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Cognitive Interventions Targeting Brain Plasticity in the Prodromal and Early Phases of Schizophrenia

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Keywords

clinical high risk, ultra high risk, recent-onset schizophrenia, cognitive therapy, cognitive training, neuroplasticity

Abstract

Several important paradigm shifts have occurred in the field of schizophrenia treatment, including an increased focus on early detection, the development of preemptive interventions, and the view of schizophrenia as a neurodevelopmental disease characterized by decreased efficiency and abnormal connectivity in cortical and subcortical neural networks. In this review, we briefly describe some of the neural impairments that contribute to the development of schizophrenia, with an emphasis on the impact of stress and trauma on cognitively vulnerable neural systems. We then present current data on two behavioral interventions that target these critical risk factors and that aim to preempt the onset of schizophrenia in vulnerable individuals or improve the clinical course in recent-onset schizophrenia: cognitive therapy and computerized cognitive training.

Contents

EARLY DETECTION AND INTERVENTION IN SCHIZOPHRENIA: THE CONCEPT OF THE CLINICAL HIGH-RISK POPULATION

Psychologists have been interested in intervening early in the course of schizophrenia for decades (Chapman et al. 1982), but they have only recently established early detection and intervention as a priority treatment target and as the basis for delivering highly specialized services across the globe. The aim of intervening early in the course of illness is to decrease the duration of untreated psychosis (DUP)—an approach that is associated with better outcomes (Norman et al. 2005)—and also to provide treatments during a time of maximum receptivity, which Birchwood et al. (1998) call the "critical period." Early intervention represents a major paradigm shift in the diagnosis and treatment of schizophrenia: from a stance of therapeutic nihilism with a focus on long-term disability, to an expectation that providing interventions at the earliest possible point will result in improved outcomes, including amelioration of symptoms and functional recovery.

A recent extension of this approach involves efforts to identify individuals prior to the onset of psychosis. The prodromal period preceding psychosis is a well-established concept (Yung & McGorry 1996a) consisting of nonspecific symptoms, including depression, anxiety, and sleep disturbance, as well as attenuated positive psychotic symptoms and brief intermittent fully psychotic symptoms (Yung & McGorry 1996b). Assessments and clinical symptom criteria have been developed to identify individuals during this period, but they do not predict development of full psychotic disorders with 100% accuracy. Therefore, rather than using the term prodromal, which

assumes definite transition to full psychosis, the term clinical high risk (CHR) is used to describe this syndrome (French & Morrison 2004). The term ultra high risk (UHR) is also often used to refer to this population. However, in order to clearly differentiate between those with clinically significant symptoms and those who may be at a genetic high risk for psychosis but who are not presenting with symptoms, we use the term clinical high risk, or CHR, in this review.

The drive to identify those at high risk of developing psychosis emanates from attempts to provide preemptive interventions to this population. Mrazek & Haggerty (1994, p. 154) stated that "the best hope now for schizophrenia lies with indicated preventive interventions targeted at individuals manifesting precursor signs and symptoms who have not yet met full criteria for diagnosis." These interventions aim to prevent or delay the transition to psychosis while treating concurrent problems such as depression, anxiety, and interpersonal difficulties. In addition, should conversion to psychosis occur, a secondary benefit of having provided intervention during the prodrome is that the individual is already engaged in treatment, thus reducing the DUP and providing a less traumatic, and by extension less disruptive, development of full-blown clinical symptoms (Yung & Nelson 2011).

In this review, we briefly describe some of the neural impairments that contribute to the development of schizophrenia, with an emphasis on the impact of stress and trauma on cognitively vulnerable neural systems. We then present current data on two behavioral interventions that aim to preempt the onset of schizophrenia in vulnerable individuals or improve the clinical course in recent-onset schizophrenia: cognitive therapy and cognitive training. We also describe the neuroscience-informed approach to cognitive training used in our laboratory and discuss other emerging interventions in the field.

NEURAL SYSTEM IMPAIRMENTS THAT CONTRIBUTE TO THE DEVELOPMENT OF SCHIZOPHRENIA

Schizophrenia is a highly heritable disorder, with various genes accounting for 80% to 85% of liability, yet concordance rates of monozygotic twins are around 50%, with the remaining variance attributed to environmental insults such as maternal infection during gestation, perinatal hypoxia, fetal malnutrition, and the like (Brown 2011). Genetic factors interact with environmental insults, many of them occurring during the pre- and perinatal period, with the result that at-risk individuals are vulnerable to a range of environmental stressors. This interaction of genes and environment leads to aberrations in brain development and neural network functioning, which are not typically evident until adolescence or very early adulthood, when brain maturation is nearing completion (Andreasen 2010, Hoffman & McGlashan 1997). At that point, usually as a response to environmental stressors, the individual (who may until then have had no observable symptoms or only mild nonspecific symptoms), experiences a break with reality and experiences psychosis—often initially in mild or attenuated form, which if left untreated then progresses into a full-blown psychotic episode. Understanding schizophrenia as a neurodevelopmental disorder characterized by decreased efficiency and abnormal connectivity in cortical and subcortical neural networks—rendering them particularly vulnerable to the deleterious effects of stress—sheds light on why interventions that help an individual to respond more adaptively to stressful stimuli, or that target abnormal neural system processing, may help to ameliorate the early course of illness (**Figure 1**).

In healthy neural development, the maximal proliferation of synapses and the peak of synaptic density occur at approximately two years of age, which is then followed by a steady drop in synaptic density during childhood followed by a steep decline in adolescence (Spear 2003). This process is referred to as synaptic pruning, which especially in prefrontal brain regions is essential for
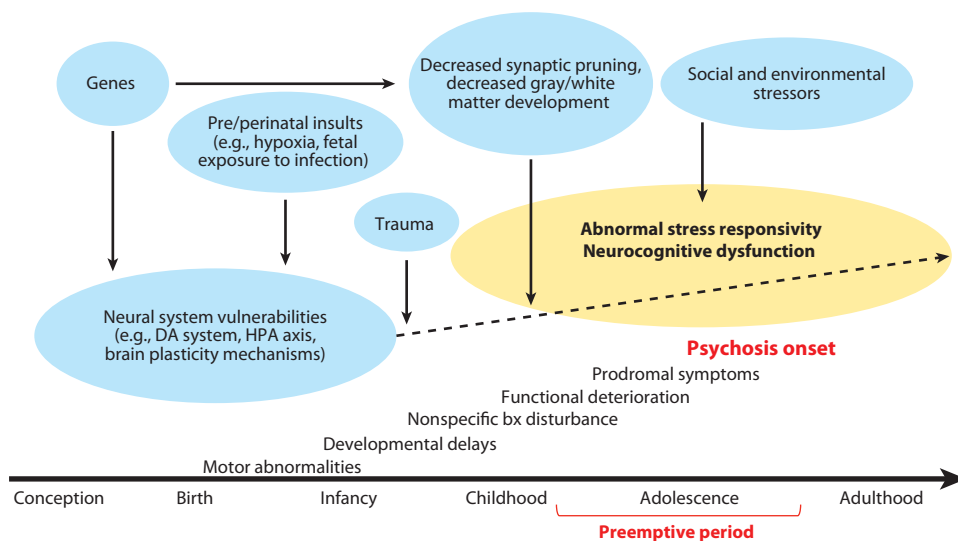
Figure 1

The neurodevelopmental model of schizophrenia, highlighting the preemptive period and intervention targets discussed in this review (adapted and modified by permission of Tyrone D. Cannon). Bx, behavioral; DA, dopamine; HPA, hypothalamic-pituitary-adrenal.

increased efficiency of neural processing (Spear 2003). The behavioral concomitants of synaptic pruning in the prefrontal cortex are an increased ability to solve abstract and complex problems and enhanced reasoning and planning capabilities (Spear 2003). Several studies suggest that an overly aggressive or abnormal synaptic pruning process may be a contributing factor to the onset of psychosis in adolescence (Andreasen et al. 2011, McGlashan & Hoffman 2000); for example, individuals with schizophrenia exhibit decreased dendritic spine density (Glantz & Lewis 2000) but intact number of neurons (Selemon et al. 1995). At present it is not known which specific gene products or molecular/cellular processes may be contributing to the development of abnormal synapse pruning and synaptic functioning in schizophrenia, but the net effect is a reduction in gray matter volume in key cortical and subcortical regions. For example, in a recent meta-analysis on CHR patients, those who later converted to psychosis showed baseline decreases in gray matter in frontal and temporal areas (Fusar-Poli et al. 2012). It is entirely plausible that a cascade of aberrant neural system functioning in schizophrenia, including reductions in neuronal integrity and synaptic density, could be the cumulative result of one or more abnormalities in basic plasticity mechanisms, with ongoing maladaptive changes being generated throughout distributed cortical neural networks (Balu & Coyle 2011).

