0.5%) had a QTc $\geq$ 450 ms. QTc prolongation $\geq$30 ms was observed in 337 subjects (8.9%); 22 (0.6%) had QTc prolongation $\geq$60 ms; and 5 (0.1%) had QTc prolongation $\geq$75 ms. Mean change from baseline to endpoint in QTc was 3.1 msec (20.31 ms) from a baseline mean of 387.0 ms (21.90 ms). Comparable mean (SD) QTc change values (in ms) in the pooled placebo (N = 829), haloperidol (N = 865), olanzapine (N = 387), and risperidone (N = 341) subjects were −0.6 (20.45), −1.5 (20.77), −1.8 (19.86), and −0.8 (23.09), respectively. Data from group 2 and 3 demonstrate similar QTc changes as seen in group 1. Conclusion: The present analyses of Pfizer clinical trial data show that ziprasidone causes a small mean increase in QTc interval. However, the incidence of subjects reaching a clinically significant threshold for increase from baseline in QTc interval of $\geq$60 ms is rare, with infrequent reports of QTc interval $\geq$480 ms.

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ID: 978486

SAFETY, PHARMACOKINETICS AND EARLY SIGNALS FOR EFFICACY WITH ITI-007, A NOVEL INVESTIGATIONAL NEW DRUG FOR THE TREATMENT OF SCHIZOPHRENIA AND RELATED DISORDERS

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Background: ITI-007 is an investigational new antipsychotic drug with a novel pharmacological profile. ITI-007's mesolimbic/mesocortical dopamine receptor phosphoprotein modulation (DPPM) predicts antipsychotic efficacy against positive symptoms with lesser liability for extrapyramidal side effects (EPS) and mesolimbic glutamatergic phosphoprotein modulation predicts antipsychotic efficacy against negative symptoms. As additional key differentiating features, ITI-007 enhances sleep maintenance in patients with insomnia with potent serotonin 5-HT2A receptor antagonism and exhibits antidepressant-like efficacy via serotonin reuptake inhibition. Reduced affinity for off-target receptors predicts improved tolerability. The purpose of the present study was to determine the safety, tolerability and pharmacokinetics (PK) of ITI-007 in patients with schizophrenia. Exploratory measures for efficacy were included. Methods: The study was conducted as an inpatient, double-blind, randomized, placebo-controlled multiple ascending dose study in patients with stabilized schizophrenia or schizoaffective disorder. Patients received ITI-007 (30–140 mg) or placebo for 5 days. Safety assessments included vital signs, clinical laboratory tests, 12-lead ECGs, the Simpson-Angus Scale and Barnes Akathisia Rating Scale. Serial blood samples were collected on Day 1 and Day 5 for pharmacokinetic analysis. Exploratory efficacy measures included the Positive and Negative Syndrome Scale (PANSS) and the Calgary Depression Scale for Schizophrenia (CDSS). Results: ITI-007 was safe and well-tolerated with repeated administration at doses up to and including 140 mg. There were no clinically significant changes in vital signs or 12-lead ECGs. There was no EPS. ITI-007 plasma concentrations increased with increasing doses. Exploratory analyses indicated that total PANSS scores and CDSS scores improved with ITI-007 administration. Conclusion: The present results demonstrate that ITI-007 is safe and well-tolerated with dose-proportional linear PK in patients with schizophrenia. The lack of EPS with ITI-007 is consistent with its mesolimbic/mesocortical selectivity. While ITI-007 was only administered for 5 days to stable patients, signals consistent with efficacy emerged with improved total PANSS and CDSS scores. Although the present study was not powered to measure statistically significant effects on these measures, the data are encouraging and will be evaluated more fully in future efficacy studies.

ID: 978885

NEUROPLASTICITY-BASED AUDITORY TRAINING IMPROVES COGNITION IN YOUNG INDIVIDUALS WITH RECENT ONSET SCHIZOPHRENIA

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Background: The cognitive deficits that characterize patients with established schizophrenia are present even before illness onset and typically worsen as the individual progresses into the first episode of psychosis. Moreover, the severity of the initial deficits predicts functional outcome several years later. Cognitive dysfunction thus should be a primary target for aggressive early intervention in young recent-onset populations. Methods: We applied neuroplasticity-based cognitive training to 50 young individuals within 5 years of onset of their first psychotic episode (mean age of 21 years). We performed a 2-site randomized controlled trial of 40 hours of cognitive training vs. 40 hours of commercial computer games, delivered over 8 weeks. We examined MATRICS-recommended neurocognitive outcome measures, symptoms, and role functioning. Results: Subjects in the auditory training group demonstrated significant improvements in global cognition (P = .03), verbal learning and memory (P = .02), and problem-solving (P = .05), as compared with computer games control subjects, and gains in speed of processing approaching trend level (P = .13). There were no significant differences in symptoms or functional outcome measures in this short time period. Conclusion: Neuroplasticity-based cognitive training represents a highly promising treatment approach to target the cogni-

tive dysfunction in early psychosis. Future studies must investigate whether it improves long-term outcome and community functioning, and how best to integrate it into critical psychosocial interventions such as supported education and supported employment.
ID: 978953

