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Electrophysiological Endophenotypes for Schizophrenia

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Abstract

Endophenotypes are quantitative, heritable traits that may help to elucidate the pathophysiologic mechanisms underlying complex disease syndromes, such as schizophrenia. They can be assessed at numerous levels of analysis; here, we review electrophysiological endophenotypes that have shown promise in helping us understand schizophrenia from a more mechanistic point of view. For each endophenotype, we describe typical experimental procedures, reliability, heritability, and reported gene and neurobiological associations. We discuss recent findings regarding the genetic architecture of specific electrophysiological endophenotypes, as well as converging evidence from EEG studies implicating disrupted balance of glutamatergic signaling and GABA-ergic inhibition in the pathophysiology of schizophrenia. We conclude that refining the measurement of electrophysiological endophenotypes, expanding genetic association studies, and integrating datasets are important next steps for understanding the mechanisms that connect identified genetic risk loci for schizophrenia to the disease phenotype.

Introduction

Despite substantial heritability, the genetic architecture of schizophrenia is incompletely understood.[1] Using population-based genome-wide association (GWA), susceptibility loci for schizophrenia have been localized.[2-8] Indeed, the most recent analysis from the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC) compared 36,989 cases and 113,075 controls to identify 108 conservatively defined loci that meet genome-wide significance, 83 of which had not been previously reported.[9] This work represents an important step forward for genetics of psychoses in understanding the genetic determinants for schizophrenia. However, the identified loci do not directly imply the involvement of specific genes, and identified quantitative trait loci (QTL) explain only a small proportion of the heritable risk.[10] Endophenotypes have been proposed as a way to link genetic risk loci to disease phenotype in a mechanistic way.[2] Given the lack of objective laboratory-based diagnostic measures for neuropsychiatric disorders like schizophrenia, as

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well as the substantial phenotypic heterogeneity, endophenotypes can provide important quantitative metrics that may be closer to the underlying disease biology.[3]

Furthermore, data are rapidly accumulating that rare variants may have a substantial cumulative effect on disease risk relative to common variants captured in conventional GWA studies.[11-18] Recently, Lee and colleagues calculated that only 23% of the variation in schizophrenia can be ascribed to common variants, suggesting that more than 2/3 of the genetic variation may be due to rare variants.[19] Data from the 1000 Genomes Project confirm that rare (<1%) variants constitute the vast majority (73%) of polymorphic sites in humans.[20] A recent exome sequencing study focused on rare functional variants examined 2,536 schizophrenia cases and 2,543 controls of European ancestry, providing the strongest evidence to date for specific genetic variants that increase risk for psychosis.[21,22] Purcell and colleagues identified numerous primarily rare (<1 in 10,000) mutations across many genes that, when considered in aggregate, are strongly associated with schizophrenia risk.[21] While these genes were distributed throughout the genome, functional characterization identified their involvement in networks that directly influence neuronal function, including the voltage-gated calcium ion channel, the activity-regulated cytoskeleton-associated scaffold protein (ARC), and the N-methyl-D- aspartate receptor (NMDAR) postsynaptic signaling complex, gene sets previously implicated in schizophrenia risk through analyses of copy number variants (CNVs).[23] No individual variant or gene-based test achieved statistical significance, which suggests that a complex polygenic burden increases risk for psychotic disorders through multiple targets within each metabolic pathway. Examining exome sequence data from 623 schizophrenia parent proband trios, Fromer and colleagues demonstrated that de novo mutations were over-represented among glutamatergic postsynaptic proteins comprising the ARC and NMDAR complexes, strikingly consistent with the much larger case-control data presented by Purcell and colleagues.[21,22] Although it is possible that with additional samples individual rare variants identified with exome or whole genome sequencing may become significant, the current findings clearly demonstrate the polygenic nature of psychosis risk, and suggest that both common and rare variants confer risk for schizophrenia.

This new understanding regarding the involvement of both common and rare variants in the genetic architecture of schizophrenia is consistent with the notion that multiple rare mutations occurring within common gene pathways appear to contribute to risk for psychotic illness.[24] If so, biologically characterizing the impact of identified gene sets on illness risk could be quite difficult using affection status alone. In this context, using a genetically informed quantitative diagnostic proxy could dramatically improve our ability to conceptualize the impact of specific mutations/variants, gene sets, or networks on biological processes predisposing to schizophrenia. At one level, an endophenotype is such a proxy.[25] Our manuscript reviews research designed to identify and implement endophenotypes to better understand schizophrenia. We will focus on electrophysiological putative endophenotypes, given the consistent evidence for electrophysiological markers as genetically mediated intermediate traits as well as their potential relevance to underlying disease biology.[26,27] Furthermore, electrophysiological endophenotypes have high translational value, as they can also be effectively modeled in animals.[28-31].

Endophenotype: A Definition

An endophenotype is a trait that is related to the genetic liability for an illness, but is not itself a measure of that illness[32]. In other areas of medical genetics, the terms "allied phenotype" or even "risk factor" may be used, though the term "endophenotype" has a close association with psychiatric genetics. Most researchers agree that for a trait to be considered an endophenotype, it must: (1) be heritable; (2) associated with the illness; (3) mostly independent of clinical state; and (4) impairment must co-segregate with the illness within a family; and (5) represent reproducible measurements.[33-36] As quantitative endophenotypes may provide a more precise estimate of the underlying liability distribution, they are thought to provide greater power to localize disease-related genes than affection status alone.[25,36-38] We previously argued that the criteria for an endophenotype can be reduced to evidence for heritability and evidence for a genetic relationship (i.e., pleiotropy) with the illness.[25,39] This requirement of pleiotropy implies that endophenotypes are directly comparable to allied phenotypes discussed in other areas of complex disease genetics.[40] In this context, we conceptualize endophenotypes as quantitative, laboratory-based measures that represent intermediate links between genetic contributions and clinical phenotypes.

While most attempts to define endophenotypes focus on a specific illness[41,42] there is growing evidence that endophenotypes often elucidate neurobiological mechanisms that are shared across disorders.[25,38] Given substantial evidence for pleiotropy between schizophrenia and bipolar disorder,[43-45] and to a lesser extent major depression,[46] the lack of diagnostic specificity of many endophenotypes is not surprising. Thus, endophenotypes may lack specificity to particular neuropsychiatric disorders, but that may be an accurate reflection of genetic and neurobiological mechanisms shared by the disorders.

Electrophysiological Endophenotypes

Electroencephalography (EEG) is an excellent tool for studying endophenotypes in clinical populations because it is relatively inexpensive, comfortable for subjects, and collects data with high temporal resolution.[47] Several candidate neurophysiological endophenotypes in schizophrenia have been proposed, including the P50 event-related potential amplitudes and gating, oculomotor antisaccade, mismatch negativity (MMN), and the P300 event-related potential.[26,48,49] The acoustic startle reflex, or prepulse inhibition (PPI), is another commonly investigated EEG marker proposed as a schizophrenia endophenotype, but substantial variability and the presence of PPI deficits across numerous neuropsychiatric disorders has tempered the case for PPI as a specific endophenotype of schizophrenia.[50,51] Each measure has demonstrated strong evidence of abnormality in patients with schizophrenia, and all show heritability and have been observed in unaffected first-degree relatives. This review will briefly address how each measure shows: 1) evidence of deficits in schizophrenia; 2) stability over time; 3) relative independence of fluctuations in clinical symptoms; 4) deficits in unaffected family members; and 5) heritability. Turetsky and colleagues and Light and colleagues provide more extensive reviews of empirical data supporting the relationships of each endophenotype to schizophrenia; here we provide an updated review of each potential endophenotype, with discussion of major findings related to neural mechanism and putative genetic links.[26,49] We also consider potential emerging

electrophysiological endophenotypes not discussed in previous reviews. It should serve as a critical evaluation of the current evidence supporting each potential endophenotype as a useful tool in aiding the investigation of schizophrenia genetics. We used the search engines Google Scholar and PubMed to complete the following search: [electrophysiol* OR EEG OR ERP] AND [schizophrenia OR psychosis] AND [endophenotype OR intermediate phenotype OR inherited]. To describe deficits in individuals with schizophrenia relative to healthy controls, we focused on studies that included individuals at clinical high-risk or prodromal states, first episode states, and/or chronic states. Studies on childhood onset schizophrenia were not included in this review. For genetic research, we prioritized studies with very large sample sizes but also included ones with smaller sample sizes to better characterize publications the field and the diversity of results. Titles and abstracts were used to select studies that were associated with the goals of the present review. See Table 1 for a summary of findings on each endophenotype.

Sensory gating and P50

Deficits in sensory gating have been studied extensively as potential endophenotypes for schizophrenia, and are among the most robust biological findings associated with the disorder.[52-54] Sensory gating deficits refer to Venables' theory that abnormalities of attention and information processing in schizophrenia are partly caused by stimulus "flooding" via sensory overload, or the failure of normal sensory filtering and gating mechanisms.[55] A prominent method for demonstrating this impairment is the P50 paradigm, in which EEG recordings measure the response to two identical auditory stimuli (named S1 and S2) that occur 500 ms apart. Healthy control participants typically show a reduced or suppressed P50 to S2 relative to S1 (typically depicted as a ratio, S2/S1). The suppressed P50 to S2 is thought to be the result of inhibitory processes activated by S1 that protect the processing of the first stimulus (S1) from the disruptive impact of the second stimulus (S2).[56] In accordance with the theory that patients with schizophrenia have deficits in sensory gating mechanisms, patients typically fail to exhibit P50 suppression to S2 and therefore have larger P50 ratios.

A meta-analysis showed a large pooled standardized effect size of P50 ratio in patients with schizophrenia relative to healthy controls (1.56, 95% CI: 1.06-2.05), with no significant influence of duration of illness or antipsychotic medication.[26,52] In a one-year test-retest study, no significant associations were found between change in P50 ratio (Time 1 – Time 2) and change in positive or negative symptom severity (Time 1 – Time 2) which suggests that P50 ratio is largely independent of clinical state.[26] P50 suppression deficits have also been found in individuals at clinical high risk for psychosis regardless of whether or not they developed fully psychotic symptoms within a two-year follow-up period.[57] The P50 ratio has been criticized by some for lack of reliability due to its inherent mathematical properties, i.e., S1 and S2 are not independent, so the shared variance between them cannot be completely eliminated and noise in both the numerator and denominator will introduce even greater variability.[26,58,59] This has led many investigators to use P50 difference scores (S2-S1) either instead of or in conjunction with P50 ratio scores, typically without correcting for multiple comparisons. One study found high test-retest reliability of the P50 ratio, but did so by applying stringent trial inclusion criteria.[60] Light and colleagues rated P50 ratio and P50

difference scores as two of the lowest ranking potential endophenotypes of schizophrenia based on a summary score considering state-independence, one-year stability, and magnitude of deficits in patients.[26]

P50 ratio has shown heritability estimates ranging from to $h^2 = 0.10$ (not significant) (Greenwood et al., 2007) to $h^2 = 0.68$.[60] The former study found higher and statistically significant heritability estimate for P50 difference (S2-S1; $h^2 = 0.28$). Multimodal evidence suggests involvement of noradrenergic, dopaminergic, and cholinergic neurotransmission in sensory gating.[61-63] Two genes have been identified and studied as potential candidate genes for the P50 endophenotype: the α7 nicotinic acetylcholine receptor subunit gene (*CHRNA7*) and the Catechol-O-methyltransferase (*COMT*) gene.[64,65] Pharmacologic blockade of the CHRNA7 receptor in animal models has been shown to induce a gating deficit that resembles deficits observed in patients with schizophrenia. It ishypothesized that one source of the gating deficit may stem from impaired acetylcholine-mediated hippocampal filtering.[66] In accordance with this theory, EEG source localization studies suggest involvement of the hippocampus, as well as thalamus, superior temporal gyrus, and dorsolateral prefrontal cortex (DLPFC).[67,68] Smoking-associated increases in nicotine levels, a well-known form of self-medication in patients with psychosis, may reactivate some hippocampal filtering, which bolsters the idea that CHRNA7 receptors may be critical for P50 suppression.[67] While genome-wide linkage analysis showed that P50 suppression deficits in schizophrenia were linked to the site of the α7-nicotinic receptor (chromosome 15q13-14), two recent studies did not find significant associations with SNPs in the *CHRNA7* region and P50 suppression.[48,69,70] The schizophrenia risk allele of another gene, transcription factor 4 *(TCF4),* has been shown to be significantly associated with worse P50 suppression in healthy individuals, and these gene effects were modulated by smoking behavior such that heavy smokers showed effects of *TCF4* on P50 suppression than light and never smokers.[71]

The *COMT* gene is located in a region known to be associated with psychosis (22q11.2) and its enzyme degrades extracellular catecholamine, especially dopamine in the prefrontal cortex.[72] COMT may affect P50 suppression via cortical signal-to-noise modulation by prefrontal dopamine and/or by cortical norepinephrine.[73] Two studies have found evidence for a selective deficit in P50 ratio for individuals with schizophrenia who are homozygotes for the *COMT* Val158 allele.[74,75] However, in a pedigree study of 534 individuals in families with multiple members affected with schizophrenia, the Consortium on the Genetics of Schizophrenia (COGS) study failed to find an association between *COMT* and P50 difference.[48] Notably, the COGS study did find associations between several genes associated with glutamatergic N- methyl-D-aspartate (NMDA) receptor signaling and P50 difference score.[48] Specifically, P50 difference score was significantly associated with variants in glutamate receptor, ionotropic, kainite 4 (*GRIK4)*, glutamate receptor, ionotropic, delta 2 (*GRID2*) and most robustly associated with glutamate receptor, metabotropic 3 (*GRM3*).[48] Additional pre-clinical evidence supports the role of glutamatergic NMDA-receptor signaling in sensory gating dysfunction. For example, rodents with reduced expression of the NR1 subunit of the NMDA receptor, which impairs NMDA-receptor signaling, had impaired auditory gating relative to wild-type rodents.[76] However, another

rodent study that used the NMDA receptor antagonist phencyclidine (PCP) did not find impaired auditory gating. Additional rodent model and human studies are needed to elucidate the associations between glutamatergic signaling and P50 suppression.