Another critical process in neurodevelopment is increased white matter density. Starting in adolescence and leading into early adulthood, the hippocampus and frontal lobe undergo a substantial process of myelination, which is in a large part driven by experience-dependent plasticity mechanisms in the brain (or simply put, adaptive learning). Again, in schizophrenia, accumulating evidence suggests that this process is disrupted; the net result is that decreased white matter density impairs the fast and efficient integration of information processing both within and across cortical zones and contributes to cognitive impairment (Dwork et al. 2007). For example, diffusion tensor imaging studies show that CHR patients do not show the normal increase in white matter with age and that this is associated with poor functional outcome (Carletti et al. 2012, Karlsgodt et al. 2009).

In the largest longitudinal study to date investigating brain volume changes over time in a cohort of patients with schizophrenia, the results confirmed decreases in multiple gray and white matter regions, which were most pronounced two years after the first episode of psychosis (Andreasen et al. 2011). It is again highly likely that the reduced white matter development that characterizes schizophrenia is a reflection of the distributed effects of abnormal and inefficient information-processing mechanisms that arise from very basic impairments in the normal representational and plasticity functions of the cortex. Overall, the picture in early schizophrenia is one of a brain that has undergone aberrant patterns of neurodevelopment, with reduced functional connectivity among key neural systems and reduced efficiency in its cognitive and socio-affective operations. This suggests that, in order to prevent a deteriorating course, interventions must be designed to address and, if possible, "correct" the abnormal neural system functioning before the individual has undergone what might be irreversible maladaptive changes in his/her cortical representational systems.

THE IMPACT OF STRESS AND TRAUMA ON THE DEVELOPMENT OF SCHIZOPHRENIA

The stress-vulnerability hypothesis of schizophrenia posits that environmental stressors interact with the underlying neurocognitive vulnerabilities described above in at-risk individuals to trigger the onset of psychosis (Nuechterlein & Dawson 1984, Walker & Diforio 1997). A number of studies have shown an association between stressors and psychotic relapse in individuals with established illness, and there is growing evidence of a link between stress and attenuated psychosis during the prodromal phase. The primary mechanism proposed to underlie this relationship is dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, the main neural stress-response system in mammals. The HPA axis functions to regulate the response to stress through a cascade of hormones that proceeds through the HPA pathway. Cells in the periventricular nucleus of the hypothalamus secrete corticotropin-releasing hormone, which increases adrenocorticotropic hormone secretion by the pituitary gland, which stimulates the adrenal gland to release glucocorticoids (cortisol in humans), which then feed back via glucocorticoid receptors in the hippocampus to dampen the system once the stressor has passed.

A wealth of basic science evidence demonstrates the neurobiological consequences of stress that can mimic aspects of psychosis. Chronic stress and ongoing elevation of glucocorticoids in response to stress can cause stress "sensitization," resulting in a reduction in hippocampal neurons, reduction of glucocorticoid receptors in the hippocampus (Sapolsky 1985, Sapolsky et al. 1990, Stein-Behrens et al. 1994), and suppression of long-term potentiation (Pavlides et al. 1993), which impairs declarative memory consolidation. Chronic stress not only impairs hippocampal function but also enhances unlearned and conditioned fear through its effects on the amygdala, which persist even after recovery from stress (Conrad et al. 2004, Vyas et al. 2004). In animal models (Meaney et al. 1989), prolonged stress has been shown to result in a dysregulated negative feedback circuit, whereby damaged hippocampi fail to correctly modulate HPA axis activity (Sapolsky et al. 1990), and has also been shown to increase glutamate in both the prefrontal cortex (PFC) and the hippocampus, which can result in altered dopamine levels (Moghaddam 2002). Although the exact molecular mechanisms linking stress and psychosis are beyond the scope of this review, there is sufficient evidence to suggest that chronic stress and dysregulated stress responsivity impact the same neural systems implicated in psychosis (**Figure 2**).

Numerous studies have demonstrated a dysregulated stress response system in schizophrenia, primarily using cortisol assays to assess HPA axis integrity. Walder and colleagues (2000) reported that salivary cortisol levels were related to symptom severity in a sample of patients with schizophrenia, as well as performance on neuropsychological tasks within a combined sample of
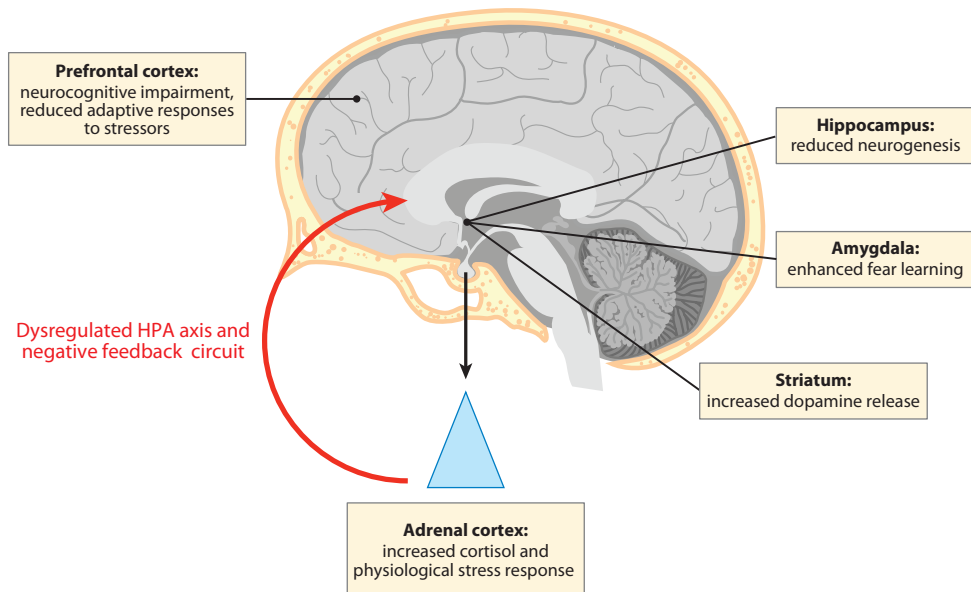
Figure 2

The impact of stress on neural circuits related to psychosis. HPA, hypothalamic-pituitary-adrenal.

patients with schizophrenia, affective disorder, or no history of psychiatric illness. Basal cortisol and adrenocorticotropic hormone levels are higher in recent-onset and chronic schizophrenia patients (medicated and nonmedicated) than in healthy controls (for a review, see Bradley & Dinan 2010). Both medicated and unmedicated schizophrenia patients show a heightened cortisol response to laboratory stressors (Jansen et al. 1998) and higher rates of nonsuppression in response to dexamethasone, which tests the reduction of natural cortisol secretion in response to negative biological feedback (Mück-Seler et al. 1999), although some inconsistencies have been observed (Braehler et al. 2005; Iqbal et al. 1991; Jansen et al. 1998, 2000). Although the exact nature of hypo- and hyperresponsiveness of the HPA axis in psychosis is unclear, schizophrenia patients undoubtedly show a dysregulated stress response.

A smaller but growing area of work suggests that stress responsivity and HPA axis functioning are also dysregulated during the prodromal phase of schizophrenia, relate to symptom levels, and are associated with the transition to full psychosis (for two recent reviews in this area, see Aiello et al. 2012 and Holtzman et al. 2012). In a sample of adolescents with schizotypal personality disorder (SPD), a group with a high rate of transition to schizophrenia, baseline salivary cortisol levels were associated with severity of schizotypal symptoms at 12- and 24-month follow-up (Walker et al. 2001) as well as transition to full psychosis within the group (Walker & Bollini 2002). Corcoran and colleagues found an association between basal cortisol and clinician ratings of anxiety, suspiciousness, and impaired stress tolerance (Corcoran et al. 2012). In a third study, CHR youth showed elevated resting baseline cortisol levels relative to healthy controls (Yee et al. 2007). Following a laboratory social stress test, the magnitude of the patients' cortisol response was less than that in controls, but they did show a stress response of increased cortisol, with a delayed pattern of cortisol recovery compared to controls (Yee et al. 2007). In two early studies with very small sample sizes, three young people who developed full psychosis within the two-year follow-up period of the study had lower blood cortisol levels at baseline and higher cortisol levels

at the latter stages of a dexamethasone/corticotrophin-releasing hormone test, compared to nine nonconverters (Thompson et al. 2007a,b), but the reliability of these results has not been replicated in larger samples, suggesting that HPA axis overactivation is more common during the prodrome.