THE NITRIC OXIDE SIGNALING SYSTEM AS A NOVEL TREATMENT TARGET FOR SCHIZOPHRENIA

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Background: Accumulating clinical research findings support that the brains nitric oxide (NO) signaling system may be part of the pathophysiology of schizophrenia. The presented translational research project demonstrates that the brains NO-signaling pathway may be a potentially new treatment target by providing pre-clinical and clinical support for a "NO-signaling imbalance hypothesis" of schizophrenia. Methods: A series of behavioral rodent tests were undertaken in which the animals were acutely challenged with NO-synthase (NOS) inhibitors and the psychotomimetic compound phencyclidine (PCP). To investigate the in vivo effects of PCP in the rodent brain, a NO-sensitive micro-sensor was surgically implanted into the rat prefrontal cortex (PFC) and cGMP, a downstream messenger molecule of NO, was measured in the mouse PFC using microdialysis. One way of inhibition NO-production is by L-lysine treatment, as it competes with cellular uptake of the NO substrate L-arginine. Thus, L-lysine was administered to mice in combination with PCP, as well as an adjunctive (6 g/day) to conventional antipsychotic treatment in 10 patients with schizophrenia, in a single-blinded, crossover 4-week pilot study investigating its effect on cognition and symptom severity. Results: NOS-inhibition blocked several schizophrenia-like PCP-induced deficits in rodents, ranging from pre-attentive sensory information processing and memory, to social cognition. In addition, acute PCP-treatment increase in vivo NO-levels in the rat PFC as well as cGMP levels in the mouse PFC. Sub-chronic L-lysine treatment normalized PCP-induced deficits in sensory information processing in mice. In humans, a significant increase in blood concentration of 6 g L-lysine/day was found after 4 weeks of treatment, but no adverse side effects. Furthermore, there was a significant decrease in positive symptom severity over the whole study period and L-lysine treatment normalized the forward masking deficit in the inferior colliculus, compared with baseline. Conclusion: Taken together, these translational findings suggest that the brain NO-signaling system is important for the effects of PCP in animals and may constitute a potentially novel treatment-target for schizophrenia. Supported by: The Stanley Medical Research Institute, The Swedish Research Council (4247) and The Swedish Foundation for Medical Research.
ID: 977537

A COMPARISON OF RESPONDERS AND NON-RESPONDERS TO A PLACEBO AS AN ADJUNCTIVE TREATMENT IN SCHIZOPHRENIA PATIENTS

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Background: This paper studies the determinants of response vs. non-response to placebo as an add-on to anti-psychotics in schizophrenia. Methods: Response to placebo was defined as an improvement of 20% or more in total PANSS after 8 weeks. Data included patients receiving placebo from 2 add-on studies with differing inclusion criteria: a study on add-on allopurinol (N = 109 points received placebo, 40.4% responded to placebo) included patients with at least 2 PANSS positive symptoms>4 with no negative symptom criteria ("Positive symptom study"), and a study on D-serine, (N = 82 points receiving placebo of whom 18.3% responded to placebo) which included stabilized patients with PANSS negative symptom scores>18 ("Negative symptom study"). Baseline measures included age, gender, years of education, the Positive and Negative Syndrome Scale (PANSS), and cognitive test scores. Results: In the positive symptom study more males responded to placebo compared with females, 51.9% vs. 29.1%, P = .02. Placebo responders had significantly lower motor speed (Effect size = .04), P = .046 and greater severity in positive symptoms at baseline (controlling for age and education), effect size = .05, P = .019. A significant interaction was found between response and gender on the general psychopathology score, with a higher score in general psychopathology among male responders in comparison with male non-responders, a difference that was not found among women, Effect size = .067, P = .009. None of the variables tested differentiated between placebo responders and non-responders in the negative symptom study. Conclusion: In patients participating in add-on studies with significant positive symptoms, male gender, higher baseline positive PANSS scores, and lower motor speed were predictors of placebo response. However, the differences were not large. No predictors were identified for placebo response in patients with predominantly negative symptoms. These base-line clinical and demographic characteristics do not seem to enable effective identification of placebo responders vs. non-responders in add-on studies for schizophrenia; other characteristics must be sought.
ID: 979117

CLINICAL CHARACTERISTICS OF PEOPLE IN RANDOMIZED CLINICAL TRIALS OF FIRST EPISODE SCHIZOPHRENIA SPECTRUM DISORDERS: ATTRITION VS. NON-ATTRITION GROUPS