In summary, while some evidence suggests *COMT* and *CHRNA7* may be associated with P50 deficits in individuals with schizophrenia, non-significant findings linking these genes to abnormal P50 in schizophrenia from large-scale GWA studies (e.g. COGS and Psychiatric Genomics Consortium) challenge this notion.[48,69] Larger sample sizes and uniformity of sensory gating measures (P50 ratio vs. P50 difference) are needed to understand the genetic contributions to this endophenotype. In general, conflicting findings regarding P50's state-independence, reliability, and heritability must be resolved in order for P50 to be considered a useful endophenotype of schizophrenia.

Antisaccade Task

The antisaccade (AS) task is typically measured using infrared oculography or electro-oculogram (EOG).[77] A trial begins with the participant fixating on a central point, followed after 1-2 seconds by an unpredictable stimulus either on the left or right. The participant is asked to look at the mirror image location on the opposite side of the screen. Results are typically discussed using proportion of incorrect saccades (reflexive error or prosaccades), or proportion of correct AS, over all trials. Producing a correct response in an AS task requires two abilities: one must suppress a reflexive saccade towards the stimulus, and then one must generate a voluntary saccade in the opposite direction. The inability to suppress the reflexive response is posited to be indicative of deficits in executive control and will result in a high number of incorrect saccades.[78] A deficit in the generation of voluntary saccades will result in a low number of correct antisaccades. Accordingly, it is thought that AS inhibition relies on frontal cortical areas (primarily DLPFC) for inhibition and parietal regions for preparation of voluntary oculomotor movement.[79] Evidence supporting this notion comes from patients with lesions of the DLPFC who are impaired at inhibiting incorrect saccades during the AS task, but have normal visually-guided prosaccades.[80] However, patients with lesions of the posterior parietal cortex show delayed prosaccades but normal performance on AS tasks.[80] A more detailed overview of AS neurobiology and performance in various clinical populations can be found in a review by Everling & Fischer.[81]

A large body of research has shown that individuals with schizophrenia exhibit more errors on the AS task than do matched healthy controls, with large effect sizes.[82] Patients with schizophrenia have also been found to exhibit longer latencies on correct AS responses relative to healthy controls, therefore it seems that both abilities required to perform the AS task are impaired in schizophrenia.[81-83] While some studies have suggested that antisaccade deficits in schizophrenia are primarily due to PFC-related dysfunction, others point to slow saccadic responses that are the result of reduced white matter organization in anterior cingulate, parietal, and frontal eye field areas.[84,85] The parietal cortex has also been suggested to mediate successful cue disengagement (i.e., disengaging from the fixation cue to initiate a saccade)[86] and is involved in inhibitory activity.[87] Thus, the neural mechanisms involved in AS are complex; for further overview of these mechanisms and their dysfunction

in schizophrenia, see the review by Munoz & Everling.[78] Deficits in the AS task for individuals with schizophrenia have been shown to be reliable, temporally stable, and largely unaffected by medications or nicotine administration, which serves as evidence for a trait-like deficit.[26,49] Practice effects for antisaccade performance have been found over periods of weeks to months.[88,89] Age-related improvements in inhibiting incorrect saccades have also been found between children (age 6-11) and adults (age 18-26), which is in line with assumed development of prefrontal functions and should be considered when comparing younger first episode or prodromal patients to patients with chronic schizophrenia.[90] Antisaccade errors in patients with schizophrenia are significantly correlated with spatial working memory performance and Wisconsin Card Sorting Task perseverative errors, further supporting the notion that AS deficits in schizophrenia are related to PFC dysfunction.[91,92] Two meta-analyses found evidence for impairments in nonpsychotic first-degree relatives of schizophrenia patients relative to healthy controls (mean Cohen's $d = 0.43$[93] and 0.61[94]) although there are studies that have failed to find this effect.[95] Impairments in AS have also been found in clinically unaffected twins discordant for schizophrenia.[96]

While EOG is used to measure the latency, duration, velocity, size, and accuracy of saccades, cortical evoked-response potentials (ERPs) may also be measured in AS tasks. Saccadic eye movements are preceded by a negative-going component (similar to a readiness potential before finger movements, i.e., “contingent negative variation”) and a positive-going slow wave (similar to a premotor positivity prior to finger movements).[81,97] These components can be measured to better understand deficits in the antisaccade task for individuals with schizophrenia by parsing apart defective inhibition (resulting in a high number of incorrect prosaccades) versus defective correct response activation (resulting in a low number of correct antisaccades) and the cortical sources of such deficits. Decreased presaccadic positivity in the last 100 ms prior to saccade onset has been demonstrated for antisaccades compared to prosaccades, typically in centroparietal sites.[98-100] This difference potential has been interpreted as indicative of frontal inhibitory mechanisms.[99] Additionally, increased presaccadic negativity over central and frontal sites has been demonstrated in antisaccades compared to prosaccades and is often referred to as the contingent negative variation.[86,100,101] This has been interpreted to reflect preparatory activity in the frontal eye fields to initiate saccades.[100] Of note, eliciting the contingent negative variation seems to be dependent on task design: studies with block-designs in which subjects respond to stimuli in a fixed manner seems to produce the contingent negative variation, while designs using unpredictable cues do not.[99,102] The contingent negative variation can be elicited through a variety of task designs and is not specific to the AS task; for a general review of this measure, see Brunia & Boxtel, as this review will only focus on the contingent negative variation as it relates to the AS task.[103]

Cortical source analysis of the presaccadic positive slow wave in healthy controls revealed a common set of sources in the ventral anterior cingulate and orbital frontal gyrus.[101] Patients with schizophrenia have been shown to have smaller difference potentials (antisaccade minus prosaccade) over lateral prefrontal cortex areas relative to healthy controls, and this attenuation is associated with less accurate AS performance.[102,104,105] Healthy first-degree

relatives of patients with schizophrenia have demonstrated similar deficits relative to healthy controls.[102] Given the complexity of the AS task and the variety of interpretations that can be made about poor performance on it, these results of ERP studies allow for more targeted conclusions. Specifically, that lateral frontal cortical dysfunction during volitional saccade generation may be a marker of genetic vulnerability for schizophrenia, and that in patients this is associated with lower antisaccade accuracies.[102] Patients with schizophrenia also show deficits in contingent negative variation, which is assumed to be a physiological correlate of selective attention and of anticipation in a mental/motor performance.[106,107] While healthy controls generally show a larger component during antisaccades relative to prosaccades, patients fail to show this augmentation and have smaller components in general.[108-110] Deficits in contingent negative variation are not specific to schizophrenia (e.g., depression;[111] ADHD[112]). More research is needed to understand the reliability of both EEG measures in relation to AS performance, their state-dependence, and impairments in biological relatives.

It is important to note that increased AS error rates are not specific to schizophrenia, as they have also been found in patients with other neuropsychiatric disorders, including autism spectrum disorders[113], ADHD[114] and bipolar disorder[115], which may suggest cross-diagnostic genetic contributions. Behavior genetic investigations have found heritability estimates for AS performance of $h^2 = 0.57$[116] in a sample of healthy adolescent twins and $h^2 = 0.42$[117] in families of individuals with schizophrenia. A GWAS of the AS error rate also found that approximately 50% of the variance in responses was attributable to additive genetic effects.[118] "Missing heritability", which refers to estimated heritability that is unaccounted for by single nucleotide polymorphism (SNPs), seems to be less of a problem for AS error rate relative to other potential endophenotypes, as most of the biometric heritability in AS was accounted for by SNPs that were identified by GWAS.[118] Although no SNP achieved genome-wide significance in this study, a gene that codes for glutamatergic system proteins (*GRM8*) was significantly implicated in the AS response when evaluating a set of 204 genes from the NeuroSNP database (https://zork5.wustl.edu/nida/neurosnp.html).[118] Specifically, genes those involved in major neurotransmitter systems (e.g., dopamine, noradrenaline, GABA, glutamate) and those related to substance use (e.g., alcohol-relate genes, opioid genes).[118] The COGS study investigated an array of SNPs in 94 functionally relevant candidate genes for schizophrenia and found that AS deficits were related to 9 candidate genes for schizophrenia, the most robust being *GRIK4* with additional significant results for *RELN* and *HTR2A*.[48] *GRIK4* and *RELN* are genes involved in glutamatergic signaling, while *HTR2A* is involved in serotonin-receptor signaling.[48] Combining all significant SNPs for AS suggests a possible role of glutamate, serotonin receptor, dopamine receptor, and neuregulin-mediated signaling in AS response.[48] Other genes have been found to be associated with AS performance, including the gene encoding the regulator of G-protein signaling subtype 4 (*RGS4*)[119] and *COMT*.[120] However, the pedigree-based COGS study did not find these effects.[48]

In summary, behavioral and electrophysiological deficits in the AS task for patients with schizophrenia have been well established. More research is needed to understand the reliability and state-dependence of these measures. There are multiple variants of the AS

paradigm, which can affect performance[82]; therefore, researchers must be precise and comprehensive in their methodological descriptions in order to reduce variability when combining or comparing data. To our knowledge, no genetic investigations have been done for positive slow wave or contingent negative variation in the AS task. Future genetic studies using these EEG measures may help parse the complex neurobiological underpinnings of the AS task into its component mechanisms. This increased specificity may lead to stronger and more consistent genetic results.

Mismatch Negativity (MMN)

Mismatch negativity (MMN) is an auditory ERP component that is thought to be an objective index of auditory sensory memory functioning and is involved in the assessment of stimulus familiarity/unfamiliarity. Auditory sensory memory refers to the ability of the brain to retain representations of the physical features (e.g., pitch, intensity) of simple auditory stimuli for up to 30 seconds.[121] MMN is elicited when a sequence of repetitive standard sounds is interrupted infrequently (10% of total trials) by deviant "oddball" stimuli, which differ in duration or pitch from the standard sounds. The MMN is present as early as 50 ms after stimulus onset and peaks after an additional 100 to 150 ms. MMN is measured by subtracting the auditory evoked potential to the standard tone from that of the deviant tone, which produces a difference waveform with a prominent negative potential. The response is maximally present at frontocentral scalp recording sites and is thought to be generated within the primary and secondary auditory cortices with contributions from bilateral, dorsolateral prefrontal cortices.[122]

A meta-analysis has shown a large effect size ($d = \sim 1.0$) for group differences in MMN in patients with schizophrenia relative to healthy controls, with patients showing smaller MMN than healthy controls regardless of age, gender, or paradigm type.[123,124] MMN appears to reflect an automatic, memory-based comparison process between sounds and has been shown to have good reliability.[60,125-127] Eliciting MMN does not require any response from the participant, making it an excellent tool for studying individuals with varying levels of functioning: as a pre-attentional cognitive measure, researchers can use MMN to characterize the integrity of sensory network function independent of attentional or motivational artifacts.[49] Interestingly, MMN deficits are highly associated with impairments in real-world functioning and psychosocial functioning.[127-129] See review by Todd and colleagues for a more detailed review of the neurobiology of MMN.[130]

MMN deficits in patients with schizophrenia appear to remain stable over time despite antipsychotic use or episodic state.[49] MMN was the highest ranking "longitudinal endophenotype", calculated by summing the effect sizes of state-independence (no significant relationship with positive or negative symptoms), long-term stability (ICC > .80) and magnitude of deficits ($d = 0.8$) in patients in a 1 year test-retest study.[26] While these studies show that MMN demonstrates stability in a 1-year time frame, cross-sectional studies in patients suggest it may show increasing deficits over longer periods of time (see below). Recently, deficits in MMN have been demonstrated in individuals at clinical or genetic high risk for psychosis[124,131] and have been shown to predict psychosis onset in clinically high risk individuals.[124,132-136]

Heritability of MMN has been estimated to be .63 and .68 for peak amplitude and mean amplitude, respectively.[60] Healthy family members of individuals with schizophrenia, individuals at risk for developing schizophrenia, and recent-onset patients have all been reported to have reduced MMN amplitudes.[131,137-140] One study found normal MMNs in unaffected family members of schizophrenia patients, and two studies have found normal MMN in first-episode patients.[52,141,142] The first study may have restricted the variance of MMN amplitudes by using a common average EEG reference, thus reducing power to find effects.[52] The latter studies both found reduced MMN in patients who had been diagnosed with a psychotic disorder for at least 18 months, but failed to find an effect in first-episode patients who had very recently undergone their first hospitalization, suggesting that MMN may become more impaired with illness progression.[142] Other evidence exists to suggest that MMN deficits may increase with illness progression: a 1.5 year prospective study of first-hospitalized individuals with schizophrenia found a strong relationship between MMN amplitude reductions and left hemisphere Heschl gyrus gray matter volume reductions.[143] The patients in this study did not differ from healthy controls or psychotic bipolar disorder individuals at study onset (time of first hospitalization), but did at follow-up.[143] Jahshan and colleagues additionally found progressively smaller MMN amplitudes across at-risk, recent-onset, and chronic patients.[131]

Collectively, the studies reviewed above suggest that conclusions regarding changes in MMN over time are mixed: the studies that show normal MMN in first episode patients with schizophrenia suggest that MMN indexes a progressive process and is not a marker of vulnerability for the disorder,[141-143] while other studies have found reduced MMN in at risk populations.[131-136] A recent meta-analysis also concludes that, while individuals with chronic schizophrenia have decreased MMN amplitudes relative to first episode individuals, a meta-regression analysis showed no relationship between duration of illness and MMN effect size.[124] Additionally, clinical high-risk individuals who later converted to psychosis had MMN amplitudes indistinguishable from individuals with chronic schizophrenia, but healthy first-degree relatives and high-risk participants who did not convert to psychosis both had nonsignificant reductions in MMN amplitude.[124] These findings suggest that: 1) MMN impairment across the illness is a nonlinear process, and 2) reductions in MMN in a high-risk state may be a marker for likely conversion to psychosis rather than a marker of genetic vulnerability.[124] Strong studies capable of finding a subtle link between genetic risk for psychosis and MMN have not been done; therefore the latter conclusion is speculative. With regard to the nonlinearity hypothesis, the larger deficits in individuals at clinical high risk and those with chronic schizophrenia relative to those with first episode schizophrenia may also suggest that there exists non-shared variance associated with underlying risk and current clinical state. That is, processes related to being in a clinical high-risk state and processes related to chronic psychosis are independently related to MMN amplitude. Again, large-scale studies capable of parsing these components have not yet been performed.