Structural magnetic resonance imaging (MRI) studies have revealed some evidence of differences in brain regions associated with the HPA axis in CHR patients that suggests hyperactivity during the prodromal phase. Two reports of increased pituitary volumes in CHR participants who later converted to full psychosis compared to those who did not convert are in line with this theory (Büschlen et al. 2011, Garner et al. 2005). Hippocampal volumes in CHR patients are typically larger than those of fully psychotic patients but smaller than those of healthy controls, with mixed evidence of size predicting transition to psychosis (Pantelis et al. 2009). Of note, impaired hippocampal function can be both a cause and a consequence of HPA axis overactivity, leaving the "chicken and egg" question of which comes first currently undetermined.

Interestingly, a growing literature has documented higher rates of childhood trauma in schizophrenia patients compared to controls, suggesting an environmental mechanism for increased stress responsivity in schizophrenia, although causality cannot be assumed (see Sideli et al. 2012 for a recent review and Matheson et al. 2012 for a meta-analysis). The relationship between early adversity and later psychiatric symptoms is not specific to psychosis and is well documented in depression and other disorders, but it may have some interaction with specific genes in producing different phenotypes in adulthood (Laucht et al. 2012) as well as interaction with other environmental risk factors for schizophrenia, such as early pre- or perinatal insults or later cannabis use (Pelayo-Terán et al. 2012).

More recently, investigators have begun examining the impact of everyday stress on full and attenuated psychosis. Fully psychotic patients who have experienced childhood trauma reported increased negative affect and psychotic symptoms in response to daily stress compared to psychotic patients without childhood trauma (Lardinois et al. 2011), and a genetic polymorphism has been found to mediate the relationship between daily stressors and momentary increases in psychotic symptoms (Collip et al. 2011). Adolescents with SPD, who also develop full psychosis at an elevated rate of 21% by 2.5 years, have reported a greater number of total independent and undesirable life events compared to healthy adolescents and report more distress in response to daily hassles (Tessner et al. 2011). Additionally, frequency of daily stressors predicted an increase in positive symptoms one year later. In another study, CHR youth had lower levels of stressful life events and similar levels of daily hassles in comparison with an age-matched healthy control group, but nonetheless reported being more distressed by events and using different coping strategies (Phillips et al. 2012). Most relevant, in comparison with healthy controls, CHR youth show a dopaminergic hyperresponse via positron emission tomography (PET) imaging after exposure to a laboratory stressor, similar to antipsychotic-naïve schizophrenia patients (Mizrahi et al. 2012). Finally, genetic variations on the *COMT* and *MTHFR* genes interact to predict reactivity to daily stressors in schizophrenia patients (Peerbooms et al. 2012). Altogether, these studies suggest that stress reactivity is heightened in adolescents with attenuated and full psychosis, triggering fluctuations of dopamine transmission and the severity (and possibly the onset) of psychotic symptoms, and may be influenced by both genetic vulnerabilities and environmental inputs.

Given that CHR patients have been found to report even higher stress levels than first-episode psychosis patients (Pruessner et al. 2011), reducing stress and improving coping in CHR youth are critical targets for the development of preemptive interventions for schizophrenia. New areas of research are starting to focus on the natural plasticity of the HPA axis during adolescent development, with the aim of developing interventions during the prodromal phase that promote resiliency to stress. Some examples include cognitive therapy approaches that help individuals to reappraise their interpretation of stressful stimuli in a more adaptive manner; behavioral

stress-reduction techniques that teach individuals to take an active role in reducing their exposure to stressors; family therapy to reduce stressful familial interactions and increase family support; and cognitive training exercises that aim to improve the accuracy and fidelity of the processing of cognitive and socio-affective stimuli and increase the brain's "cognitive resilience" to data in its environment.

SHIFTING THE VIEW OF SCHIZOPHRENIA FROM NEURODEGENERATION TO NEUROPLASTICITY AND RECOVERY

As suggested in the previous section, a shift has occurred in the field of schizophrenia treatment development. The nihilistic conceptualization of the illness as a neurodegenerative disease associated with progressive functional deterioration (a view that dominated clinical thinking for the past 50 years) has changed to a perspective that—with early detection and intervention—intact brain plasticity mechanisms can be harnessed in an adaptive manner to promote healthier neural system functioning, increased resiliency to stressors, symptom reduction, and functional recovery. Indeed, if applied early enough in the course of illness, it is possible to envision harnessing these mechanisms to support true preemption of the usual illness trajectory.

Neuroplasticity refers to the brain's capacity to change the molecular and structural features and systems that dictate its function (Cramer et al. 2011). The basic principles of brain plasticity have been extensively studied in animal experiments and clinically in the context of cortical recovery and remapping after injury or trauma, such as a stroke or amputation of a limb (Nudo et al. 1996, Ramachandran & Rogers-Ramachandran 2000). In the past decade, an increasing understanding of these principles has led to the development of cognitive training interventions aimed at exploiting the malleability of the cortex in order to drive behavioral improvements in neuropsychiatric disorders, with some of the most significant advances occurring in the field of schizophrenia (for a review, see Vinogradov et al. 2012). Previously, there was some skepticism about the ultimate possibility of neural system improvement or restoration of functioning in serious neuropsychiatric disorders such as schizophrenia, due in part to the fact that these illnesses are characterized by impairments in multiple distributed limbic, prefrontal, and frontostriatal neural circuits. Further, recent findings by Balu & Coyle (2011) indicate that schizophrenia risk genes such as those related to DISC-1, dysbindin, brain-derived neurotrophic factor, and the *N*-methyl-D-aspartate receptor are involved in regulating neuroplasticity; as described previously, it is possible that alterations in their expression and/or functioning may contribute to the abnormal patterns of synapse formation and cortical connectivity observed in schizophrenia. This would suggest that there may be some inherent limitations in the brain plasticity mechanisms of individuals with schizophrenia.

Despite these areas of skepticism, emerging data suggest that it is indeed possible to develop intensive computerized cognitive training methods that successfully harness the brain learning machinery in schizophrenia to generate widespread adaptive behavioral and neural responses (Dale et al. 2010; Eack et al. 2009, 2010a; Fisher et al. 2009; Subramaniam et al. 2012). These adaptive improvements are accompanied by evidence of plastic changes in distributed cortical representational systems that have been driven by the cognitive training intervention and increases in gray matter volume (Adcock et al. 2009, Eack et al. 2010b, Subramaniam et al. 2012). Although this research has focused on computerized cognitive training methods, we wish to emphasize that a large body of work examining psychological treatment methods in young early psychosis individuals (such as cognitive therapy and multifamily groups), although not explicitly focused on understanding how these methods make use of cortical neuroplasticity, demonstrate successful and enduring behavioral effects. These methods are also likely optimized when they make use of the greater malleability of cortical representational systems early in the course of the illness.

COGNITIVE THERAPY AS A PREEMPTIVE INTERVENTION IN CLINICAL HIGH-RISK SCHIZOPHRENIA

One of the most frequently studied individual behavioral interventions for schizophrenia, particularly in the United Kingdom, is cognitive therapy (CT). CT for psychosis addresses the relationship between thoughts, feelings, and behaviors, with a particular focus on assisting clients to examine, and ultimately alter, their interpretation of a situation. The main goal of this cognitive restructuring is distress reduction as a result of the client learning skills to interpret and assess stressful situations in a more adaptive, resilient, and helpful manner. Within this approach, skills are also taught to assist the client in recognizing and managing personal stressors, thus targeting an individual's stress responsivity.

Wykes et al. (2008) concluded from a meta-analysis of adults with schizophrenia that CT for psychosis has a beneficial effect on positive symptoms, negative symptoms, mood, and functioning. Moreover, recent evidence suggests that CT interventions in schizophrenia and in other disorders, such as depression and anxiety, result in functional neural network changes. For instance, Goldapple et al. (2004) used PET to examine regional changes in glucose metabolism and modulation of the limbic-cortical network in 17 unmedicated unipolar depressed outpatients who completed a 15- to 20-session course of CT relative to 13 paroxetine-treated responders. A full course of CT resulted in increased glucose metabolic changes in the hippocampus and dorsal cingulate and decreases in dorsal, ventral, and medial frontal cortex. In contrast, paroxetine responders demonstrated prefrontal increases and hippocampal and subgenual cingulate decreases. Although both groups experienced "clinical recovery," as indicated by Hamilton Depression Ratings, the CT group's recovery appeared to be facilitated through top-down frontal neural modulation of limbic and cortical regions. Goldapple and colleagues (2004) speculated that the directionality of the findings in the CT group suggests CT-induced increases in attention to appropriate emotional and environmental stimuli and a decrease in overprocessing of irrelevant information and ruminations. These findings suggest that successful CT can modulate maladaptive responses to anxiety-provoking stimuli, making it an ideal intervention for CHR populations.