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Background: Early identification of psychosis and intensive treatment has been the focus of the treatment of people with a first episode (FE) schizophrenia spectrum disorder (SSD). Attrition rates in studies of people in the first episode are high, making it difficult to understand the meaning of the study outcomes. High attrition rates affect the validity of a study by decreasing its power and the study's ability to detect differences between treatment groups. Additionally, the people who leave a study may be different from those who stay in demographic, illness and treatment characteristics. Methods: This study is a secondary analysis of a group of FE SSD participants (N = 82) enrolled in 1 of 3 separate double-blind, randomized, drug

trials with a mean duration of 1.67 years. Attrition was defined as those who left the study during the first 6 months of the drug trials for any reason. Before merging the 3 studies, the variables were found to be comparable between the studies. Exploratory and descriptive statistics of study participants were conducted in a comparison of the 3 studies, for the merged group, and for the attrition and non-attrition groups. Effect sizes (Cohen's *d*) were calculated for each variable in the individual studies and in the merged dataset for the magnitude of difference between the attrition and non-attrition groups. Results: The 3 studies were merged after analysis found no consistent difference in demographic and illness characteristics between the 3 studies. There was no significant difference between the attrition (66%, $n = 54$) and non-attrition groups in the merged data in demographic and illness characteristics. Treatment characteristics consistently found lack of efficacy and patient withdrawal of consent to be the 2 most frequent reasons for attrition from the studies. In addition, participants receiving a typical agent were less likely to complete the study. Effect size calculations found the attrition group to more likely be Caucasian, with a lower median income. The attrition group had more years of education, but was not in school in the year previous to hospitalization. Conclusion: Historically, attrition is a major problem in clinical trials of people in a first episode of schizophrenia spectrum disorders. People receiving typical antipsychotic medication are more likely to leave a study. Most common reasons for attrition include lack of efficacy and withdrawal of consent.
ID: 979727

GLOBAL INTER-RATER RELIABILITY, SCALE VALIDITY, AND LOCAL PERCEPTION: PANSS RATINGS AND REACTIONS FROM 4 COUNTRIES

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Background: There is a considerable body of literature suggesting that standardized rater training is critical to inter-rater reliability. With the expansion of clinical and research trials to locations worldwide, there have been challenges in adapting and translating instruments not only in terms of language but also culture. In this study we compare different cohorts of raters from different countries receiving training in the use of the PANSS. We attempted to determine if there was any consistent by-country impact on specific items, factors, or subscales. We queried raters about their perceptions of the instruments they are asked to use vis-à-vis their local patient populations. Methods: The data set comes from standardized rater training events involving raters from 4 countries: India ($n = 83$), Russia ($n = 59$), the US ($n = 63$), and Romania ($n = 76$). Different groups of raters scored taped interviews of 2 schizophrenic patients using the Positive and Negative Syndrome Scale (PANSS). Scores were compared across countries and intraclass correlation coefficients (ICCs) and rater agreement with gold standard scores were evaluated. These results were viewed against global raters' responses to questions about how well PANSS items correlated to the presentation of symptoms among their patients. Results: Raters from the US and Russia demonstrated a higher level of inter-rater consistency than India or Romania with ICCs of 0.883 and 0.835 respectively. For 8 PANSS items, all 4 countries, raters demonstrated at least 80% agreement with the gold standard scores. For 10 PANSS items, there was at least 1 country whose raters scored below 60% agreement with the gold standard scores. The PANSS items with lower inter-rater reliability tended to be the same items raters indicated as problematic in local settings. Conclusion: The differences in rater performance across the 4 countries indicate that standardized rater training is broadly effective in cohorts selected to participate in clinical trials. However, further analysis indicated that there are some important differences in the way that different groups conceptualize items. This suggests a need to tailor training to those items that are less reliable in certain groups to ensure reliability and validity in the use of this instrument.
ID: 978061

EFFECTIVENESS OF SWITCHING FROM ARIPIPRAZOLE TO ZIPRASIDONE IN PATIENTS WITH SCHIZOPHRENIA

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Background: Aripiprazole and ziprasidone are 2 antipsychotic medications that are relatively devoid of the metabolic side effects associated with the second generation antipsychotics. This study aimed to evaluate the effectiveness of switching to ziprasidone in patients who had insufficient response or intolerance to aripiprazole for treatment of schizophrenia. Methods: Nineteen patients receiving aripiprazole treatment for schizophrenia participated in this open-label, 12-week study. Outcome measures included the Positive and Negative Syndrome Scale, Social and Occupational Functioning Assessment Scale, Calgary Depression Scale for Schizophrenia, Beck Depression Inventory, and Subjective Wellbeing under Neuroleptics Scale. Safety measures included metabolic parameters and scales to evaluate extrapyramidal side effects. Results: After switching to ziprasidone from aripiprazole, significant improvement of scores on the negative symptom subscale of the Positive and Negative Syndrome Scale, the Social and Occupational Functioning Assessment Scale, the Calgary Depression Scale for Schizophrenia, and the Beck Depression Inventory were observed at the study end-point evaluation. Metabolic parameters including body weight, waist and hip circumference, fasting blood glucose, and ALT showed statistically significantly decreases. However, serum prolactin levels were significantly increased, and sedation was the most common adverse event. Conclusion: Switching to ziprasidone in patients with schizophrenia who showed insufficient response or intolerance to aripiprazole improved depression, negative symptoms, and metabolic disturbances. However, sedation and hyperprolactinemia were commonly associated with the switch to ziprasidone.
ID: 980219