Attenuated MMN amplitude and prolonged peak latency has been found in a large number of neuropsychiatric, neurological, and neurodevelopmental disorders, as well as in normal aging, suggesting that MMN deficiency may index cognitive decline in general.[144] However, other studies have failed to find MMN deficits in individuals with bipolar disorder,[143,145,146] major depression,[146] and obsessive-compulsive disorder.[147] Prospective

studies are needed to delineate the specificity of MMN deficits in schizophrenia and whether individuals with schizophrenia have a greater rate of decline relative to other neuropsychiatric populations.

Studies have demonstrated that disruption of NMDA signaling may play a crucial role in MMN generation and contribute to MMN deficits in patients with schizophrenia.[121,148] Research on nonhuman primates has shown that both competitive and noncompetitive NMDA antagonists reduce MMN amplitude without affecting prior ERPs in the primary auditory cortex.[121,149] The same NMDA antagonists have been shown to elicit some symptoms of schizophrenia when administered to healthy subjects, suggesting that the glutamatergic NMDA receptor system plays a crucial role both in neurocognitive deficits and psychotic symptoms of schizophrenia.[56,148] Dopaminergic systems may also play a role in MMN production: two studies have found diminished MMN in adolescents with 22q11.2 deletion syndrome, which includes the *COMT* gene (discussed above).[150,151] Contrary to P50 results, one study found reduced MMN in individuals with the Met allele, suggesting differential effects of dopamine on these two ERPs.[150] To our knowledge, no GWA studies have investigated genetic variants associated with MMN deficits, so it is unclear whether COMT or other genes are associated with MMN deficits.

In summary, MMN represents a promising endophenotype for further study in schizophrenia. Its potential ability to predict onset to psychosis is particularly intriguing and should be investigated further. GWA studies on MMN are needed to further elucidate the genetic and neurobiological contributions to this measure and whether meaningful genetic overlap exists between neuropsychiatric disorders characterized by MMN deficits.

P300

The P300 event-related potential, referred to in some literature as P3, is an index of a variety of cognitive processes, including onset of an unexpected stimulus,[152] context updating,[153,154] working memory updating and consolidation,[155] and the attribution of salience to a deviant stimulus.[156] The P300 can be identified as a large, positive component with peak latency around 300 ms after stimulus onset when evoked by an auditory stimulus (about 100-200 ms later when evoked by a visual stimulus). The auditory P300 is typically studied using the oddball task in which an infrequent tone is randomly interspersed within an ongoing train of a repeating tone, presented at a rate of about once per second. The P300 is distinct from the MMN in that it requires attention; an MMN will still be elicited even when attention is directed toward a different sensory modality, while a P300 will not.[157] Additionally, the stimulus train optimal for eliciting an MMN involves presentations at a rate faster than once per second. Lastly, violations of expectation that occur during the infrequent stimulus can occur on much more abstract properties of the stimulus, consistent with the notion that it represents a more complex level of stimulus evaluation and categorization. MMN appears when a violation is tied to very basic, physical stimulus properties (e.g., duration, pitch, intensity).[157]

The P300 has been widely investigated in both healthy and clinical populations. Smaller amplitudes of P300 have been found in studies of chronic,[158] recent onset,[159] and

unmedicated schizophrenia patients,[160] and has been replicated by numerous independent investigators.[26] Considerable evidence also exists that a significant level of P300 amplitude reduction is a trait abnormality and exists independent of duration of illness, or symptom severity.[161] A meta-analysis found an effect size of $d = 0.89$ for auditory P300 amplitude reduction and $d = 0.59$ for delayed peak latency in patients with schizophrenia compared to healthy controls.[162]

The P300 has a broad, centrally-maximal scalp distribution, and reflects a composite of anatomically and functionally distinct neural generators.[156,163,164] Accordingly, it is often separated into two discrete subcomponents. The P3a subcomponent is elicited by novel or unexpected stimuli, occurs slightly earlier, has frontocentral scalp topography, and is thought to reflect attentional orienting processes.[165,166] Source localization studies suggest that the P3a stems from activity in the lateral prefrontal and superior temporal areas.[164] The P3b subcomponent is elicited by task relevant stimuli – it is sometimes referred to as the "target P300" – especially when the task relevant stimulus occurs relatively rarely among a series of irrelevant stimuli. It occurs later, has parietal scalp topography, and is thought to reflect cognitive processes associated with stimulus evaluation and response formation.[165] Source localization studies suggest that P3b scalp activity arises from the inferior parietal cortex, particularly the supramarginal gyrus, in addition to sensory modality-specific regions.[164] There has been some suggestion that P3a is more strongly associated with dopaminergic neurotransmitter actions, while P3b may be more strongly associated with noradrenergic pathways.[165] Both P3a and P3b components are diminished in patients with schizophrenia and also fluctuate with clinical symptoms and state.[167] Diminished P3a and P3b amplitude have also been found in individuals determined prospectively to be at high risk (or determined retrospectively to be in a prodromal state) of developing schizophrenia.[131,168] Diminished P3b amplitude is additionally present in unaffected biological relatives.[169] There is some evidence that diminished P3a amplitude is apparent across psychotic disorders in general, while reduced P3b amplitude specific to schizophrenia.[170-172] P3b amplitude reduction was also correlated with a wide range of clinical measures, including severity of symptoms, overall functioning, and clinical traits that had been assessed 15 years earlier.[170] Therefore, it was suggested that P3b reduction is a more stable trait-like endophenotype of vulnerability to disease and predictor of outcome rather than a reflection of disease state.[170] Alternatively, the P3b has failed to differentiate schizophrenia and bipolar psychosis in other studies.[173,174]

Disrupted P300, P3a and P3b are not specific to schizophrenia, and in fact have been found in a variety of disorders, including Alzheimer's disease,[175] substance use,[176,177] disinhibited pathology,[178] and bipolar and unipolar depression,[179] although there may be some variations that are unique to each disorder.[180] As discussed in the introduction, one can consider whether the usefulness of an endophenotype varies by its specificity to a particular disorder.

Considerable evidence exists for a genetic contribution to P300 amplitude; a heritability estimate of 0.60 to 0.69 has been established among healthy individuals.[60,172,181] There is also evidence for a genetically-mediated P300 deficit in first degree relatives of patients with schizophrenia.[182] More evidence comes from a meta-analysis showed that P300 amplitude

was reduced and its latency was delayed in non-psychotic relatives of patients with schizophrenia.[183] Of the studies that have deconstructed the heritability of P3a and P3b subcomponents, two have found stronger familial deficits of the P3a, which would suggest stronger heritability for abnormalities of attentional orienting.[184,185]

A GWAS study of P300 conducted on a large community sample (N=4026) showed that 65% of the variance in P300 amplitude was due to additive genes, which is consistent with a previous meta-analysis.[186] Estimates of SNP heritability, or phenotypic variance due to the measured genetic variants on the genotyping array, yielded a heritability estimate of .29 for P300 amplitude, which represents about 40% to 50% of the heritable variance of this trait.[186] This suggests that about half of the additive genetic influence is likely due to common genetic variants as opposed to rare variants or shared environmental influences.[116] Despite this fact, analyses of individual SNPs did not yield any significant associations. In the same study, a genome-wide analysis of 17,601 autosomal genes did find a novel association with myelin expression factor 2 *MYEF2*, which codes for a major component of the myelin sheath surrounding cells in the central nervous system- an effect that has not been found in prior GWAS studies of P300.[186] This study demonstrates that even when working with substantial heritability and a relatively large sample, samples may still be underpowered to detect genome-wide significant effects. This issue is discussed further in the section, “Promise of Electrophysiologic Traits as Genetically Tractable Endophenotypes”.

Smaller studies of schizophrenia patients and healthy controls have found significant genetic associations with P300, but have yielded different results. For example, a study that selected 21 genetic markers that had prior evidence of association with schizophrenia found that the risk allele of SNP rs1344706 in *ZNF804A* was significantly associated with P300 amplitude.[187] Another study also found that having this risk allele yields higher P300 amplitude for both schizophrenia patient and healthy control carriers compared to noncarriers.[188] However, this study did not investigate other SNPs.[188] *ZNF804A*, a gene implicated in transcriptional regulatory function, has been implicated in risk of schizophrenia by a GWAS and subsequently replicated by several targeted association studies.[187] Another study investigated 19 risk SNPs associated with schizophrenia and did not find an effect for *ZNF804A*, but found that the *TCF4* SNP rs17512836 allele was associated with significant reduction in P300 amplitude and delayed P300 latency.[189] One large pedigree study of a family with a (1;11)(q42;q14.3) translocation, which is associated with major psychiatric disorders including schizophrenia, found that translocation in the *DISC1* gene was associated with reduced P300 amplitudes, regardless of psychiatric symptomatology[190], an effect which was not observed in the former two studies.

Difficulties associating P300 amplitude with a specific genetic variant may be due to a variety of state-dependent contributions, which could be addressed by conducting measurements over multiple occasions.[191] Differing inclusion criteria for SNPs may also be a problem; for example, the aforementioned studies by Del Re and colleagues[187] and Hall and colleagues[189], both initially selected a limited number of SNPs to investigate based on findings by published GWAS that the selected SNPs confer risk for schizophrenia. Both then go on to include different additional SNPs based on prior findings that these SNPs are

associated with other traits related to schizophrenia, such as nicotine dependence or functional neuroimaging measures. SNPs of interest were also then removed if there were too few minor allele carriers in the sample.[187] While narrowing the SNPs of interest to those that are likely to be associated with schizophrenia may improve power by reducing the number of comparisons,[192] varying criteria for inclusion of SNPs will undoubtedly cause problems in replication.

In summary, the P300 is altered in schizophrenia, both in terms of reduced amplitude and delayed peak latency.[162] Diminished P300 amplitude has been found in several neuropsychiatric disorders, which may reflect shared physiological mechanisms. When individually studying the P300's subcomponents, P3a and P3b, there is evidence to suggest that P3b amplitude reductions may be more specifically related to schizophrenia diagnosis rather than broadly defined psychosis, and may be more stable and therefore better able to predict outcome than P3a.[170] If P3b is more specifically related to schizophrenia, this may be an excellent case for breaking down endophenotypes into more specific sub-measures in order to create potentially more genetically tractable traits (discussed below). Lastly, while there is ample evidence that P300 amplitude is heritable, lack of replication remains a problem for discovering specific genetic contributions to this endophenotype.[60,172,181,193]

Gamma

A potential electrophysiological endophenotype gaining increasing attention is abnormal activity in the gamma range (30-80 Hz) of scalp EEG.[194,195] In the case of EEG activity, as opposed to the time-locked, voltage-averaged ERP measures discussed above, neural time series data are decomposed into constituent oscillating activity across standard frequency bands, producing estimates of signal amplitude (or, when squared, power) and phase.

At the present time, there is little about gamma band activity – from its underlying neural generators, to its functional significance in typical cognition and in schizophrenia – that is *not* controversial.[196] For instance, although there is an emerging consensus that gamma power changes reflect the dynamic balance of excitatory and inhibitory influences on small-scale, localized populations of pyramidal neurons in the cortex,[197-200] disagreement exists regarding the influence of thalamo-cortical circuits on local gamma power,[201] as well as regarding the capacity of gamma power or phase to play a significant role in the functional synchronization across populations of pyramidal neurons-[201-203] the reason for much of the interest in gamma activity in the first place.[204,205]

Regardless of the theoretical motivation, a number of studies have shown that gamma band activity is abnormal in people with schizophrenia.[206] Kwon and colleagues[207] were first, reporting that people with schizophrenia are slower to entrain oscillatory brain activity to auditory “steady state” stimulation at 40 Hz and also show lower power in response to the stimulation overall. Since then, these findings have been replicated independently,[208] including among older patients with a chronic course of schizophrenia,[209] first-episode schizophrenia patients,[210] and unmedicated patients.[211,212] However, evidence that gamma band abnormalities are present prior to the onset of psychosis, is far from robust,[213] and if present, may be restricted to the later portion of the auditory steady-state response.[214] As

such, this pattern of findings may cast doubt on its role as a trait-like vulnerability marker. On the other hand, as discussed below, unaffected relatives of patients with schizophrenia also show gamma effects, which is consistent with an inherited, trait-like deficit.