Furmark and colleagues (2002) also conducted a PET study to examine region-specific functional changes in social phobia patients treated with eight sessions of CT or citalopram relative to a wait-list comparison group. Similar to the results of Goldapple et al. (2004), both treatments resulted in symptomatic remission, as well as attenuated neural activity, during a public speaking challenge in the amygdala and hippocampus and rhinal, parahippocampal, and periamygdaloid cortices. Only in the CT group, however, was decreased activation in the amygdaloid-hippocampal region predictive of one-year clinical outcome—indicating that enduring plastic changes in cortical representational systems may require behavioral interventions and may not occur from pharmacotherapy alone. Again, these data underscore the potential suitability of CT as a preemptive intervention in early schizophrenia.

Van der Gaag (2006) proposed that CT for psychosis would have the potential to modify or "rewire" neural circuitry in a manner similar to these anxiety and depression treatment trials. Van der Gaag suggested that CT trains an individual to reappraise and reinterpret potentially threatening stimuli, resulting in reduced emotional responsivity to the stimuli. And indeed, very recently, Kumari and colleagues (2011) demonstrated that CT for psychosis, delivered over an average of 16 sessions, led to significant clinical improvement and attenuation of activation in neural systems associated with threat perception. Specific functional regions included the inferior frontal gyrus, anterior insula, putamen, thalamus, and occipital areas. Interestingly, contrary to the investigators' hypothesis, CT did not induce a significant change in amygdale activation. This study was the first to show that CT was associated with a neurofunctional change, suggesting a

modification in the representation and/or appraisal of stressful environmental stimuli, consistent with the behavioral skills learned in CT. The average age of the participants in this study was 35, with an average length of psychosis of 10 years. As such, one would predict that if CT were administered to those at risk of developing psychosis—who are typically 10 to 20 years younger, with far less exposure to repeated episodes of psychotic symptoms and environmental insults—the neural effects of CT for psychosis would induce even more significant adaptive plasticity in neural representational systems and would prove to be preemptive.

To date, there exist only six randomized control trials of CT for the CHR population, and interpretation of results from these trials is hampered by their small sizes, the use of concomitant treatments, and attrition at follow-up. Two studies (Addington et al. 2011, Morrison et al. 2004) explored the effectiveness of CT delivered as a stand-alone treatment. McGorry et al. (2002) and Yung et al. (2011) both examined CT combined with an antipsychotic medication, although Yung and colleagues (2011) included a CT-plus-placebo group. Bechdolf et al. (2012) compared supportive counseling with a package of interventions they termed Integrated Psychological Intervention (IPI), which included CT along with multifamily psychoeducation, group social skills, and cognitive remediation. More recently, Morrison et al. (2012) reported a multisite randomized control trial of CT compared with monitoring alone; it is the largest randomized controlled trial to date exploring CT as an intervention to delay or prevent transition to psychosis. **Table 1** briefly summarizes these studies.

Despite early optimism that CT would be effective in preventing the onset of psychosis in at-risk individuals (McGorry et al. 2002, Morrison et al. 2004), initial promising results have not been maintained at follow-up and/or have not been replicated in later studies (Addington et al. 2011, Yung et al. 2011). As is common in longitudinal research, the follow-up studies suffered from attrition and small sample sizes, which may have compromised power to detect clinically significant differences between groups. Morrison et al. (2012) collaborated across five sites and recruited a total of 288 participants, but despite this larger sample size, the study failed to detect differences between the CT group and the control group (which only received monitoring of symptoms) in conversion to psychosis. The authors attributed this to the low rate of conversion across the two groups and to the possible benefit to participants in the control condition of receiving regular assessment and monitoring. This study also raised the issue of accurate detection of a truly "clinical high-risk" population.

In contrast, Bechdolf et al. (2012) demonstrated that their multimodal IPI package, studied in 63 participants, was effective in reducing conversion to psychosis in participants exhibiting early initial prodromal states (EIPS) when compared with supportive therapy ($N = 65$). These individuals were identified as experiencing self-reported changes in thought and perception, which are believed to precede the onset of subthreshold psychotic symptoms that define CHR; in earlier studies, 70% of those identified with the EIPS were found to convert to psychosis over five years (Klosterkötter et al. 2001). Bechdolf et al. (2012) suggest that individuals with EIPS experience less severe symptoms, lower disability, and fewer neurobiological deficits than the UHR population experiences and are therefore more amenable to preemptive interventions. The IPI package provided participants with CT, multifamily psychoeducation, group social skills, and computerized cognitive remediation. This multidomain approach to intervention, which targeted both the individual and family, capitalized on multiple points of entry into reducing stressors and improving cognitive resilience in vulnerable youth.

A number of factors may account for the unclear findings on the usefulness of CT for preemption of psychosis in CHR individuals. First, multiple investigators have noted a global trend toward lower conversion rates in CHR youth, from an average range of 40% to 50% conversion reported in the earliest published studies to rates of around 10% to 15% reported

Table 1   Randomized controlled trials of cognitive therapy in individuals at clinical high risk

Study and sample size	Intervention and control group	Conversion to psychosis[a]	Clinical outcomes (e.g., symptoms, functioning)
McGorry et al. (2002); N = 59	Intervention: CT plus low dose atypical antipsychotic (risperidone) for six months Control: care management	Lower conversion rate to psychosis at end of treatment (p = 0.03) No significant difference at 6-month follow-up	No significant difference between groups on any of the symptom or functioning measures
Phillips et al. (2007); N = 41	36-month follow-up to McGorry et al. (2002)	No significant difference	Active treatment group less negative symptoms (p = 0.004)
Morrison et al. (2004); N = 58	Intervention: CT plus monitoring Control: monitoring alone	96% reduction in odds of making transition to psychosis (odds ratio 0.04, p = 0.028)	Active treatment group less positive symptoms (p = 0.001)
Morrison et al. (2007); N = 27	36-month follow-up to Morrison et al. (2004)	No significant difference	87% reduction in prescription of antipsychotics (p = 0.024)
Yung et al. (2011); N = 130	Intervention: CT plus risperidone or CT plus placebo, over 12 months Control: supportive therapy plus monitoring or monitoring only, over 12 months	No significant difference	No significant difference between groups on any of the symptom or functioning measures
Addington et al. (2011); N = 51	Intervention: CT over 6 months Control: supportive therapy	No significant difference	Rapid decline in positive symptoms for both groups CT improved faster, with the most improvement in first 3 months (p = 0.0001)
Morrison et al. (2012); N = 288	Intervention: CT + monitoring + TAU Control: monitoring + TAU	No significant difference	Significant difference in severity of psychotic symptoms (p = 0.005)
Bechdolf et al. (2012); N = 127	Intervention: computerized cognitive training (CogPack), individual cognitive-behavioral therapy, group skills training, and multifamily psychoeducation Control: supportive counseling	At 12 months, lower conversion rate to psychosis (p = 0.08) At 24 months, lower conversion rate to psychosis (p = 0.019)	No significant difference between groups in antidepressant use

[a]Conversion to psychosis compared with comparison group. CT, cognitive therapy; TAU, treatment as usual.

in 2007 (Yung et al. 2007). Yung et al. (2011) discuss lower conversion rates in CHR youth in relation to their longitudinal study of CT and pharmacologic treatment and posit that it may be the explanation for a lack of difference between treatment groups. They suggest that the decrease in conversion may be an artifact of improved referral strategies, resulting in more people entering treatment with "incidental psychotic experiences" that are not in fact the manifestation of an incipient psychotic illness. If this is indeed the case, then further research is required in order to establish assessment methods that differentially identify those truly at risk of developing psychotic illness from those experiencing incidental psychotic experiences.

Second, Yung et al. (2011) also note that individuals in the very early stages of the CHR period may be quite responsive to nonspecific psychological therapies, such as supportive therapy.
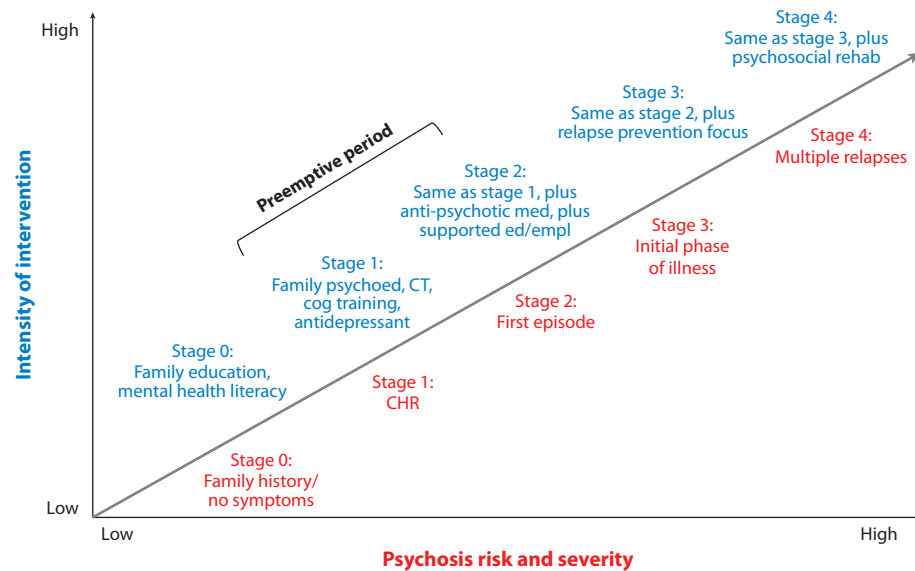
Figure 3

The clinical staging model for treatment decision making. CHR, clinical high risk; cog, cognitive; CT, cognitive therapy; ed/empl, education/employment; med, medication; psychoed; psychoeducation; rehab, rehabilitation.