In addition to passive auditory stimulation, gamma activity has also been examined while patients are at rest and while they perform challenging cognitive tasks. Overall, studies show evidence that resting[215,216] and pre-stimulus baseline gamma activity is elevated,[217,218] while task-driven gamma-band responses are reduced in schizophrenia,[205,219,220] suggesting deficits in signal-to-noise ratio between neural network states.[28]

Also worth considering is the likelihood that the ERP measures discussed earlier and EEG measures like gamma band power and phase are not independent of each other.[221] In fact, gamma abnormalities may be an important contributor to these potential endophenotypes. For example, decreased magnitude and delayed latency of gamma synchrony (occurs -150 to 150ms post-stimulus) was demonstrated in patients with schizophrenia relative to healthy controls in a traditional auditory oddball paradigm, which also elicits the P300.[210] Another study showed smaller P50 amplitude and weaker gamma response attenuation in patients with schizophrenia with perceptual disturbances relative to patients without perceptual disturbances and healthy controls.[222] With respect to the familial distribution of gamma band abnormalities, studies have detected more subtle abnormalities in unaffected first-degree relatives.[223] Additionally, both evoked gamma power and phase-locking of the early auditory gamma-band response were shown to be heritable in a study of twins concordant and discordant for schizophrenia ($h^2 = 0.65$, $h^2 = 0.63$, respectively).[224,225]

Future studies are needed to compare various measures within the same subjects to better understand the associations between gamma oscillations during resting-state, sensory-driven and cognitively-driven tasks. Along these same lines, innovative methods are needed to establish with certainty that the gamma band findings derived from animal models actually reflect the “same” gamma as is measured in non-invasive human studies. Factors like developmental stage must also be taken into account, as sensory-evoked gamma activity has been shown to have a distinct non-linear developmental trajectory over the course of adolescence and young adulthood,[226] a key epoch in schizophrenia pathophysiology. Furthermore, whether gamma alterations are specific to schizophrenia,[205] are general across psychosis, or are present across a range of diverse pathologies,[227] must be established. Although seemingly contradictory results have been published, (e.g., [173,228]), the most recent study -consisting of a large sample of schizophrenia and bipolar patients and their relatives - showed that gamma abnormalities are a feature of psychosis, regardless of diagnosis, and are heritable.[171]

LTP-Analog Paradigm

In the long list of neurobiological mechanisms that contribute to endophenotypes in schizophrenia, NMDA-receptor hypofunction and disrupted glutamatergic signaling are increasingly highlighted as key targets.[229-233] A relatively new EEG paradigm may extend our understanding of NMDAR-mediated signaling and, more specifically, its importance in learning and memory. Long-term potentiation (LTP) refers to the process whereby the

efficacy of communication between neurons can be rapidly increased, and is the principal candidate mechanism underlying learning and memory formation.[234] NMDARs play a central role in LTP (and in plasticity more generally) at glutamatergic synapses.[235] LTP can be induced in a number of ways, but most conveniently by delivering a tetanus (stimulus presentedat a high rate of frequency, typically 100 Hz or more). Changes in presynaptic and postsynaptic responses can then be measured in a variety of ways, but historically has been accomplished using electrodes surgically implanted in the hippocampus. Decades of animal research have helped us understand some of the complex interactions that modulate LTP at NMDAR sites: for example, metabotropic glutamate receptor agonists can reverse the effects of NMDAR antagonists,[236] D1 agonists and D2 antagonists increase NMDAR-dependent LTP,[237] and cholinergic mechanisms modulate NMDA-dependent LTP and LTD in the visual cortex.[238] Until recently, inquiry of the functional significance of LTP has been hindered by the absence of a human model. There is now evidence that the rapid repetitive presentation of a photic tetanus leads to persistent enhancement of an early visual evoked potential in humans, the N1b.[239] This paradigm has recently been used to show impaired cortical plasticity in patients with schizophrenia relative to healthy controls.[240] The paradigm consists of two types of stimulus presentation: at baseline, participants view a checkerboard flashing at a rate slightly below 1 Hz, then during the photic tetanus period ("high frequency stimulation"), the checkerboard flashes at a rate of almost 9 Hz.[240] The slower rate is then presented again in several post-high frequency stimulation blocks.[240] Initial studies show enhanced negativity for the C1 and N1b components that appears in blocks after the presentation of the high frequency stimulation.[239,241] Enhanced negativity has been shown to be significant for healthy controls but not individuals with schizophrenia, and in individuals with schizophrenia is the enhanced negativity is associated with improved reaction time to oddball targets.[240] Given the aforementioned relationships between brain plasticity, glutamate, NMDA-receptor functioning and schizophrenia, future studies using this paradigm may have broad implications for predicting the onset of schizophrenia and understanding and possibly improving positive symptoms and cognitive deficits in schizophrenia.

Promise of Electrophysiologic Traits as Genetically Tractable Endophenotypes

A recent series of studies published by Iacono and colleagues from the Minnesota Center for Twin and Family Research (MCTFR) attempted to uncover the genetics involved in 17 psychophysiological endophenotypes using a wide range of genetic approaches: biometric heritability analyses, molecular- genetic heritability analyses, GWAS, candidate gene studies, rare variant analyses of nonsynonymous SNPs in the exome, and analyses using variants identified through whole-genome sequencing.[242] The endophenotypes studied by the MCTFR group are broadly implicated in psychopathology (i.e., substance use disorders, mood disorders, and schizophrenia).[242] While these studies represent unprecedented work in terms of effort, sample size and cutting-edge statistical methods, they did not reveal specific genetic effects on endophenotypes: a 153-cell summary table of the statistically significant effects of SNP- and gene-based tests for all 17 endophenotypes investigated was mostly (89%) empty.[243] If endophenotypes are indeed genetically less complex than psychiatric

disorders, why are we still having so much difficulty finding genes that are implicated in psychopathology? One possibility is that electrophysiology is not optimal for measuring endophenotypes. However, as discussed in Munafó & Flint's response to the MCTFR studies, the effect sizes found are consistent with findings from GWAS of other potential endophenotypes, including brain structural variation and cognitive performance.[244] Thus, power to detect genome-wide significant effects may have been limited due to sample size: as pointed out in another response, the sample size of the MCTFR studies is actually small compared to other disorder-based studies (∼4,200 vs. ∼149,000).[9,245] Additionally, because the studies relied on a community sample, the data may be too centrally distributed and lacking in extreme values at the tails to garner much power.[246] Iacono and colleagues replied they had ample power to detect small effects (d = .014) and that, statistically speaking, at least 20% of their sample were affected by disorders like depression and substance abuse, but admittedly more “extreme” pathology like schizophrenia or autism were not represented.[243]

It is also possible that the assumption that endophenotypes are genetically less complex than other traits is wrong.[247] While other disorders have had success linking electrophysiological endophenotypes to susceptibility genes (see COGA study[248-250]), the field of schizophrenia research has not enjoyed consistent success. As discussed in Flint and colleagues' review, the premise that endophenotypes are genetically less complex than other traits assumes that the endophenotype is part of the causal pathway from genetic variant to disease and inflicts the naïve notion that “biology causes psychology”.[247,251] Focusing only on the effect size of endophenotypes may lead to: 1) ignoring potentially important information from an endophenotype because it is genetically “too complex”, or 2) increasing statistical efficiency at the cost of meaningfully translated outcomes.[247] If we assume that endophenotypes are no more genetically tractable than other complex traits, then the results from the MCTFR studies are in fact expected, and instead can be used to ask new questions. One important consequence of studies such as MCTFR is the realization of the need for larger datasets and data sharing, such as the development of RDoC's “information commons” based on the National Database for Autism Research (ndar.nih.gov). In order to achieve the desired sample sizes, it is essential that researchers share experimental protocols and paradigms. If we accept that we are working with small effect sizes, we must focus on gaining power wherever we can, and this should begin with reducing measurement error. Shared data inherently has larger measurement error than data collected within a single lab due to logistical differences that are difficult to reconcile (e.g., EEG system type, number of channels collected, monitor type and size, room size and lighting). While there are recommendations for many EEG measurements, uniform protocols and paradigms would drastically improve variation in measurement and, therefore, improve power when combining datasets. Another method involves developing a single, multivariate psychophysiological endophenotype that combines several indices into one summary score. The rationale for doing so is that the combination of features may provide extra group differentiation, making the positive predictive power substantially higher.[252] This has been done using MMN, P50 suppression, P300 auditory oddball, and antisaccadic error rate; the resulting multivariate endophenotype was shown to be more closely related to diagnosis than to any individual feature.[253] Similarly, the Consortium on the Genetics of

Schizophrenia (COGS) study combined results from three neurophysiological measures (P50 gating, PPI and AS) along with 12 neurocognitive tasks using factor analysis to yield 5 distinct factors.[254] These 5 factors were then evaluated for heritability and differences across probands, siblings and healthy controls. A similar concept was proposed for structural neuranatomic traits and termed "extended endophenotype", created by combining brain morphometric measures in individuals with schizophrenia.[255] Techniques such as these can help identify the utility of individual measures while improving statistical power by both increasing the reliability of individual measures (removing measurement error) and limiting the number of statistical comparisons. An alternative approach is to break down endophenotypes into even more distinct measurements, thereby providing "endophenotypes for endophenotypes".[50] For example, one can break the P300 down into its separate components, which may prove to be genetically more tractable.[191] Both methods are viable approaches for increasing the signal to noise ratio in these endophenotypes.

Another take-away from the lack of significant genetic findings could be the need to expand genetic studies beyond individuals of European ancestry, which may improve the likelihood of finding rare variants of at least moderate effect size.[242,243] Future studies should also augment GWA studies with studies that link structural genomics with functional genomics (e.g, gene expression or eQTL studies) and epigenetic effects, e.g. DNA methylation. While currently such studies are inherently more difficult, such effects are likely to be an extremely important source of variance in human health and behavior. For example, the psychoneuroimmunology field has recently focused on a pattern of up-regulated proinflammatory immune response gene activity and down-regulated antiviral immune response gene activity called a "conserved transcriptional response to adversity" (CTRA), which can be activated by social adversity.[256] Defining and characterizing these shifts in gene expression has helped explain chemical, cellular, and behavioral changes, some of which last for years.[256] Identifying such changes in the brain and their effects on neurophysiology and clinical phenomena could be a crucial next step in our understanding of schizophrenia.

Conclusion

Research on the etiology, course, and treatment of schizophrenia is complicated by the diversity of clinical presentation and risk factors. Objectively measureable endophenotypes are therefore needed in order to causally link genetic liability to clinical symptoms and clinical disorder.[50] Electrophysiological endophenotypes may be particularly useful, as most of them have been studied extensively in both human and animal models and are relatively inexpensive and therefore able to be used in large studies. We reviewed some of the most researched and most promising electrophysiological endophenotypes for schizophrenia: P50, antisaccade, MMN, P300, and gamma power and phase measures. With the exception of gamma measures, which are relatively recently-studied phenomena in schizophrenia, these measures show evidence that they are disrupted both in patients with schizophrenia and their clinically unaffected first degree relatives, heritable, and have genetic associations (see Table 1). Other than P300, which appears to be driven by dopaminergic and noradrenergic signaling pathways,[165] each of these putative endophenotypes has demonstrated evidence for a role in glutamate signaling and/or NMDA-receptor dependent signaling. Several lines

of evidence converge to suggest a prominent role of glutamatergic and NMDA-receptor dependent signaling in schizophrenia, including: cellular processes, which show changes in dendrite growth with LTP;[235] pharmacologic induction of psychotic symptoms,[257] reduced MMN[258] and impaired sensory gating[76] with NMDA antagonists; and GWA studies that have found candidate genes for schizophrenia involved in glutamatergic and NMDAR-dependent signaling.[9,48,118,259] Continued investigations into the mechanisms that link these genetic and biological alterations to deficits in endophenotypes may be a promising next step for schizophrenia research.[260] While the present review did not specifically address the clinical utility of these endophenotypes, this is also an important avenue for future research. The ability to use endophenotypes in a clinical context may improve efforts to take into account individual variability in the prevention and treatment of disorders, in line with the National Institute of Health's initiative, “precision medicine” (http://www.nih.gov/precisionmedicine/). However efforts to use endophenotypes as diagnostic tools may be muddled by evidence that endophenotypes lack specificity to particular neuropsychiatric disorders (see Introduction). For schizophrenia in particular, variability in treatment makes it considerably more difficult to understand changes in endophenotypes over time. Usefulness of endophenotypes in a clinical context may be improved by more research on the longitudinal course of these endophenotypes prior to disease onset, i.e., in genetically high risk or prodromal populations. Lastly, while these endophenotypes may not be genetically less complex than psychiatric disorders, a substantial amount of variance in each has been shown to be due to genetic factors, making them important trans-diagnostic tools.[243] By improving our measurement of endophenotypes and advancing our genetic association studies with the techniques described above, we can look forward to continued improvement in our understanding of the genetic, biological and psychological mechanisms in schizophrenia.

References

1. Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. Nat Rev Genet. 2012; 13(8):537–51. [PubMed: 22777127]
2. Stefansson H, Ophoff RA, Steinberg S, et al. Common variants conferring risk of schizophrenia. Nature. 2009; 460(7256):744–7. [PubMed: 19571808]
3. Yue W-H, Wang H-F, Sun L-D, et al. Genome-wide association study identifies a susceptibility locus for schizophrenia in Han Chinese at 11p11. 2 Nat Genet. 2011; 43(12):1228–31. [PubMed: 22037552]
4. Consortium TSPG-WASG. Genome-wide association study identifies five new schizophrenia loci. Nat Genet. 2011; 43(10):969–76. [PubMed: 21926974]
5. Purcell SM, Wray NR, et al. International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009; 460(7256):748–52. [PubMed: 19571811]
6. Shi J, Potash JB, Knowles JA, et al. Genome-wide association study of recurrent early-onset major depressive disorder. Mol Psychiatry. 2011; 16(2):193–201. [PubMed: 20125088]
7. Rietschel M, Mattheisen M, Degenhardt F, et al. Association between genetic variation in a region on chromosome 11 and schizophrenia in large samples from Europe. Mol Psychiatry. 2012; 17(9): 906–17. [PubMed: 21747397]
8. O'Donovan MC, Norton N, Williams H, et al. Analysis of 10 independent samples provides evidence for association between schizophrenia and a SNP flanking fibroblast growth factor receptor 2. Mol Psychiatry. 2009; 14(1):30–6. [PubMed: 18813210]

9. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014; 511(7510):421–7. [PubMed: 25056061]
10. So HC, Gui AHS, Cherny SS, Sham PC. Evaluating the heritability explained by known susceptibility variants: a survey of ten complex diseases. Genetic Epidemiology. 2011; 35(5):310–7. [PubMed: 21374718]
11. Ji W, Foo JN, O'Roak BJ, et al. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. Nat Genet. 2008; 40(5):592–9. [PubMed: 18391953]
12. Li B, Leal SM. Methods for detecting associations with rare variants for common diseases: application to analysis of sequence data. The American Journal of Human Genetics. 2008
13. La Vega De FM, Bustamante CD, Leal SM. Genome-Wide Association Mapping and Rare Alleles: From Population Genomics to Personalized Medicine. Pac Symp Biocomput. 2011:74–5. [PubMed: 21121034]
14. Cirulli ET, Goldstein DB. Uncovering the roles of rare variants in common disease through whole-genome sequencing. Nat Rev Genet. 2010; 11(6):415–25. [PubMed: 20479773]
15. Gibson G. Rare and common variants: twenty arguments. Nat Rev Genet. 2011; 13(2):135–45. [PubMed: 22251874]
16. McClellan J, King M-C. Genetic Heterogeneity in Human Disease. Cell. 2010; 141(2):210–7. [PubMed: 20403315]
17. Gorlov IP, Gorlova OY, Sunyaev SR, Spitz MR, Amos CI. Shifting Paradigm of Association Studies: Value of Rare Single-Nucleotide Polymorphisms. The American Journal of Human Genetics. 2008; 82(1):100–12. [PubMed: 18179889]
18. Blangero J. Localization and identification of human quantitative trait loci: King Harvest has surely come. Current Opinion in Genetics & Development. 2004; 14(3):233–40. [PubMed: 15172664]
19. Lee SH, DeCandia TR, Ripke S, et al. Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs. Nat Genet. 2012; 44(3):247–50. [PubMed: 22344220]
20. Marth GT, Yu F, Indap AR, et al. The functional spectrum of low-frequency coding variation. Genome Biology. 2011; 12(9):R84. [PubMed: 21917140]
21. Purcell SM, Moran JL, Fromer M, et al. A polygenic burden of rare disruptive mutations in schizophrenia. Nature. 2014; 506(7487):185–90. [PubMed: 24463508]
22. Fromer M, Pocklington AJ, Kavanagh DH, et al. De novo mutations in schizophrenia implicate synaptic networks. Nature. 2014; 506(7487):179–84. [PubMed: 24463507]
23. Kirov G, Pocklington AJ, Holmans P, et al. De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia. Mol Psychiatry. 2012; 17(2):142–53. [PubMed: 22083728]
24. Walsh T, McClellan JM, McCarthy SE, et al. Rare Structural Variants Disrupt Multiple Genes in Neurodevelopmental Pathways in Schizophrenia. Science. 2008; 320(5875):539–43. [PubMed: 18369103]
25. Glahn DC, Knowles E, McKay DR. Arguments for the sake of endophenotypes: Examining common misconceptions about the use of endophenotypes in psychiatric genetics - Glahn - 2014 - American Journal of Medical Genetics Part B: Neuropsychiatric Genetics - Wiley Online Library. Am J Med Genet. 2014
26. Light GA, Swerdlow NR, Rissling AJ, et al. Characterization of neurophysiologic and neurocognitive biomarkers for use in genomic and clinical outcome studies of schizophrenia. PLoS ONE. 2012; 7(7):e39434. [PubMed: 22802938]
27. Braff DL, Light GA, Swerdlow NR. Prepulse inhibition and P50 suppression are both deficient but not correlated in schizophrenia patients. Biological Psychiatry. 2007; 61(10):1204–7. [PubMed: 17161386]
28. Rosen AM, Spellman T, Gordon JA. Electrophysiological Endophenotypes in Rodent Models of Schizophrenia and Psychosis. Biological Psychiatry. 2015:1–9.
29. Bickel S, Javitt DC. Neurophysiological and neurochemical animal models of schizophrenia: Focus on glutamate. Behavioural Brain Research. 2009; 204(2):352–62. [PubMed: 19433116]
30. Kellendonk C, Simpson EH, Kandel ER. Modeling cognitive endophenotypes of schizophrenia in mice. Trends Neurosci. 2009; 32(6):347–58. [PubMed: 19409625]

31. Amann LC, Gandal MJ, Halene TB, et al. Mouse behavioral endophenotypes for schizophrenia. Brain Res Bull. 2010; 83(3-4):147–61. [PubMed: 20433908]
32. John B, Lewis KR. Chromosome Variability and Geographic Distribution in Insects. Science. 1966; 152(3723):711–21. [PubMed: 17797432]
33. Gershon ES, Goldin LR. Clinical methods in psychiatric genetics: I. Robustness of genetic marker investigative strategies. Acta Psychiatr Scand. 1986; 74(2):113–8. [PubMed: 3465198]
34. Leboyer M, Leboyer M, Leboyer M, et al. Psychiatric genetics: search for phenotypes. Trends Neurosci. 1998; 21(3):102–5. [PubMed: 9530915]
35. Lenox RH, Gould TD, Manji HK. Endophenotypes in bipolar disorder. American Journal of Medical Genetics. 2002; 114(4):391–406. [PubMed: 11992561]
36. Gottesman II, Gould TD. The Endophenotype Concept in Psychiatry: Etymology and Strategic Intentions. American Journal of Psychiatry. 2003; 160(4):636–45. [PubMed: 12668349]
37. Puppala S, Dodd GD, Fowler S, et al. A genomewide search finds major susceptibility loci for gallbladder disease on chromosome 1 in Mexican Americans. American Journal of Psychiatry. 2006; 78(3):377–92.
38. Bearden CE, Freimer NB. Endophenotypes for psychiatric disorders: ready for primetime? Trends Genet. 2006; 22(6):306–13. [PubMed: 16697071]
39. Glahn DC, Curran JE, Winkler AM, et al. High dimensional endophenotype ranking in the search for major depression risk genes. Biological Psychiatry. 2012; 71(1):6–14. [PubMed: 21982424]
40. Almasy L, Blangero J. Endophenotypes as quantitative risk factors for psychiatric disease: rationale and study design. American Journal of Medical Genetics. 2001; 105(1):42–4. [PubMed: 11424994]
41. Glahn DC, Almasy L, Barguil M, et al. Neurocognitive Endophenotypes for Bipolar Disorder Identified in Multiplex Multigenerational Families. Arch Gen Psychiatry. 2010; 67(2):168–77. [PubMed: 20124116]
42. Light GA, Swerdlow NR, Thomas ML, et al. Validation of mismatch negativity and P3a for use in multi-site studies of schizophrenia: Characterization of demographic, clinical, cognitive, and functional correlates in COGS-2. Schizophrenia Research. 2014
43. Craddock N, O'Donovan MC, Owen MJ. Psychosis Genetics: Modeling the Relationship Between Schizophrenia, Bipolar Disorder, and Mixed (or “Schizoaffective”) Psychoses. Schizophrenia Bulletin. 2009:sbp020.
44. Purcell SM, Wray NR, Stone JL, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009; 460(7256):748–52. [PubMed: 19571811]
45. Lichtenstein P, Yip BH, Björk C, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. The Lancet. 2009; 373(9659):234–9.
46. Lee SH, Ripke S, et al. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet. 2013; 45(9):984–94. [PubMed: 23933821]
47. Niedermeyer, E.; da Silva, FL. Electroencephalography: Basic Principles, Clinical Applications, and Related Fields. Lippincot Williams & Wilkins; 2004.
48. Greenwood TA, Lazzeroni LC, Murray SS, et al. Analysis of 94 candidate genes and 12 endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia. Am J Psychiatry. 2011; 168(9):930–46. [PubMed: 21498463]
49. Turetsky BI, Calkins ME, Light GA, Olincy A, Radant AD, Swerdlow NR. Neurophysiological Endophenotypes of Schizophrenia: The Viability of Selected Candidate Measures. Schizophrenia Bulletin. 2007; 33(1):69–94. [PubMed: 17135482]
50. Miller GA, Rockstroh B. Endophenotypes in Psychopathology Research: Where Do We Stand? Annu Rev Clin Psychol. 2013; 9(1):177–213. [PubMed: 23297790]
51. Powell SB, Zhou X, Geyer MA. Prepulse inhibition and genetic mouse models of schizophrenia. Behavioural Brain Research. 2009; 204(2):282–94. [PubMed: 19397931]
52. Bramon E, Croft RJ, McDonald C, et al. Mismatch negativity in schizophrenia: a family study. Schizophrenia Research. 2004; 67(1):1–10. [PubMed: 14741319]

53. Heinrichs RW. Meta-analysis and the science of schizophrenia: variant evidence or evidence of variants? Neurosci Biobehav Rev. 2004; 28(4):379–94. [PubMed: 15341034]
54. Cannon TD, Keller MC. Endophenotypes in the Genetic Analyses of Mental Disorders. Annu Rev Clin Psychol. 2006; 2(1):267–90. [PubMed: 17716071]
55. Venables PH. Input dysfunction in schizophrenia. Progress in experimental personality research. 1963
56. Adler CM, Malhotra AK, Elman I, Goldberg T, Egan M. Comparison of ketamine-induced thought disorder in healthy volunteers and thought disorder in schizophrenia. American Journal of Psychiatry. 2014; 156(10):1646–9. [PubMed: 10518181]
57. Brockhaus-Dumke A, Schultze-Lutter F, Mueller R, et al. Sensory Gating in Schizophrenia: P50 and N100 Gating in Antipsychotic-Free Subjects at Risk, First-Episode, and Chronic Patients. Biological Psychiatry. 2008; 64(5):376–84. [PubMed: 18395700]
58. Fuerst DR, Gallinat J, Boutros NN. Range of sensory gating values and test-retest reliability in normal subjects. Psychophysiology. 2007; 44(4):620–6. [PubMed: 17437554]
59. Smith DA, Boutors NN, Schwarzopf SB. Reliability of P50 auditory event-related potential indices of sensory gating. Psychophysiology. 1994; 31(5):495–502. [PubMed: 7972604]
60. Hall M-H, Schulze K, Rijsdijk F, et al. Heritability and reliability of P300, P50 and duration mismatch negativity. Behav Genet. 2006; 36(6):845–57. [PubMed: 16826459]
61. Adler LE, Hoffer L, Nagamoto HT, Waldo MC, Kisley MA, Giffith JM. Yohimbine impairs P50 auditory sensory gating in normal subjects. Neuropsychopharmacology. 1994; 10(4):249–57. [PubMed: 7945735]
62. Moxon KA, Gerhardt GA, Adler LE. Dopaminergic modulation of the P50 auditory-evoked potential in a computer model of the CA3 region of the hippocampus: its relationship to sensory gating in schizophrenia. Biol Cybern. 2003; 88(4):265–75. [PubMed: 12690485]
63. Petrovsky N, Quednow BB, Ettinger U, et al. Sensorimotor gating is associated with CHRNA3 polymorphisms in schizophrenia and healthy volunteers. Neuropsychopharmacology. 2010; 35(7): 1429–39. [PubMed: 20393456]
64. la Salle de S, Smith D, Choueiry J, et al. Effects of COMT genotype on sensory gating and its modulation by nicotine: Differences in low and high P50 suppressors. Neuroscience. 2013; 241:147–56. [PubMed: 23535252]
65. Leonard S, Gault J, Hopkins J, et al. Association of promoter variants in the alpha7 nicotinic acetylcholine receptor subunit gene with an inhibitory deficit found in schizophrenia. Arch Gen Psychiatry. 2002; 59(12):1085–96. [PubMed: 12470124]
66. Freedman R, Olincy A, Ross RG, et al. The genetics of sensory gating deficits in schizophrenia. Curr Psychiatry Rep. 2003; 5(2):155–61. [PubMed: 12685995]
67. Adler LE, Olincy A, Waldo M, et al. Schizophrenia, sensory gating, and nicotinic receptors. Schizophrenia Bulletin. 1998; 24(2):189–202. [PubMed: 9613620]
68. Williams TJ, Nuechterlein KH, Subotnik KL, Yee CM. Distinct neural generators of sensory gating in schizophrenia. Psychophysiology. 2011; 48(4):470–8. [PubMed: 20735757]
69. Hall M-H, Chen C-Y, Cohen BM, et al. Genomewide association analyses of electrophysiological endophenotypes for schizophrenia and psychotic bipolar disorders: A preliminary report. Am J Med Genet B Neuropsychiatr Genet. 2015; 168(3):151–61. [PubMed: 25740047]
70. Freedman R, Coon H, Myles-Worsley M, et al. Linkage of a Neurophysiological Deficit in Schizophrenia to a Chromosome 15 Locus. Proc Natl Acad Sci USA. 1997; 94(2):587–92. [PubMed: 9012828]
71. Quednow BB, Brinkmeyer J, Mobascher A, et al. Schizophrenia risk polymorphisms in the TCF4 gene interact with smoking in the modulation of auditory sensory gating. Proc Natl Acad Sci USA. 2012; 109(16):6271–6. [PubMed: 22451930]
72. Tunbridge EM, Harrison PJ, Weinberger DR. Catechol-o-Methyltransferase, Cognition, and Psychosis: Val158Met and Beyond. Biological Psychiatry. 2006; 60(2):141–51. [PubMed: 16476412]
73. Weickert TW, Goldberg TE, Mishara A, et al. Catechol-O-methyltransferase val108/158met genotype predicts working memory response to antipsychotic medications. Biological Psychiatry. 2004; 56(9):677–82. [PubMed: 15522252]

74. Liu X, Hong X, Chan RCK, et al. Association study of polymorphisms in the alpha 7 nicotinic acetylcholine receptor subunit and catechol-o-methyl transferase genes with sensory gating in first-episode schizophrenia. Psychiatry Research. 2013

75. Lu BY, Martin KE, Edgar JC, et al. Effect of Catechol O-Methyltransferase Val158Met Polymorphism on the P50 Gating Endophenotype in Schizophrenia. Biological Psychiatry. 2007; 62(7):822–5. [PubMed: 17448448]

76. Bickel S, Lipp H-P, Umbricht D. Early auditory sensory processing deficits in mouse mutants with reduced NMDA receptor function. Neuropsychopharmacology. 2008; 33(7):1680–9. [PubMed: 17712349]

77. Hallett PE. Primary and secondary saccades to goals defined by instructions. Vision Research. 1978; 18(10):1279–96. [PubMed: 726270]

78. Munoz DP, Everling S. Look away: the anti-saccade task and the voluntary control of eye movement. Nat Rev Neurosci. 2004; 5(3):218–28. [PubMed: 14976521]

79. Matthews A, Flohr H, Everling S. Cortical activation associated with midtrial change of instruction in a saccade task. Exp Brain Res. 2002; 143(4):488–98. [PubMed: 11914795]

80. Pierrot-Deseilligny C, Rosa A, Masmoudi K, Rivaud S, Gaymard B. Saccade deficits after a unilateral lesion affecting the superior colliculus. J Neurol Neurosurg Psychiatr. 1991; 54(12): 1106–9. [PubMed: 1783927]

81. Everling S, Fischer B. The antisaccade: a review of basic research and clinical studies. Neuropsychologia. 1998; 36(9):885–99. [PubMed: 9740362]

82. Hutton SB, Ettinger U. The antisaccade task as a research tool in psychopathology: a critical review. Psychophysiology. 2006; 43(3):302–13. [PubMed: 16805870]

83. McDowell JE, Myles-Worsley M, Coon H, Byerley W, Clementz BA. Measuring liability for schizophrenia using optimized antisaccade stimulus parameters. Psychophysiology. 1999; 36(1): 138–41. [PubMed: 10098389]

84. Fukumoto-Motoshita M, Matsuura M, Ohkubo T, et al. Hyperfrontality in patients with schizophrenia during saccade and antisaccade tasks: a study with fMRI. Psychiatry Clin Neurosci. 2009; 63(2):209–17. [PubMed: 19335390]