This has led these investigators to propose a clinical staging model to aid treatment decision making: Individuals in the earliest stages of clinical presentation should receive nonspecific (and thus less costly and less intensive) treatments such as supportive therapy, whereas those who have progressed further in the course of the CHR period and who present with specific attenuated symptoms should receive specialized CT (**Figure 3**).

However, Bechdolf et al. (2012) demonstrated that individuals experiencing EIPS benefited from a specialized multimodal intervention package that was superior to supportive counseling. Again, a clinical staging approach requires advances in our ability to accurately differentiate between individuals exhibiting incidental psychotic experiences, who may benefit from less intensive treatment, and those experiencing true risk for a psychotic illness (such as demonstrated by the EIPS, for example), who may require specialized intervention.

Addington et al. (2011) have also endorsed the clinical staging model but highlight the difficulties associated with providing specialized CT to the CHR population. In interpreting the nonsignificant difference they found between supportive therapy and CT, they cited the lack of experience of their trial therapists, who were not doctoral-level CT specialists. Addington et al. (2011) suggest that interventions aimed at treating individuals with specific attenuated psychotic symptoms should be undertaken by specially trained and experienced therapists. However, community treatment settings are predominantly staffed by clinicians with Master's-level training, and further research must explore the feasibility and effectiveness of training community clinicians to provide high-fidelity specialized CT for the CHR population.

Although conversion to psychosis, or preemption, is the key outcome measure for CT studies in CHR individuals, it is also important to consider the impact of CT on symptoms and functioning. **Table 1** shows that, in some instances, CT appears to induce a more rapid amelioration of positive symptoms (Addington et al. 2011, Morrison et al. 2004) as well as decreased severity of positive

symptoms (Morrison et al. 2012). This may be of benefit, given research that suggests that DUP is associated with long-term morbidity (Thompson et al. 2001). Thus a more rapid amelioration of psychotic symptoms results in less exposure to potentially traumatizing and distressing experiences as well as less induction of maladaptive neuroplastic changes in response to those experiences.

FUTURE DIRECTIONS FOR COGNITIVE THERAPY

Although early results are inconclusive for CT delivered as a stand-alone preemptive treatment, a number of treatment elements require further investigation and development. Studies typically have used either French & Morrison's (2004) manual or the Personal Assessment and Crisis Evaluation (PACE) model described by Phillips & Francey (2004). French and Morrison's manual is based on Morrison's cognitive model of psychosis (2001); although there are no formal modules, treatment advances through engagement, assessment, formulation, intervention, and relapse prevention. The PACE model is based upon a stress-vulnerability rationale (Zubin & Spring 1977) and works through specific phases (engagement, assessment, treatment, and termination), with modules for each of these. Thus, within CT there are both specific and nonspecific treatment elements, such as specific cognitive formulation of attenuated psychotic symptoms (Morrison 2001) and more generic therapeutic elements such as engagement and interpersonal effectiveness. Further study is required to identify the "active ingredients" in CT so that the development and implementation of a staged intervention approach can reflect the trajectory from nonspecific supportive interventions to specific CT that targets attenuated psychotic symptoms. Such a staged intervention approach could also guide the training of clinicians in services for early psychosis, with less experienced staff providing early engagement and supportive therapy to clients early in the CHR period and more experienced and specialized staff working with clients who have identified target symptoms.

In sum, although some early results show promise, determining whether CT is an effective preemptive treatment will require further research using sufficiently powered sample sizes, algorithm-derived and operationalized staged interventions, assessment of effectiveness in community settings, and generalizability to non-Western contexts. In their study of the clinical efficacy of CT in a CHR sample in Korea, Kim et al. (2011b) suggest that this is a transportable intervention beyond traditional Western clinical settings, but further research in this area is required. The recent work of Bechdolf et al. (2012) suggests that preemption may be best achieved when CT is one component of a multimodal intervention that targets multiple domains of psychological, interpersonal, and cognitive functioning.

THE ROLE OF IMPAIRED COGNITION IN CLINICAL HIGH-RISK AND RECENT-ONSET SCHIZOPHRENIA

Abundant evidence indicates that, in addition to increased stress responsivity, CHR individuals show cognitive impairment well before illness onset. Relative to normative samples and healthy control subjects, high-risk individuals show deficits in vigilance, speed of processing, working memory, verbal learning and memory, executive functioning, global cognition, and IQ prior to the first psychotic episode (Becker et al. 2010, Brewer et al. 2005, Eastvold et al. 2007, Jahshan et al. 2010, Keefe et al. 2006, Kim et al. 2011a, Lencz et al. 2006, Niendam et al. 2006, Seidman et al. 2006, Simon et al. 2007). A recent meta-analysis comparing 1,188 high-risk subjects and 1,029 healthy controls found small to moderate impairments in high-risk subjects in general intelligence, executive functioning, verbal and visual memory, verbal fluency, attention and working memory, and social cognition (Fusar-Poli et al. 2012). In the largest study to date on neurocognition in high-risk individuals, the North American Prodrome Longitudinal Study (NAPLS) consortium found

that processing speed and verbal learning and memory were the most sensitive in discriminating high-risk individuals from controls (Seidman et al. 2010).

From high-risk status to first psychotic episode, individuals show continued cognitive impairment (Becker et al. 2010, Hawkins et al. 2008) or further cognitive decline (Jahshan et al. 2010, Keefe et al. 2006, Simon et al. 2007, Wood et al. 2007), and CHR patients have been shown to perform intermediately between recent-onset patients and control subjects (Keefe et al. 2006, Seidman et al. 2010, Simon et al. 2007). At first psychotic episode, multiple cognitive deficits are evident that approach or match the degree of deficit shown in chronic schizophrenia, with the largest impairments seen in processing speed and immediate verbal memory [for a meta-analysis of 43 studies ($N = 2{,}204$) of recent-onset schizophrenia, see Mesholam-Gately et al. (2009)].

Most importantly, strong evidence indicates that cognitive functioning in the prodromal phase is a significant predictor of conversion to psychosis. At-risk individuals who later develop psychosis show deficits in a range of cognitive abilities such as verbal memory, verbal executive functions, verbal IQ, visuospatial processing, visual memory, composite measures of cognition, and social cognition (Brewer et al. 2005, Eastvold et al. 2007, Keefe et al. 2006, Kim et al. 2011a, Lencz et al. 2006, Pukrop et al. 2007). In the meta-analysis of Fusar-Poli et al. (2012), high-risk individuals who later transitioned to psychosis showed significantly lower general intelligence and poorer cognitive functioning in verbal fluency, verbal and visual memory, and working memory compared to high-risk individuals who did not transition to psychosis.

Verbal memory appears to be a particularly important indicator of vulnerability to psychosis. For example, Pukrop et al. (2007) found that a deficit in verbal memory was the strongest predictor of conversion to psychosis, followed by deficits in verbal IQ, verbal learning, and processing speed, whereas the NAPLS group found that worse verbal memory predicted more rapid conversion to psychosis (Seidman et al. 2010). Similarly, Lencz et al. (2006) found deficits on a range of measures of verbal memory, executive functioning, and working memory in high-risk individuals, whereas those who later converted to psychosis showed significant impairment in verbal memory. The authors suggest that verbal memory deficits may be an important risk marker for later conversion to psychosis, whereas generalized cognitive impairment in high-risk individuals may be a nonspecific vulnerability marker.

Cognitive deficits not only predict psychosis but also are associated with poorer functional outcome. The relationship between cognition and functional outcomes in individuals with chronic schizophrenia is well documented (e.g., Green 1996, Green et al. 2000), and emerging evidence suggests a similar relationship in high-risk individuals. For example, Niendam et al. (2006) found that poorer verbal learning and memory performance was significantly associated with poorer social functioning in individuals at high risk, and a trend-level association was found between poorer performance on reasoning and problem solving and poorer global functioning. Further, verbal memory predicted social functioning more strongly than did negative symptoms. Similarly, in recent-onset schizophrenia, verbal memory, speed of processing, and attention have been shown to predict psychosocial and vocational functioning seven years later (Milev et al. 2005).

The stronger impact of cognition on functioning relative to the effect of symptoms has important treatment implications. In both recent-onset and chronic schizophrenia, evidence suggests that cognitive functioning and symptom severity are for the most part independent of one another: Cognitive deficits are present in the absence of symptoms, and although antipsychotic medications are effective in ameliorating positive symptoms, they have little effect on cognitive impairment or long-term outcome (e.g., Goldberg et al. 2007, Keefe et al. 2007). In high-risk studies, evidence suggests a similar dissociation. Simon et al. (2007) found that an increase in symptom severity was not paralleled by an increase in cognitive impairment, whereas Hawkins et al. (2008) found that neither the onset of frank psychosis nor olanzapine treatment altered the course of cognitive

impairment. Given the relative independence of cognitive functioning and symptoms, as well as the deleterious effects of cognitive impairment on social and occupational outcomes and quality of life, it is clear that cognitive enhancement is a critical treatment goal in early psychosis and may be a means for intervening preemptively to ameliorate the course of illness, or perhaps even to inoculate the at-risk individual against the onset of a first psychotic episode.

Although a range of cognitive deficits are evident in individuals at high risk, and additional research is needed in this area, verbal memory appears to be a particularly relevant preemptive target given that deficits in this domain have been shown to predict conversion to psychosis, are associated with poorer functional outcome, and show the largest impairment in recent-onset schizophrenia. Thus, the field must move toward (*a*) early detection of cognitive impairment in individuals at high risk for psychosis and (*b*) the application of targeted interventions to enhance cognition, with an emphasis on verbal memory. To date, novel cognitive-enhancing pharmacological agents have proven disappointing (for a review, see Keefe et al. 2011); however, cognitive training approaches are showing promise and are a growing area of investigation.

OVERVIEW OF COGNITIVE TRAINING IN EARLY PSYCHOSIS

The past 15 years have seen explosive growth in research and clinical interest in cognitive remediation for chronic schizophrenia. Meta-analytic work confirms that a wide range of noncomputerized and computerized approaches results in moderate increases in global cognition measures, and significantly stronger effects on functioning are evident when cognitive training is provided together with other psychosocial rehabilitation (McGurk et al. 2007, Wykes et al. 2011). Although several randomized controlled trials are currently in progress to determine the effects of cognitive training in early psychosis (e.g., Breitborde et al. 2011, Vesterager et al. 2011, Vinogradov 2012; see also **http://clinicaltrials.gov/ct2/show/NCT00655239**), only two studies to date have reported the effects of cognitive training in individuals at clinical high risk (Bechdolf et al. 2012, Rauchensteiner et al. 2011), and four have reported on the effects in recent-onset schizophrenia (Eack et al. 2009, 2010a,b; Hansen et al. 2012; Ueland & Rund 2004, 2005; Wykes et al. 2007). A variety of intervention methods have been used, including computerized cognitive training, therapist-guided training with paper/pencil tasks, and adaptive training designed to bypass cognitive deficits using compensatory strategies. Below, we review these six studies and then describe the work being carried out by our group.

COGNITIVE TRAINING IN INDIVIDUALS AT HIGH RISK FOR PSYCHOSIS

CogPack

To date, two studies have examined the effects of cognitive training in individuals at clinical high risk for psychosis, and both used computerized exercises from CogPack (Marker 1987–2007). Designed in Germany, CogPack contains multiple exercises in each of the following subprograms: Visuomotor Skills, Vigilance/Comprehension/Reaction, Language Material, Memory, Numbers/Logic, Knowledge/Orientation/Everyday Skills, and Special Elements (e.g., executive functioning and tone and pitch discrimination). Thus, exercises provide training across a broad range of cognitive functions including attention, psychomotor speed, learning and memory, and executive functions.

In an exploratory pilot study, Rauchensteiner et al. (2011) tested the effect of 10 sessions of CogPack delivered over a four-week period in 10 individuals at risk for psychosis (mean age

27.2 years) relative to 16 individuals with fully manifested schizophrenia (mean age 30.13 years). At the group level, there were no significant differences in age. Eight CogPack tasks of attention, memory, and executive functioning were used. Before and after training, subjects were assessed on verbal learning and memory, attention/working memory [i.e., the Continuous Performance Test Identical Pairs (CPT-IP)], and progress on the eight CogPack training exercises. Between-group analyses revealed that the high-risk group made greater gains in verbal memory and on three of the eight CogPack exercises relative to the schizophrenia subject group. In a within-group analysis, the high-risk group showed significant improvement in verbal memory, hits on the CPT-IP shapes (but not numbers), and significant improvement on five of the eight CogPack exercises, whereas the schizophrenia group showed improvement on false alarms of the CPT-IP shapes only. Although results from this pilot study need to be interpreted with caution, these data raise two interesting possibilities. First, individuals at high risk show greater gains in verbal memory and on the exercises relative to individuals with established schizophrenia, which suggests increased capacity for neuroplasticity in the high-risk individuals. Second, these individuals showed gains after only 10 sessions of training, whereas 10 sessions were of limited benefit in individuals with chronic schizophrenia. However, CogPack has shown significant effects in chronic schizophrenia in several prior studies where training was delivered at a higher dose (i.e., 15 to 36 sessions) (Cavallaro et al. 2009; Lindenmayer et al. 2008; McGurk et al. 2005, 2009; Sartory et al. 2005). These differential responses to a relatively brief course of training suggest that a meaningful treatment response can be obtained with a more efficient intervention if we capitalize on the neuroplastic capacity in individuals at high risk before the deleterious effects of medications and illness chronicity set in.

As discussed previously, Bechdolf et al. (2012), in an unblinded study, tested the effects of an IPI relative to supportive counseling in 128 individuals with EIPS. IPI combined 25 sessions of individual cognitive-behavioral therapy, 15 sessions of group skills training, 12 sessions of cognitive remediation with the CogPack software, and 3 multifamily psychoeducation sessions delivered over a 12-month period. Subjects in the control condition completed 30 sessions of supportive counseling over the same period. The supportive counseling was designed to provide a minimal level of support and included basic assessment, psychoeducation, and counseling. Subjects in IPI showed a significantly lower rate of conversion to psychosis: At the end of treatment, 2 of the 63 patients in IPI converted to psychosis compared to 11 of the 65 patients in supportive counseling. At a follow-up 12 months after treatment, 2 additional patients in each condition converted to psychosis. Although these results are very encouraging, the trial design did not allow assessment of the relative contribution of computerized cognitive training to this outcome, and the effects on cognitive performance were not reported. Additional studies on the effects of cognitive training in high-risk samples are needed to determine whether this intervention can prevent conversion to psychosis or avert further cognitive decline.

COGNITIVE TRAINING IN RECENT-ONSET SCHIZOPHRENIA

Therapist-Guided Paper/Pencil Tasks

Wykes et al. (2007) tested the effects of cognitive remediation therapy (CRT) compared to treatment as usual in 40 young, primarily in-patients with adolescent-onset schizophrenia (average age of 18) who showed evidence of cognitive and social behavioral difficulties. Participants received 40 hourly sessions of CRT at an average rate of three sessions per week over three months. CRT targets memory, complex planning, and problem solving using simple paper/pencil tests and small task equipment, with the guidance of a therapist. The therapist provides information-processing

strategies and discusses the regulation, organization, and monitoring of behavior for each task to minimize errors.

Out of three primary outcome measures (cognitive flexibility, working memory, and planning), CRT showed a significant effect on cognitive flexibility (Wisconsin Card Sorting Task), with durability at three-month follow-up. There was no significant effect of CRT on any secondary outcome measures of symptoms or functioning, which (as the authors note) might only be evident when cognitive remediation is integrated with rehabilitation and other treatments where the learned strategies can be implemented. However, a moderating effect was found between planning improvements and a decrease in symptoms, and cognitive change in the total sample was associated with change in social functioning and symptoms.

Ueland & Rund (2004) tested the effects of a therapist-guided pencil/paper cognitive remediation program combined with psychoeducation compared to psychoeducation alone in 26 adolescent inpatients (average age 15) with adolescent-onset schizophrenia. The cognitive remediation program consisted of 30 hours of individual training with a therapist over 12 weeks. Training targeted cognitive differentiation, memory, social perception, and attention, which included a three-day intensive training on the Span of Apprehension Task (SPAN) with enhanced instructions and monetary reinforcement. The psychoeducation treatment included parent seminars, problem-solving sessions, milieu therapy, and network groups.