85. Manoach DS, Thakkar KN, Cain MS, et al. Neural Activity Is Modulated by Trial History: A Functional Magnetic Resonance Imaging Study of the Effects of a Previous Antisaccade. J Neurosci. 2007; 27(7):1791–8. [PubMed: 17301186]

86. Richards JE. Cortical sources of event-related potentials in the prosaccade and antisaccade task. Psychophysiology. 2003; 40:878–94. [PubMed: 14986841]

87. Ettinger U, Ffytche DH, Kumari V, et al. Decomposing the neural correlates of antisaccade eye movements using event-related FMRI. Cereb Cortex. 2008; 18(5):1148–59. [PubMed: 17728263]

88. Ettinger U, Kumari V, Crawford TJ, Davis RE, Sharma T, Corr PJ. Reliability of smooth pursuit, fixation, and saccadic eye movements. Psychophysiology. 2003; 40(4):620–8. [PubMed: 14570169]

89. Dyckman KA, McDowell JE. Behavioral plasticity of antisaccade performance following daily practice. Exp Brain Res. 2005; 162(1):63–9. [PubMed: 15551081]

90. Klein C, Foerster F. Development of prosaccade and antisaccade task performance in participants aged 6 to 26 years. Psychophysiology. 2001; 38(02):179–89. [PubMed: 11347863]

91. Crawford TJ, Haeger B, Kennard C, Reveley MA, Henderson L. Saccadic abnormalities in psychotic patients. I. Neuroleptic-free psychotic patients. Psychol Med. 1995; 25(03):461–71. [PubMed: 7480427]

92. Hutton SB, Huddy V, Barnes TRE, et al. The relationship between antisaccades, smooth pursuit, and executive dysfunction in first-episode schizophrenia. Biological Psychiatry. 2004; 56(8):553–9. [PubMed: 15476684]

93. Calkins ME, Iacono WG, Curtis CE. Smooth pursuit and antisaccade performance evidence trait stability in schizophrenia patients and their relatives. Int J Psychophysiol. 2003; 49(2):139–46. [PubMed: 12919716]

94. Levy DL, O'Driscoll G, Matthysse S, Cook SR, Holzman PS, Mendell NR. Antisaccade performance in biological relatives of schizophrenia patients: a meta-analysis. Schizophrenia Research. 2004; 71(1):113–25. [PubMed: 15374579]

95. Brownstein J, Krastoshevsky O, McCollum C, et al. Antisaccade performance is abnormal in schizophrenia patients but not in their biological relatives. Schizophrenia Research. 2003; 63(1-2): 13–25. [PubMed: 12892854]
96. Ettinger U, Picchioni M, Hall M-H, et al. Antisaccade Performance in Monozygotic Twins Discordant for Schizophrenia: The Maudsley Twin Study. American Journal of Psychiatry. 2006; 163(3):543–5. [PubMed: 16513882]
97. Becker W, Hoehne O, Iwase K, Kornhuber HH. Readiness potential, pre-motor positivity and other changes of cortical potential in saccadic eye movements. Vision Research. 1972
98. Brickett PA, Weinberg H, Davis CM. Cerebral Potentials Preceding Visually Triggered Saccades. Annals of the New York Academy of Sciences. 1984; 425(1):429–33. [PubMed: 6588861]
99. Evdokimidis I, Liakopoulos D, Constantinidis TS, Papageorgiou C. Cortical potentials with antisaccades. Electroencephalogr Clin Neurophysiol. 1996; 98(5):377–84. [PubMed: 8647040]
100. Everling S, Krappmann P, Flohr H. Cortical potentials preceding pro- and antisaccades in man. Electroencephalogr Clin Neurophysiol. 1997; 102(4):356–62. [PubMed: 9146498]
101. Richards JE. Cortical sources of ERP in prosaccade and antisaccade eye movements using realistic source models. Frontiers in Systems Neuroscience. 2013; 7:27. [PubMed: 23847476]
102. Kang SS, Dionisio DP, Sponheim SR. Abnormal mechanisms of antisaccade generation in schizophrenia patients and unaffected biological relatives of schizophrenia patients. Psychophysiology. 2011; 48(3):350–61. [PubMed: 20636287]
103. Brunia CH, van Boxtel GJ. Wait and see. Int J Psychophysiol. 2001; 43(1):59–75. [PubMed: 11742685]
104. Franke C, Reuter B, Schulz L, Kathmann N. Schizophrenia patients show impaired response switching in saccade tasks. Biological Psychology. 2007; 76(1-2):91–9. [PubMed: 17698280]
105. Reuter B, Jäger M, Bottlender R, Kathmann N. Impaired action control in schizophrenia: the role of volitional saccade initiation. Neuropsychologia. 2007; 45(8):1840–8. [PubMed: 17258779]
106. McCallum WC, Walter WG. The differential effects of distraction on the contingent negative variation in normal subjects and psychiatric patients. Electroencephalogr Clin Neurophysiol. 1968; 24(6):593–3. [PubMed: 4172745]
107. McCallum WC, Grey Walter W. The effects of attention and distraction on the contingent negative variation in normal and neurotic subjects. Electroencephalogr Clin Neurophysiol. 1968; 25(4):319–29. [PubMed: 4176536]
108. Klein C, Heinks T, Andresen B, Berg P, Moritz S. Impaired modulation of the saccadic contingent negative variation preceding antisaccades in schizophrenia. Biological Psychiatry. 2000; 47(11):978–90. [PubMed: 10838066]
109. Reuter B, Herzog E, Endrass T, Kathmann N. Brain potentials indicate poor preparation for action in schizophrenia. Psychophysiology. 2006; 43(6):604–11. [PubMed: 17076817]
110. Kirenskaya AV, Kamenskov MY, Myamlin VV, Novototsky-Vlasov VY, Tkachenko AA. The antisaccade task performance deficit and specific CNV abnormalities in patients with stereotyped paraphilia and schizophrenia. J Forensic Sci. 2013; 58(5):1219–26. [PubMed: 23899379]
111. Heimberg DR, Naber G, Hemmeter U, et al. Contingent Negative Variation and Attention in Schizophrenic and Depressed Patients. Neuropsychobiology. 1999; 39(3):131–40. [PubMed: 10087457]
112. Mayer K, Wyckoff SN, Strehl U. One size fits all? Slow cortical potentials neurofeedback: a review. J Atten Disord. 2013; 17(5):393–409. [PubMed: 23264371]
113. Minshew NJ, Luna B, Sweeney JA. Oculomotor evidence for neocortical systems but not cerebellar dysfunction in autism. Neurology. 1999; 52(5):917–22. [PubMed: 10102406]
114. Feifel D, Farber RH, Clementz BA, Perry W, Anllo-Vento L. Inhibitory deficits in ocular motor behavior in adults with attention-deficit/hyperactivity disorder. Biological Psychiatry. 2004; 56(5):333–9. [PubMed: 15336515]
115. Tien AY, Ross DE, Pearlson G, Strauss ME. Eye movements and psychopathology in schizophrenia and bipolar disorder. The Journal of Nervous and Mental Disease. 1996; 184(6): 331–8. [PubMed: 8642381]

116. Malone SM, Iacono WG. Error rate on the antisaccade task: heritability and developmental change in performance among preadolescent and late-adolescent female twin youth. Psychophysiology. 2002; 39(5):664–73. [PubMed: 12236334]

117. Greenwood TA, Braff DL, Light GA, et al. Initial heritability analyses of endophenotypic measures for schizophrenia: the consortium on the genetics of schizophrenia. Arch Gen Psychiatry. 2007; 64(11):1242–50. [PubMed: 17984393]

118. Vaidyanathan U, Malone SM, Donnelly JM, et al. Heritability and molecular genetic basis of antisaccade eye tracking error rate: A genome-wide association study. Psychophysiology. 2014; 51(12):1272–84. [PubMed: 25387707]

119. Kattoulas E, Stefanis NC, Avramopoulos D, Stefanis CN, Evdokimidis I, Smyrnis N. Schizophrenia-related RGS4 gene variations specifically disrupt prefrontal control of saccadic eye movements. Psychol Med. 2012; 42(4):757–67. [PubMed: 21910931]

120. Haraldsson HM, Ettinger U, Magnusdottir BB, et al. Catechol-O-Methyltransferase Val158Met Polymorphism and Antisaccade Eye Movements in Schizophrenia. Schizophrenia Bulletin. 2010; 36(1):157–64. [PubMed: 18562342]

121. Javitt DC, Steinschneider M, Schroeder CE, Arezzo JC. Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. Proc Natl Acad Sci USA. 1996; 93(21):11962–7. [PubMed: 8876245]

122. Baldeweg T, Klugman A, Gruzelier JH, Hirsch SR. Impairment in frontal but not temporal components of mismatch negativity in schizophrenia. Int J Psychophysiol. 2002; 43(2):111–22. [PubMed: 11809515]

123. Umbricht D, Krljes S. Mismatch negativity in schizophrenia: a meta-analysis. Schizophrenia Research. 2005; 76(1):1–23. [PubMed: 15927795]

124. Erickson MA, Ruffle A, Gold JM. A Meta-Analysis of Mismatch Negativity in Schizophrenia_ From Clinical Risk to Disease Specificity and Progression. Biological Psychiatry. 2015:1–8.

125. Naatanen R, Paavilainen P, Alho K, Reinikainen K, Sams M. Do event-related potentials reveal the mechanism of the auditory sensory memory in the human brain? Neurosci Lett. 1989; 98(2): 217–21. [PubMed: 2710416]

126. Kujala T, Kallio J, Tervaniemi M, Naatanen R. The mismatch negativity as an index of temporal processing in audition. Clin Neurophysiol. 2001; 112(9):1712–9. [PubMed: 11514254]

127. Light GA, Braff DL. Mismatch negativity deficits are associated with poor functioning in schizophrenia patients. Arch Gen Psychiatry. 2005; 62(2):127–36. [PubMed: 15699289]

128. Kawakubo Y, Kamio S, Nose T, et al. Phonetic mismatch negativity predicts social skills acquisition in schizophrenia. Psychiatry Research. 2007; 152(2-3):261–5. [PubMed: 17521744]

129. Wynn JK, Green MF, Sprock J, et al. Effects of olanzapine, risperidone and haloperidol on prepulse inhibition in schizophrenia patients: a double-blind, randomized controlled trial. Schizophrenia Research. 2007; 95(1-3):134–42. [PubMed: 17662577]

130. Todd J, Harms L, Schall U, Michie PT. Mismatch negativity: translating the potential. Front Psychiatry. 2013; 4:171. [PubMed: 24391602]

131. Jahshan C, Cadenhead KS, Rissling AJ, Kirihara K, Braff DL, Light GA. Automatic sensory information processing abnormalities across the illness course of schizophrenia. Psychol Med. 2012; 42(1):85–97. [PubMed: 21740622]

132. Atkinson RJ, Michie PT, Schall U. Duration mismatch negativity and P3a in first-episode psychosis and individuals at ultra-high risk of psychosis. Biological Psychiatry. 2012; 71(2):98–104. [PubMed: 22000060]

133. Nagai T, Tada M, Kirihara K, et al. Auditory mismatch negativity and P3a in response to duration and frequency changes in the early stages of psychosis. Schizophrenia Research. 2013; 150(2-3): 547–54. [PubMed: 24012461]

134. Perez VB, Woods SW, Roach BJ, et al. Automatic auditory processing deficits in schizophrenia and clinical high-risk patients: forecasting psychosis risk with mismatch negativity. Biological Psychiatry. 2014; 75(6):459–69. [PubMed: 24050720]

135. Bodatsch M, Ruhrmann S, Wagner M, et al. Prediction of Psychosis by Mismatch Negativity. Biological Psychiatry. 2011; 69(10):959–66. [PubMed: 21167475]

136. Light GA, Naatanen R. Mismatch negativity is a breakthrough biomarker for understanding and treating psychotic disorders. Proceedings of the National Academy of Sciences. 2013; 110(38): 15175–6.

137. Michie PT, Innes-Brown H, Todd J, Jablensky AV. Duration mismatch negativity in biological relatives of patients with schizophrenia spectrum disorders. Biological Psychiatry. 2002; 52(7): 749–58. [PubMed: 12372666]

138. Şevik AE, Anıl Yağcıoğlu AE, Yağcıoğlu S, Karahan S, Gürses N, Yıldız M. Neuropsychological performance and auditory event related potentials in schizophrenia patients and their siblings: a family study. Schizophrenia Research. 2011; 130(1-3):195–202. [PubMed: 21592733]

139. Brockhaus-Dumke A, Tendolkar I, Pukrop R, Schultze-Lutter F, Klosterkötter J, Ruhrmann S. Impaired mismatch negativity generation in prodromal subjects and patients with schizophrenia. Schizophrenia Research. 2005; 73(2-3):297–310. [PubMed: 15653275]

140. Jessen F, Fries T, Kucharski C, et al. Amplitude reduction of the mismatch negativity in first-degree relatives of patients with schizophrenia. Neurosci Lett. 2001; 309(3):185–8. [PubMed: 11514072]

141. Salisbury DF, Shenton ME, Griggs CB, Bonner-Jackson A, McCarley RW. Mismatch negativity in chronic schizophrenia and first-episode schizophrenia. Arch Gen Psychiatry. 2002; 59(8):686–94. [PubMed: 12150644]

142. Umbricht DSG, Bates JA, Lieberman JA, Kane JM, Javitt DC. Electrophysiological indices of automatic and controlled auditory information processing in first-episode, recent-onset and chronic schizophrenia. Biological Psychiatry. 2006; 59(8):762–72. [PubMed: 16497277]

143. Salisbury DF, Kuroki N, Kasai K, Shenton ME, McCarley RW. Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. Arch Gen Psychiatry. 2007; 64(5):521–9. [PubMed: 17485604]

144. Naatanen R, Kujala T, Escera C, et al. The mismatch negativity (MMN) – A unique window to disturbed central auditory processing in ageing and different clinical conditions. Clinical Neurophysiology. 2012; 123(3):424–58. [PubMed: 22169062]

145. Catts SV, Shelley AM, Ward PB, et al. Brain potential evidence for an auditory sensory memory deficit in schizophrenia. Am J Psychiatry. 1995; 152(2):213–9. [PubMed: 7840354]

146. Umbricht D, Koller R, Schmid L, et al. How specific are deficits in mismatch negativity generation to schizophrenia? Biological Psychiatry. 2003; 53(12):1120–31. [PubMed: 12814863]

147. Oades RD, Dittmann-Balcar A, Zerbin D, Grzella I. Impaired attention-dependent augmentation of MMN in nonparanoid vs paranoid schizophrenic patients: a comparison with obsessive-compulsive disorder and healthy subjects. Biological Psychiatry. 1997; 41(12):1196–210. [PubMed: 9171910]

148. Umbricht D, Schmid L, Koller R, Vollenweider FX, Hell D, Javitt DC. Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. Arch Gen Psychiatry. 2000; 57(12):1139–47. [PubMed: 11115327]

149. Gil-da-Costa R, Stoner GR, Fung R, Albright TD. Nonhuman primate model of schizophrenia using a noninvasive EEG method. Proceedings of the National Academy of Sciences. 2013; 110(38):15425–30.