The results showed no significant difference between the groups, possibly due to the small sample size. Given that the study was underpowered, within-group analyses were conducted and showed that the cognitive remediation group improved on five of the ten cognitive measures and three of the five functional outcome measures; the control group improved on three cognitive and one functioning measure. Only the cognitive remediation group showed significant improvement in early visual information processing (SPAN), visual memory, symptoms, and psychosocial functioning. The improvement in the control group on some measures suggests that the psychoeducation program may have some benefits on cognition and/or that some placebo effects are possible in cognitive performance during a randomized controlled trial [indeed, recent data show that, in pharmacologic trials, placebo responses have increased in schizophrenia participants in the past decade compared to prior decades (Kemp et al. 2010)].

In contrast to the results of Wykes et al. (2007), the authors found no relationship between change in cognition and change in functioning, which again might be due to low statistical power. At one-year follow-up (Ueland & Rund 2005), no significant group-by-time interactions were found on the cognitive, clinical, or functioning measures with the exception of the SPAN, which indicates that durable improvements in visual attention can be achieved through intensive training in these young individuals.

Cognitive Enhancement Therapy

Eack et al. (2009) examined the effects of cognitive enhancement therapy (CET) in recent-onset schizophrenia. CET is a small-group approach that combines 60 hours of computerized training in attention, memory, and problem solving using CogRehab software (Bracy 1995), with 45 1.5-hour sessions of social cognitive group exercises delivered over two years. CogRehab software (Bracy 1995) was originally designed for patients with traumatic brain injury but has been used in a number of studies in chronic schizophrenia. The exercises emphasize simple attention, executive skills, visuospatial skills, memory, and problem solving. Eight modules are completed sequentially, with two modules of increasing complexity within each cognitive domain. The developers recommend one to three hours per day of training, carried out several times a week over the course of one year, with weekly therapy sessions during which compensatory skills are taught, patients' progress is reviewed, and program parameters, such as difficulty level, are adjusted.

In Eack et al. (2009), 58 individuals with recent-onset schizophrenia were randomized to CET or enriched supportive therapy (EST)—an individual approach involving illness management and psychoeducation. After one year of treatment, improvements on cognitive measures were not evident, but after two years of treatment, moderate improvement was evident. At both one and two years, CET subjects showed significant gains on measures of social cognition, cognitive style, social adjustment, and symptoms, and a significantly greater proportion of CET subjects were engaged in competitive employment at two years. However, neither participants nor raters were blind to group assignment, and most of the social, occupational, and symptom measures were interview based. Furthermore, subjects in the CET condition received significantly more hours of clinician contact and therapeutic intervention, and it is not possible to differentiate the effects due to the cognitive training alone versus those due to increased therapist contact and the social skills groups.

A follow-up study one year after the completion of CET (Eack et al. 2010a) showed that the gains on social and symptom measures were broadly maintained whereas the effect on employment was no longer significant (i.e., a similar proportion of EST and CET subjects were employed). Cognitive assessments were not conducted at the follow-up. Consistent with Wykes et al. (2007), the gains in cognition from baseline to two years of treatment were significantly associated with gains in functional outcome, as were increases in social cognition (measured with the MSCEIT Managing Emotions subscale) (Eack et al. 2011).

Eack et al. (2010b) also found greater preservation of gray matter volume over two years in the left hippocampus, parahippocampal gyrus, and fusiform gyrus, and significantly greater gray matter increases in the left amygdala in CET subjects relative to EST subjects. Furthermore, less gray matter loss in the left parahippocampal and fusiform gyrus and greater gray matter increases in the left amygdala were significantly related to improved cognition. The findings of Eack et al. (2010b) indicate that computerized cognitive remediation combined with intensive group-based social skills therapy has beneficial effects on both cerebral gray matter volume and psychosocial functioning in recent-onset schizophrenia. However, a perplexing issue is the fact that it took two years for subjects in CET to show gains in cognition, and it is unclear as to which components of the intervention contributed to these gains. It is also unknown whether this treatment can induce cognitive gains in less time if a more intensive schedule is employed.

Cognitive Adaptation Training

Cognitive adaptation training (CAT) is a compensatory treatment for cognitive impairment in schizophrenia designed to bypass cognitive deficits by providing training in solutions to concrete, daily life problems using various tools (e.g., schedules, schemes, and signs). Hansen et al. (2012) tested the effects of CAT in combination with assertive community treatment (ACT) versus ACT alone in 62 outpatients with recent-onset schizophrenia. ACT included medication management, weekly contact with professionals, psychoeducation, social skills training groups, and psychosocial intervention with relatives. CAT was conducted in patients' homes every two weeks over a period of six months. Subjects were assessed at baseline, postintervention (six months), and follow-up (nine months) on global functioning, social problems, social needs, symptoms, quality of life, and hospitalizations. The results showed no significant group differences at postintervention or follow-up. At follow-up, both groups showed a small improvement in social problems, positive symptoms, and quality of life. These results are inconsistent with previous studies where CAT has shown positive effects in chronic schizophrenia (e.g., Velligan et al. 2009) and may be due to the sample size (the estimated number of subjects required was not reached due to a high refusal rate). In addition, CAT treatment was provided by staff without practical training in CAT or supervision

from experienced CAT providers, and the control condition was more intensive than in previous studies, which may have obscured group differences.

Brain Fitness Program

The Brain Fitness Program (BFP; developed by PositScience) is an auditory processing/verbal learning training program that is designed to restore and enhance auditory perceptual and working memory processes, with the goal of increasing the accuracy and temporal resolution of auditory inputs feeding working memory and long-term verbal memory encoding. BFP was originally designed to address the verbal memory impairments associated with aging, but it has been applied to patients with schizophrenia to address the known impairments in auditory processing and frontally mediated verbal memory operations in the illness (e.g., Foucher et al. 2005, Friston & Frith 1995, Javitt et al. 2000, Kasai et al. 2002, Light & Braff 2005, Ragland et al. 2004, Wible et al. 2001). Though many of the exercises have a heavy emphasis on auditory perceptual processing, they also explicitly require sustained attention and working memory and repeatedly engage cognitive control and response-selection mechanisms.

This explicitly "systems neuroscience"—informed approach harnesses principles of training-induced neuroplasticity (Vinogradov et al. 2012) and has the following features: (a) intensive—many thousands of learning trials are performed for each specific exercise; (b) neuroadaptive—the dimensions of each exercise (e.g., speed, working memory load) are parametrically and continuously modified on a trial-by-trial basis for each individual user during the course of each exercise in order to maintain performance at ∼80% accuracy; (c) attentionally engaging—each trial is gated by a "ready" signal from the user to indicate and require directed attention; (d) rewarding—correct responses are continuously rewarded by amusing auditory and visual stimuli in order to drive high levels of training compliance and to engage reward and novelty detection systems for successful learning. The training program consists of six exercises of increasing complexity. Exercise 1 requires subjects to make gradually more difficult distinctions between frequency modulation sweeps (i.e., progressively faster sweeps and shorter interstimulus intervals) that mimic the features of important formants in speech. Once mastered, subjects progress to exercises that use phonemes, then full words, and finally full sentences. The first four exercises heavily engage auditory and verbal working memory functions. Exercise 5 engages both working memory and verbal learning as the listener must remember a sequence of verbal instructions in order, then carry them out; the instructions get longer and more complex as the listener improves. In Exercise 6, stimuli consist of real-world scenarios of conversational narrative, and the listener must sharply focus on increasingly more difficult and elusive details of longer narratives.

Our group has previously reported the effects of BFP delivered as a stand-alone treatment in individuals with chronic schizophrenia (Fisher et al. 2009). Twenty-nine schizophrenia outpatients completed 50 hours of the training over a 10-week period and were compared to an active computer games control condition ($N = 26$) designed to control for the effects of computer exposure, contact with research personnel, and monetary payments. Relative to the control group, the auditory training group showed positive effects on measures of verbal working memory, verbal learning and memory, and global cognition. Effect sizes in verbal learning and memory, and in global cognition, were large (Cohen's d 0.86–0.89). At a six-month follow-up assessment, improved cognition was significantly associated with improved functional outcome.

Our findings of the same training in individuals with recent-onset schizophrenia show similar results (Vinogradov 2012). In this randomized controlled trial (**http://clinicaltrials. gov/ct2/show/NCT00694889**), 80 individuals with recent-onset schizophrenia (mean age of 21 years) were given laptop computers to take home, where they performed either 40 hours

of neuroplasticity-based auditory training or 40 hours of commercial computer games over an eight-week period, in conjunction with standard care. We examined neurocognitive outcome measures (Measurement and Treatment Research to Improve Cognition in Schizophrenia), symptoms, and functioning. We also investigated psychophysical improvement in auditory processing and its association with cognitive gains.

Auditory training subjects demonstrated significant improvements in global cognition, verbal learning and memory, and problem solving compared to computer games control subjects. Both groups showed a slight but significant decrease in symptoms, likely as a result of receiving clinical attention and standard treatment. Subjects in the training group also showed significant psychophysical improvement in early auditory processing that correlated with gains in cognition.

These findings suggest that the cognitive deficits of schizophrenia can be addressed very early in the course of illness, using an intensive schedule of training at home that is delivered via a portable computing device. Further, we posit that the association of improvement in early auditory processing with improvement in higher-order cognition reflects training-induced distributed plastic changes occurring throughout the neural systems subserving verbal learning and memory. Indeed, magnetoencephalography experiments in our adult subjects indicate that training induces an increase in the amplitude of the M100 response in auditory cortex (Dale et al. 2010) accompanied by changes in gamma-band oscillatory power in lateral frontal cortex (Vinogradov et al. 2012); Popov et al. (2011) found normalization of early auditory gating impairments in schizophrenia after 20 hours of training. Future studies will investigate whether this training improves long-term outcome and community functioning.

FUTURE DIRECTIONS FOR COMPUTERIZED COGNITIVE TRAINING

Taken together, the studies above provide the first indications that computerized cognitive training is a promising treatment for individuals with both CHR and recent-onset schizophrenia (**Table 2**). Individuals at high risk show greater cognitive gains relative to adults with chronic schizophrenia (Rauchensteiner et al. 2011), whereas a combined treatment of cognitive training, cognitive-behavioral therapy, group skills training, and multifamily psychoeducation resulted in lower rates of conversion to psychosis (Bechdolf et al. 2012). In recent-onset schizophrenia, computerized cognitive training, when delivered in sufficient doses, appears effective in improving multiple cognitive and social cognitive domains both as part of a multimodal treatment targeting social functioning (Eack et al. 2009) and as a stand-alone treatment delivered along with usual care (Vinogradov 2012). Furthermore, evidence indicates that gains in cognition are associated with gains in functional outcome (Eack et al. 2011, Wykes et al. 2007).

Although these results are encouraging, it is not yet possible to make direct comparisons between these cognitive training programs or draw any firm conclusions about their preemptive effects, given the small number of studies to date in early psychosis; the variety of training programs, adjunctive treatments, and control groups studied; and the disparity between studies in the assessment measures used. Until we can systematically examine the effects of an intervention under sufficiently powered, carefully controlled, randomized, and double-blind conditions, using well-defined cognitive, neurological, and functional outcome measures—and until we make a concerted effort to investigate the durability or sustainability of both behavioral and neurological effects as well as the additive (or synergistic) effects of psychosocial, vocational, and pharmacological treatments—it will continue to be difficult to assess and compare the various cognitive training methods currently available.

Table 2   Cognitive training programs to target impaired cognition in clinical high-risk and recent-onset schizophrenia

Phase of illness	Study and sample size	Cognitive function target and type of training	Cognitive training treatment intensity	Effects[a]
Clinical high risk	Rauchensteiner et al. (2011); $N = 26$	Target: attention, memory, and executive functioning Training: computerized cognitive training (CogPack)	10 hours over a maximum of 4 weeks	Improvement in verbal memory and 3 out of 8 CogPack exercises
	Bechdolf et al. (2012); $N = 128$	Target: concentration, attention, vigilance, and memory Training: computerized cognitive training (CogPack), individual cognitive-behavioral therapy, group skills training, and multifamily psychoeducation	12 sessions over 12 months	Lower rate of conversion to psychosis at 12- and 24-month follow-up
Recent-onset schizophrenia	Wykes et al. (2007); $N = 40$	Target: memory, complex planning, and problem solving Training: paper/pencil tasks with the guidance of a therapist	40 hours, 3 times per week over 3 months	Improvement in problem solving
	Ueland & Rund (2004, 2005); $N = 24$	Target: cognitive differentiation, memory, social perception, and attention including SPAN Training: paper/pencil tasks and practice on cognitive measures (e.g., SPAN) with the guidance of a teacher or therapist	30 hours, 2–3 times per week over 12 weeks	Improvement in SPAN task at 1-year follow up
	Eack et al. (2009); $N = 58$	Target: attention, memory, problem solving, and social cognition Training: computerized cognitive training (CogRehab) and social cognitive group exercises	60 hours, 1 time per week over 1–2 years	Improvement in neurocognition, social cognition, cognitive style, social adjustment, symptoms, and competitive employment
	Hansen et al. (2012); $N = 62$	Target: global and social functioning Training: compensatory training (e.g., schedules, schemes and signs to solve concrete problems related to daily life) along with assertive community treatment (ACT)	12 sessions, 1 session every 2 weeks over 6 months	None
	Vinogradov (2012); $N = 80$	Target: auditory processing and verbal memory functions Training: computerized cognitive training (BFP) of lower-level auditory processes and auditory/verbal working memory	40 hours, 5 times per week over 8 weeks	Improvement in global cognition, verbal learning and memory, problem solving

[a]Significant improvement in cognitive training subjects relative to control subjects. BFP, Brain Fitness Program; SPAN, Span of Apprehension Task.

Future research must determine not only the optimal form of training for individuals at high risk and those with recent-onset schizophrenia, but also the ideal number of hours of training and treatment intensity, how best to disseminate and supervise cognitive training in real-world settings, and the subject characteristics of those who can benefit most from this intervention. In studies of cognitive training in chronic schizophrenia, moderator variables explored to date have shown little to no effect (Wykes et al. 2011), but it is highly likely that several unexplored moderators (such as genotype, "learning potential," motivational state, and baseline neural system functional connectivity) all play a role in influencing treatment outcome. Indeed, our group has reported preliminary data showing an effect of COMT genotype on response to cognitive training (Panizzutti et al. 2013) as well as an effect of baseline prefrontal cortical connectivity (Vinogradov et al. 2012).

EMERGING AREAS OF INVESTIGATION

There is now a consensus in the field that behavioral interventions, such as CT or computerized cognitive training, offer a number of significant advantages as we seek to develop meaningful approaches to preempt schizophrenia. Bentall & Morrison (2002) note that, as compared to pharmacologic treatments, behavioral interventions have fewer deleterious side effects, are less stigmatizing, and target the presenting nonspecific symptoms through a normalizing approach. In addition, behavioral interventions are generally more tolerable and acceptable than medications (Morrison et al. 2004). We posit that, in at least some forms, they are also more scalable and can be delivered via Web-based technology to remote or underresourced clinical sites.

Although the emerging data are promising, much important work remains to be done. Basic methodologic issues such as sample size and sample characteristics, assessment criteria, clinical staging, and rigorous trial design and data analytic approaches must be implemented in order to build a convincing evidence base for both CT and computerized cognitive training as preemptive behavioral interventions. With the current rapid advances in the development of cognitive-enhancing medications, we must also be prepared to explore the most advantageous ways in which these agents can—and probably should—be combined with behavioral treatments in order to optimize patients' outcomes (Keefe et al. 2010). Indeed, some agents may be of no value when given alone but may substantially facilitate the effects of CT or of cognitive training in individuals with early psychosis.

Medications are not the only possible adjuvants to enhance the brain's response to behavioral interventions. The use of neuromodulatory techniques such as transcranial magnetic stimulation and direct current stimulation, in combination with sensory stimulation, have both shown to be inducers of cortical plasticity (Celnik et al. 2009, Khedr et al. 2010). Exercise is another potent, safe, and valuable "neurotrophic agent" that could easily become a significant part of the treatment armamentarium for preempting schizophrenia (see Pajonk et al. 2010).

Finally, advances in information technology and in interactive and entertainment software indicate that Web-based treatment delivery methods can be developed that will generate the same interest, engagement, perceived value, and social acceptability as do Web-based games. Indeed, novel collaborative efforts are already underway to develop socially networked browser-based cognitive therapy for schizophrenia as well as highly engaging game-like cognitive training tools for patients with early psychosis. We are only a few steps away from the development of Web-deliverable behavioral treatments that will be available on a scale never before imagined for any other therapeutic intervention and that may finally allow us to reach—and treat—young high-risk individuals at a population level. We are at a conceptual threshold that could not have been imagined a decade ago: facing the very real possibility that we may be able to move beyond preemption in schizophrenia, to inoculation.

DISCLOSURE STATEMENT

S. Vinogradov is a paid consultant to Brain Plasticity Inc., a company with a commercial interest in cognitive training software. She is also a paid consultant to Amgen, Genentech, and Hoffman-LaRoche. None of the other authors have any financial interest in Brain Plasticity Inc. or PositScience. The authors are unaware of any other affiliations, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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