150. Baker KD, Skuse DH. Adolescents and young adults with 22q11 deletion syndrome: psychopathology in an at-risk group. Br J Psychiatry. 2005; 186:115–20. [PubMed: 15684233]

151. Cheour M, Haapanen ML, Hukki J, et al. The first neurophysiological evidence for cognitive brain dysfunctions in children with CATCH. Neuroreport. 1997; 8(7):1785–7. [PubMed: 9189933]

152. Courchesne E, Hillyard SA, Galambos R. Stimulus novelty, task relevance and the visual evoked potential in man. Electroencephalogr Clin Neurophysiol. 1975; 39(2):131–43. [PubMed: 50210]

153. Donchin E. Presidential address, 1980. Surprise!…Surprise? Psychophysiology. 1981; 18(5):493–513. [PubMed: 7280146]

154. Verleger R. The true P3 is hard to see: Some comments on Kok's (1986) paper on degraded stimuli. Biological Psychology. 1988; 27(1):45–50. [PubMed: 3251559]

155. Vogel EK, Luck SJ. Delayed working memory consolidation during the attentional blink. Psychonomic Bulletin & Review. 2002; 9(4):739–43. [PubMed: 12613677]

156. Soltani M, Knight RT. Neural Origins of the P300. CRN. 2000; 14(3-4):26.

157. Naatanen R, Alho K. Generators of electrical and magnetic mismatch responses in humans. Brain Topography. 1995; 7(4):315–20. [PubMed: 7577329]

158. Pfefferbaum A, Wenegrat BG, Ford JM, Roth WT, Kopell BS. Clinical application of the P3 component of event-related potentials. II. Dementia, depression and schizophrenia. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section. 1984; 59(2): 104–24.

159. Salisbury DF, Shenton ME, Sherwood AR, et al. First-episode schizophrenic psychosis differs from first-episode affective psychosis and controls in P300 amplitude over left temporal lobe. Arch Gen Psychiatry. 1998; 55(2):173–80. [PubMed: 9477932]

160. Hirayasu Y, Asato N, Ohta H, Hokama H, Arakaki H, Ogura C. Abnormalities of auditory event-related potentials in schizophrenia prior to treatment. Biological Psychiatry. 1998; 43(4):244–53. [PubMed: 9513733]

161. Turetsky BI, Colbath EA, Gur RE. P300 subcomponent abnormalities in schizophrenia: I. Physiological evidence for gender and subtype specific differences in regional pathology. Biological Psychiatry. 1998; 43(2):84–96. [PubMed: 9474441]

162. Jeon Y-W, Polich J. Meta-analysis of P300 and schizophrenia: patients, paradigms, and practical implications. Psychophysiology. 2003; 40(5):684–701. [PubMed: 14696723]

163. Eichele T, Specht K, Moosmann M, et al. Assessing the spatiotemporal evolution of neuronal activation with single-trial event-related potentials and functional MRI. Proc Natl Acad Sci USA. 2005; 102(49):17798–803. [PubMed: 16314575]

164. Linden DEJ. The P300: Where in the Brain Is It Produced and What Does It Tell Us? Neuroscientist. 2005; 11(6):563–76. [PubMed: 16282597]

165. Polich J. Updating P300: An integrative theory of P3a and P3b. Clinical Neurophysiology. 2007; 118(10):2128–48. [PubMed: 17573239]

166. Squires NK, Squires KC, Hillyard SA. Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroencephalogr Clin Neurophysiol. 1975; 38(4):387–401. [PubMed: 46819]

167. Mathalon DH, Ford JM, Pfefferbaum A. Trait and state aspects of p300 amplitude reduction in schizophrenia: a retrospective longitudinal study. Biological Psychiatry. 2000

168. Bramon E. Meta-analysis of the P300 and P50 waveforms in schizophrenia. Schizophrenia Research. 2004; 70(2-3):315–29. [PubMed: 15329307]

169. Ethridge LE, Soilleux M, Nakonezny PA, et al. Behavioral response inhibition in psychotic disorders: Diagnostic specificity, familiality and relation to generalized cognitive deficit. Schizophrenia Research. 2014; 159(2-3):491–8. [PubMed: 25261042]

170. Perlman G, Foti D, Jackson F, Kotov R, Constantino E, Hajcak G. Clinical significance of auditory target P300 subcomponents in psychosis: Differential diagnosis, symptom profiles, and course. Schizophrenia Research. 2015; 165(2-3):145–51. [PubMed: 25934167]

171. Ethridge LE, Hamm JP, Pearlson GD, et al. Event-related potential and time-frequency endophenotypes for schizophrenia and psychotic bipolar disorder. Biological Psychiatry. 2015; 77(2):127–36. [PubMed: 24923619]

172. van Beijsterveldt CEM, van Baal GCM. Twin and family studies of the human electroencephalogram: a review and a meta-analysis. Biological Psychology. 2002; 61(1-2):111–38. [PubMed: 12385672]

173. Ethridge LE, Hamm JP, Shapiro JR, et al. Neural Activations During Auditory Oddball Processing Discriminating Schizophrenia and Psychotic Bipolar Disorder. Biological Psychiatry. 2012; 72(9):766–74. [PubMed: 22572033]

174. Bestelmeyer PEG, Phillips LH, Crombie C, Benson P, St Clair D. The P300 as a possible endophenotype for schizophrenia and bipolar disorder: Evidence from twin and patient studies. Psychiatry Research. 2009; 169(3):212–9. [PubMed: 19748132]

175. Polich J, Ladish C, Bloom FE. P300 assessment of early Alzheimer's disease. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section. 1990; 77(3): 179–89.

176. Hesselbrock V, Begleiter H, Porjesz B, O'Connor S, Bauer L. P300 Event-Related Potential Amplitude as an Endophenotype of Alcoholism – Evidence from the Collaborative Study on the Genetics of Alcoholism. Journal of Biomedical Science. 2001; 8(1):77–82. [PubMed: 11173979]

177. Carlson SR, Iacono WG, McGue M. P300 amplitude in nonalcoholic adolescent twin pairs who become discordant for alcoholism as adults. Psychophysiology. 2004; 41(6):841–4. [PubMed: 15563337]

178. Iacono WG, Carlson SR, Malone SM, McGue M. P3 Event-Related Potential Amplitude and the Risk for Disinhibitory Disorders in Adolescent Boys. Arch Gen Psychiatry. 2002; 59(8):750–7. [PubMed: 12150652]

179. Gangadhar BN, Ancy J, Janakiranaiah N, Umapathy C. P300 amplitude in non-bipolar, melancholic depression. Journal of Affective Disorders. 1993; 28(1):57–60. [PubMed: 8326081]

180. Salisbury DF, Shenton ME, McCarley RW. P300 topography differs in schizophrenia and manic psychosis. Biological Psychiatry. 1999; 45(1):98–106. [PubMed: 9894581]

181. O'Connor S, Morzorati S, Christian JC, Li TK. Heritable features of the auditory oddball event-related potential: peaks, latencies, morphology and topography. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section. 1994; 92(2):115–25.

182. Frangou S, Sharma T, Alarcon G, et al. The Maudsley Family Study, II: Endogenous event-related potentials in familial schizophrenia. Schizophrenia Research. 1997; 23(1):45–53. [PubMed: 9050127]

183. Bramon E, McDonald C, Croft RJ, et al. Is the P300 wave an endophenotype for schizophrenia? A meta-analysis and a family study. Neuroimage. 2005; 27(4):960–8. [PubMed: 16009570]

184. Turetsky BI, Cannon TD, Gur RE. P300 subcomponent abnormalities in schizophrenia: III. Deficits In unaffected siblings of schizophrenic probands. Biological Psychiatry. 2000; 47(5): 380–90. [PubMed: 10704950]

185. Kimble M, Lyons M, O'Donnell B, Nestor P, Niznikiewicz M, Toomey R. The effect of family status and schizotypy on electrophysiologic measures of attention and semantic processing. Biological Psychiatry. 2000; 47(5):402–12. [PubMed: 10704952]

186. Malone SM, Vaidyanathan U, Basu S, Miller MB, McGue M, Iacono WG. Heritability and molecular-genetic basis of the P3 event-related brain potential: a genome-wide association study. Psychophysiology. 2014; 51(12):1246–58. [PubMed: 25387705]

187. Del Re EC, Bergen SE, Mesholam-Gately RI, et al. Analysis of schizophrenia-related genes and electrophysiological measures reveals ZNF804A association with amplitude of P300b elicited by novel sounds. Transl Psychiatry. 2014; 4:e346. [PubMed: 24424392]

188. O'Donoghue T, Morris DW, Fahey C, et al. Effects of ZNF804A on auditory P300 response in schizophrenia. Transl Psychiatry. 2014; 4(1):e345. [PubMed: 24424391]

189. Hall MH, Levy DL, Salisbury DF. Neurophysiologic effect of GWAS derived schizophrenia and bipolar risk variants. Am J Med Genet. 2014

190. Blackwood DH, Fordyce A, Walker MT, St Clair DM, Porteous DJ, Muir WJ. Schizophrenia and affective disorders--cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: clinical and P300 findings in a family. American Journal of Psychiatry. 2001; 69(2):428–33.

191. Ford JM. Decomposing P300 to identify its genetic basis. Psychophysiology. 2014; 51(12):1325–6. [PubMed: 25387713]

192. Newton-Cheh C, Hirschhorn JN. Genetic association studies of complex traits: design and analysis issues. Mutat Res. 2005; 573(1-2):54–69. [PubMed: 15829237]

193. Malone SM, Burwell SJ, Vaidyanathan U, Miller MB, McGue M, Iacono WG. Heritability and molecular-genetic basis of resting EEG activity: a genome-wide association study. Psychophysiology. 2014; 51(12):1225–45. [PubMed: 25387704]

194. Gonzalez-Burgos G, Cho RY, Lewis DA. Alterations in Cortical Network Oscillations and Parvalbumin Neurons in Schizophrenia. Biological Psychiatry. 2015; 77(12):1031–40. [PubMed: 25863358]

195. Mathalon DH, Sohal VS. Neural Oscillations and Synchrony in Brain Dysfunction and Neuropsychiatric Disorders: It's About Time. JAMA Psychiatry. 2015; 72(8):840–4. [PubMed: 26039190]

196. Buzsáki G, Schomburg EW. What does gamma coherence tell us about inter-regional neural communication? Nat Neurosci. 2015; 18(4):484–9. [PubMed: 25706474]

197. Cardin JA, Carlén M, Meletis K, et al. Driving fast-spiking cells induces gamma rhythm and controls sensory responses. Nature. 2009; 459(7247):663–7. [PubMed: 19396156]

198. Gulyás AI, Szabó GG, Ulbert I, et al. Parvalbumin-containing fast-spiking basket cells generate the field potential oscillations induced by cholinergic receptor activation in the hippocampus. Journal of Neuroscience. 2010; 30(45):15134–45. [PubMed: 21068319]

199. Ford JM, Krystal JH, Mathalon DH. Neural Synchrony in Schizophrenia: From Networks to New Treatments. Schizophrenia Bulletin. 2007

200. Sohal VS, Zhang F, Yizhar O, Deisseroth K. Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. Nature. 2009; 459(7247):698–702. [PubMed: 19396159]

201. Ray S, Maunsell JHR. Do gamma oscillations play a role in cerebral cortex? Trends in Cognitive Sciences. 2015; 19(2):78–85. [PubMed: 25555444]

202. Bastos AM, Vezoli J, Fries P. Communication through coherence with inter-areal delays. Current Opinion in Neurobiology. 2015; 31:173–80. [PubMed: 25460074]

203. Fries P, Nikolić D, Singer W. The gamma cycle. Trends Neurosci. 2007; 30(7):309–16. [PubMed: 17555828]

204. Engel AK, Fries P, Singer W. Dynamic predictions: Oscillations and synchrony in top–down processing. Nat Rev Neurosci. 2001; 2(10):704–16. [PubMed: 11584308]

205. Gandal MJ, Edgar JC, Klook K, Siegel SJ. Gamma synchrony: towards a translational biomarker for the treatment-resistant symptoms of schizophrenia. Neuropharmacology. 2012; 62(3):1504–18. [PubMed: 21349276]

206. Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. Nat Rev Neurosci. 2010; 11(2):100–13. [PubMed: 20087360]

207. Kwon JS, O'Donnell BF, Wallenstein GV, et al. Gamma frequency-range abnormalities to auditory stimulation in schizophrenia. Arch Gen Psychiatry. 1999; 56(11):1001–5. [PubMed: 10565499]

208. Light GA, Hsu JL, Hsieh MH, et al. Gamma Band Oscillations Reveal Neural Network Cortical Coherence Dysfunction in Schizophrenia Patients. Biological Psychiatry. 2006; 60(11):1231–40. [PubMed: 16893524]

209. Vierling-Claassen D, Siekmeier P, Stufflebeam S, Kopell N. Modeling GABA alterations in schizophrenia: a link between impaired inhibition and altered gamma and beta range auditory entrainment. J Neurophysiol. 2008; 99(5):2656–71. [PubMed: 18287555]

210. Symond MB, Harris AWF, Gordon E, Williams LM. “Gamma Synchrony” in First-Episode Schizophrenia: A Disorder of Temporal Connectivity? American Journal of Psychiatry. 2005

211. Krishnan GP, Hetrick WP, Brenner CA, Shekhar A, Steffen AN, O'Donnell BF. Steady state and induced auditory gamma deficits in schizophrenia. Neuroimage. 2009; 47(4):1711–9. [PubMed: 19371786]

212. Gallinat J, Winterer G, Herrmann CS, Senkowski D. Reduced oscillatory gamma-band responses in unmedicated schizophrenic patients indicate impaired frontal network processing. Clin Neurophysiol. 2004; 115(8):1863–74. [PubMed: 15261865]

213. Perez VB, Roach BJ, Woods SW, et al. Early auditory gamma-band responses in patients at clinical high risk for schizophrenia. Supplements to Clinical neurophysiology. 2013; 62:147–62. [PubMed: 24053038]

214. Tada M, Nagai T, Kirihara K, et al. Differential Alterations of Auditory Gamma Oscillatory Responses Between Pre-onset High-risk Individuals and First-episode Schizophrenia. Cereb Cortex. 2014:bhu278.

215. Venables NC, Bernat EM, Sponheim SR. Genetic and Disorder-Specific Aspects of Resting State EEG Abnormalities in Schizophrenia. Schizophrenia Bulletin. 2009; 35(4):826–39. [PubMed: 18381357]

216. Rutter L, Carver FW, Holroyd T, et al. Magnetoencephalographic gamma power reduction in patients with schizophrenia during resting condition. Hum Brain Mapp. 2009; 30(10):3254–64. [PubMed: 19288463]

217. Reinhart RMG, Mathalon DH, Roach BJ, Ford JM. Relationships between pre-stimulus gamma power and subsequent P300 and reaction time breakdown in schizophrenia. International Journal of Psychophysiology. 2011; 79(1):16–24. [PubMed: 20816708]

218. M Spencer K. Baseline gamma power during auditory steady-state stimulation in schizophrenia. Frontiers in Human Neuroscience. 2012; 5

219. Cho RY, Konecky RO, Carter CS. Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. Proc Natl Acad Sci USA. 2006; 103(52):19878–83. [PubMed: 17170134]

220. Minzenberg MJ, Firl AJ, Yoon JH, Gomes GC, Reinking C, Carter CS. Gamma oscillatory power is impaired during cognitive control independent of medication status in first-episode schizophrenia. Neuropsychopharmacology. 2010; 35(13):2590–9. [PubMed: 20827271]

221. Makeig S, Westerfield M, Jung TP, et al. Dynamic Brain Sources of Visual Evoked Responses. Science. 2002; 295(5555):690–4. [PubMed: 11809976]

222. Johannesen JK, Bodkins M, O'Donnell BF, Shekhar A, Hetrick WP. Perceptual anomalies in schizophrenia co-occur with selective impairments in the gamma frequency component of midlatency auditory ERPs. Journal of Abnormal Psychology. 2008; 117(1):106–18. [PubMed: 18266489]

223. Hong L, Summerfelt A, McMahon R, et al. Evoked gamma band synchronization and the liability for schizophrenia. Schizophrenia Research. 2004; 70(2-3):293–302. [PubMed: 15329305]

224. Leicht G, Karch S, Karamatskos E, et al. Alterations of the early auditory evoked gamma-band response in first-degree relatives of patients with schizophrenia: hints to a new intermediate phenotype. Journal of Psychiatric Research. 2011; 45(5):699–705. [PubMed: 21067772]

225. Hall M-H, Taylor G, Sham P, et al. The early auditory gamma-band response is heritable and a putative endophenotype of schizophrenia. Schizophrenia Bulletin. 2011; 37(4):778–87. [PubMed: 19946013]

226. Cho RY, Walker CP, Polizzotto NR, et al. Development of Sensory Gamma Oscillations and Cross-Frequency Coupling from Childhood to Early Adulthood. Cereb Cortex. 2015; 25(6): 1509–18. [PubMed: 24334917]

227. Hamm JP, Ethridge LE, Shapiro JR, et al. Spatiotemporal and frequency domain analysis of auditory paired stimuli processing in schizophrenia and bipolar disorder with psychosis. Psychophysiology. 2012; 49(4):522–30. [PubMed: 22176721]

228. Hall MH, Taylor G, Sham P, et al. The Early Auditory Gamma-Band Response Is Heritable and a Putative Endophenotype of Schizophrenia. Schizophrenia Bulletin. 2011; 37(4):778–87. [PubMed: 19946013]

229. Howes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: an update for the 21st century. Journal of Psychopharmacology. 2015; 29(2):97–115. [PubMed: 25586400]

230. Jadi MP, Margarita Behrens M, Sejnowski TJ. Abnormal Gamma Oscillations in N-Methyl-D-Aspartate Receptor Hypofunction Models of Schizophrenia. Biological Psychiatry. 2015

231. Cohen SM, Tsien RW, Goff DC, Halassa MM. The impact of NMDA receptor hypofunction on GABAergic neurons in the pathophysiology of schizophrenia. Schizophrenia Research. 2015; 167(1-3):98–107. [PubMed: 25583246]

232. Heckers S, Konradi C. GABAergic mechanisms of hippocampal hyperactivity in schizophrenia. Schizophrenia Research. 2015; 167(1-3):4–11. [PubMed: 25449711]

233. Iwata Y, Nakajima S, Suzuki T, et al. Effects of glutamate positive modulators on cognitive deficits in schizophrenia: a systematic review and meta-analysis of double-blind randomized controlled trials. Mol Psychiatry. 2015; 20(10):1151–60. [PubMed: 26077694]

234. Citri A, Malenka RC. Synaptic plasticity: multiple forms, functions, and mechanisms. Neuropsychopharmacology. 2008; 33(1):18–41. [PubMed: 17728696]

235. Stephan KE, Baldeweg T, Friston KJ. Synaptic plasticity and dysconnection in schizophrenia. Biological Psychiatry. 2006; 59(10):929–39. [PubMed: 16427028]

236. Moghaddam B. Bringing order to the glutamate chaos in schizophrenia. Neuron. 2003; 40(5): 881–4. [PubMed: 14659087]
237. Centonze D, Usiello A, Costa C, et al. Chronic haloperidol promotes corticostriatal long-term potentiation by targeting dopamine D2L receptors. Journal of Neuroscience. 2004; 24(38):8214–22. [PubMed: 15385604]
238. Kirkwood A, Rozas C, Kirkwood J, Perez F, Bear MF. Modulation of long-term synaptic depression in visual cortex by acetylcholine and norepinephrine. J Neurosci. 1999; 19(5):1599–609. [PubMed: 10024347]
239. Teyler TJ, Hamm JP, Clapp WC, Johnson BW, Corballis MC, Kirk IJ. Long-term potentiation of human visual evoked responses. European Journal of Neuroscience. 2005; 21(7):2045–50. [PubMed: 15869500]
240. Cavus I, Reinhart RMG, Roach BJ, et al. Impaired Visual Cortical Plasticity in Schizophrenia. Biological Psychiatry. 2012; 71(6):512–20. [PubMed: 22364738]
241. Kirk IJ, McNair NA, Hamm JP, et al. Long-term potentiation (LTP) of human sensory-evoked potentials. WIREs Cogni Sci. 2010; 1(5):766–73.
242. Iacono WG, Malone SM, Vaidyanathan U, Vrieze SI. Genome-wide scans of genetic variants for psychophysiological endophenotypes: A methodological overview. Psychophysiology. 2014; 51(12):1207–24. [PubMed: 25387703]
243. Iacono WG, Vaidyanathan U, Vrieze SI, Malone SM. Knowns and unknowns for psychophysiological endophenotypes: Integration and response to commentaries. Psychophysiology. 2014; 51(12):1339–47. [PubMed: 25387720]
244. Munafò MR, Flint J. The genetic architecture of psychophysiological phenotypes. Psychophysiology. 2014; 51(12):1331–2. [PubMed: 25387716]
245. Cuthbert BN. Translating intermediate phenotypes to psychopathology: The NIMH Research Domain Criteria. Psychophysiology. 2014; 51(12):1205–6. [PubMed: 25387702]
246. Braff DL. Genomic substrates of neurophysiological endophenotypes: Where we“ve been and where we”re going. Psychophysiology. 2014; 51(12):1323–4. [PubMed: 25387712]
247. Flint J, Timpson N, Munafò M. Assessing the utility of intermediate phenotypes for genetic mapping of psychiatric disease. Trends Neurosci. 2014; 37(12):733–41. [PubMed: 25216981]
248. Rice JP, Saccone SF. Alcoholism and related traits: a summary of Group 13 contributions. Genetic Epidemiology. 2005; 29(S1):S96–S102. [PubMed: 16342188]
249. Porjesz B, Begleiter H, Reich T, et al. Amplitude of Visual P3 Event-Related Potential as a Phenotypic Marker for a Predisposition to Alcoholism: Preliminary Results from the COGA Project. Alcoholism: Clinical and Experimental Research. 1998; 22(6):1317–23.
250. Dick DM, Jones K, Saccone N, et al. Endophenotypes Successfully Lead to Gene Identification: Results from the Collaborative Study on the Genetics of Alcoholism. Behav Genet. 2006; 36(1): 112–26. [PubMed: 16341909]
251. Miller GA. Mistreating Psychology in the Decades of the Brain. Perspectives on Psychological Science. 2010; 5(6):716–43. [PubMed: 21949539]
252. Iacono WG. Identifying psychophysiological risk for psychopathology: examples from substance abuse and schizophrenia research. Psychophysiology. 1998; 35(6):621–37. [PubMed: 9844425]
253. Price GW, Michie PT, Johnston J, et al. A Multivariate Electrophysiological Endophenotype, from a Unitary Cohort, Shows Greater Research Utility than Any Single Feature in the Western Australian Family Study of Schizophrenia. Biological Psychiatry. 2006; 60(1):1–10. [PubMed: 16368076]
254. Seidman LJ, Hellemann G, Nuechterlein KH, et al. Factor structure and heritability of endophenotypes in schizophrenia: Findings from the Consortium on the Genetics of Schizophrenia (COGS-1). Schizophrenia Research. 2015
255. Prasad KM, Keshavan MS. Structural Cerebral Variations as Useful Endophenotypes in Schizophrenia: Do They Help Construct “Extended Endophenotypes? Schizophrenia Bulletin. 2008; 34(4):774–90. [PubMed: 18408230]
256. Slavich GM, Cole SW. The Emerging Field of Human Social Genomics. Clinical Psychological Science. 2013; 1(3):331–48. [PubMed: 23853742]

257. Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry. 1994; 51(3):199–214. [PubMed: 8122957]

258. Javitt DC, Steinschneider M, Schroeder CE, Vaughan HG, Arezzo JC. Detection of stimulus deviance within primate primary auditory cortex: intracortical mechanisms of mismatch negativity (MMN) generation. Brain Res. 1994; 667(2):192–200. [PubMed: 7697356]

259. Ehrlichman RS, Luminais SN, White SL, et al. Neuregulin 1 transgenic mice display reduced mismatch negativity, contextual fear conditioning and social interactions. Brain Res. 2009; 1294:116–27. [PubMed: 19643092]

260. Coyle JT. The glutamatergic dysfunction hypothesis for schizophrenia. Harv Rev Psychiatry. 1996; 3(5):241–53. [PubMed: 9384954]

261. Shaikh M, Hall MH, Schulze K, et al. Do COMT, BDNF and NRG1 polymorphisms influence P50 sensory gating in psychosis? Psychol Med. 2010; 41(02):263–76. [PubMed: 20102668]

262. Radant AD, Dobie DJ, Calkins ME, et al. Successful multi-site measurement of antisaccade performance deficits in schizophrenia. Schizophrenia Research. 2007; 89(1-3):320–9. [PubMed: 17023145]

263. Naatanen R, Gaillard AW, Mäntysalo S. Early selective-attention effect on evoked potential reinterpreted. Acta Psychol (Amst). 1978; 42(4):313–29. [PubMed: 685709]

264. Lee KH, Williams LM, Haig A, Gordon E. “Gamma (40 Hz) phase synchronicity” and symptom dimensions in schizophrenia”. Cogn Neuropsychiatry. 2003; 8(1):57–71. [PubMed: 16571550]

Table 1

Summarized Evidence for Electrophysiological Endophenotypes for Schizophrenia

EEG/ERP measure	Dependent Variable	Neurocognitive Function	Effect size	Heritability (h^2)	Impairment in unaffected relatives	GWAS and linkage results	Candidate genes
P50	Ratio (S2/S1) or difference (S2-S1) score, measured using peak amplitude of each response	Auditory sensory gating or filtering mechanism[67]	d = 1.56[168]	0.10[117] - 0.68[60]	9.17% more impaired[261]	15q13-q14[70]SNP rs10149105 (*FLRT2*)[69]	*CHRNA7, COMT, FLRT2*[69]*GRIK4, GRID2, GRM3*[48]
AS	Proportion of incorrect (or correct) saccades over all trials	Assessment of ability to suppress reflexive responses using top-down inhibitory control[78]	d = 1.06[262]	0.42[117] - 0.57[116]	d = 0.43[93] - 0.61[94]	SNP rs13240504[118]	*GRM8*[118]*GRIK4, RELN, HTR2A*[48]
MMN	Peak or mean amplitude of difference waveform (deviant tone response - standard tone response)	Index of auditory sensory memory functioning; measure of stimulus feature analysis[263]	d = 1.0[123]	0.63 (mean amp)0.68 (peak amp)[60]	d = 0.81[140]	???	*NRG1*[259]
P300	Peak amplitude and latency	Updating and consolidation of perceptual information into mental representation[161]	d = 0.89 (amp)d = 0.59 (latency)[162]	0.65[186] – 0.69[4]	PSES = 0.61 (amp)PSES= 0.50 (latency)[183]	No individual SNPs[186]	*TCF4*[189]*MYEF2*[186]*DISC1*[190]
Gamma	Event-related gamma power and gamma phase-locking (>30Hz)	Associated with perceptual activity, including object detection and basic analysis[205]	d = 0.43 (G1 amp)d = 0.63 (G2 amp)[264]d = 0.80 (evoked gamma amp)[224]	0.65 (gamma power)0.63 (phase locking)[228]	d = 1.13[224]	???	???

AS = Antisaccade

MMN = Mismatch Negativity

Amp = amplitude

PSES = Pooled standardized effect size

SNP = single nucleotide polymorphism

G1 = gamma 1

G2 = gamma 2