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Cognitive Control Deficits in Schizophrenia: Mechanisms and Meaning

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Although schizophrenia is an illness that has been historically characterized by the presence of positive symptomatology, decades of research highlight the importance of cognitive deficits in this disorder. This review proposes that the theoretical model of cognitive control, which is based on contemporary cognitive neuroscience, provides a unifying theory for the cognitive and neural abnormalities underlying higher cognitive dysfunction in schizophrenia. To support this model, we outline converging evidence from multiple modalities (eg, structural and functional neuroimaging, pharmacological data, and animal models) and samples (eg, clinical high risk, genetic high risk, first episode, and chronic subjects) to emphasize how dysfunction in cognitive control mechanisms supported by the prefrontal cortex contribute to the pathophysiology of higher cognitive deficits in schizophrenia. Our model provides a theoretical link between cellular abnormalities (eg, reductions in dentritic spines, interneuronal dysfunction), functional disturbances in local circuit function (eg, gamma abnormalities), altered inter-regional cortical connectivity, a range of higher cognitive deficits, and symptom presentation (eg, disorganization) in the disorder. Finally, we discuss recent advances in the neuropharmacology of cognition and how they can inform a targeted approach to the development of effective therapies for this disabling aspect of schizophrenia.
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INTRODUCTION

Cognitive dysfunction represents a core deficit in schizophrenia, and a number of studies (Green, 1996; Green *et al*, 2000) illustrate how cognitive deficits may strongly influence the clinical presentation and daily functioning of people with this illness. Cognitive deficits in schizophrenia have been associated with disorganization and negative symptoms (eg, see Cohen *et al*, 1999; Green *et al*, 2000; Kerns and Berenbaum, 2002) as well as with poor functional outcomes (Green, 1996, 1998; Weinberger and Gallhofer, 1997). Despite these links, cognitive dysfunction shows only modest improvement with currently available therapies and the vast majority of patients treated with second-generation antipsychotic drugs continue to experience significant cognitive disability (Green, 1998; Harvey and Keefe, 2001; Weinberger and Gallhofer, 1997). In response to the increased awareness of the clinical importance of impaired cognition in schizophrenia, there has been a dramatic increase in research directed toward understanding the pathophysiological mechanisms underlying these deficits as well as developing effective therapies for this aspect of the illness.

Previous studies in schizophrenia have utilized standardized neuropsychological batteries to examine various aspects of cognition in the disorder. Findings reveal that cognitive deficits are present in schizophrenia regardless of illness stage, as individuals experiencing their first episode of schizophrenia show a pattern of deficits on tasks related to frontal and temporal lobe functioning, including attention, processing speed, executive functioning, verbal fluency, verbal memory, and learning (Censits *et al*, 1997; Hoff *et al*, 1992; Mohamed *et al*, 1999; Riley *et al*, 2000; Saykin *et al*, 1994; Schuepbach *et al*, 2002; Townsend *et al*, 2001). Deficits in these domains have been consistently associated with poor social functioning as well as poor work/school outcome (Addington and Addington, 1999;

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Addington *et al*, 1998; Bell and Bryson, 2001; Bilder *et al*, 2000; Bowen *et al*, 1994; Brekke *et al*, 1997; Corrigan and Toomey, 1995; McGurk and Meltzer, 2000a; Smith *et al*, 2002; Velligan *et al*, 2000). Furthermore, impairment in such cognitive domains has been associated with negative and disorganization symptoms, including formal thought disorder (Addington and Addington, 1999, 2000; Bilder *et al*, 2000; Breier *et al*, 1991; Cohen *et al*, 1999; Dibben *et al*, 2009; Dickerson *et al*, 1996; Goldman *et al*, 1993; Greenwood *et al*, 2008; Heslegrave *et al*, 1997; Kerns and Berenbaum, 2002; Lenior *et al*, 2001; MacDonald *et al*, 2005; McGurk and Meltzer, 2000a; McGurk *et al*, 2000b; Moriarty *et al*, 2001; Perlstein *et al*, 2001; Velligan *et al*, 1997; Yoon *et al*, 2008a). Moreover, cognitive improvement in schizophrenia is typically associated with a reduction in negative symptoms, but not positive symptoms (Censits *et al*, 1997; Mohamed *et al*, 1999; Schuepbach *et al*, 2002).

Although previous studies have revealed important information with regard to the impact of impaired cognition in schizophrenia, the use of standard neuropsychological measures limits our ability to understand the complexity of the underlying impairment, as a particular test may engage numerous cognitive processes (Cho *et al*, 2005). One example is the Wechsler Digit Symbol—Coding subtest (Wechsler, 1997), which shows one of the most reliably documented impairments in the clinical neuropsychological literature of schizophrenia (Dickinson *et al*, 2007). Although this task is typically categorized as a measure of attention, accurate and rapid performance requires simple visual attention, active maintenance of symbol–digit pairings in working memory, as well as psychomotor speed. Thus, interpretation of lower performance in a patient population is difficult, as poor performance may be owing to an isolated deficit in any one of the component processes mentioned above and/or a deficit in the fluid integration of these processes. Consequently, the recruitment of multiple cognitive processes during a task restricts the ability to isolate specific neural systems and accurately identify functional neural markers of risk.

In response to these limitations, research utilizing cognitive science paradigms that isolate particular cognitive processes within schizophrenia has increased dramatically over the past decade. Within the domain of higher cognitive functions, disturbances have been described in selective attention (Carter *et al*, 1992; Cornblatt *et al*, 1989; Mirsky, 1969; Nuechterlein and Dawson, 1984), working memory (Carter *et al*, 1996; Glahn *et al*, 2000; Gold *et al*, 1997; Keefe *et al*, 1995; Park and Holzman, 1992), episodic memory (Clare *et al*, 1993; Ranganath *et al*, 2008; Saykin *et al*, 1991; Schwartz *et al*, 1992; Tamlyn *et al*, 1992), language production (Barch and Berenbaum, 1996a; Docherty *et al*, 1988, 1996; Harvey, 1983), and comprehension (Condray *et al*, 1995; Morice and McNicol, 1985). Although it is possible that schizophrenia patients have discrete deficits in multiple cognitive systems, a parsimonious account of many of these deficits, as suggested by Kraepelin a century ago (Kraepelin (1919, 1971), 'The mind in dementia praecox is like an orchestra without a conductor'), is that they reflect impaired cognitive control.

This review proposes that the theoretical model of cognitive control, which is based on contemporary cognitive neuroscience, provides a unifying theory for the cognitive and neural abnormalities underlying higher cognitive dysfunction in schizophrenia. In support of this theory, we summarize the literature on impaired cognition in schizophrenia as well as in high-risk populations and discuss the clinical and etiological significance of these deficits. In doing so, we hope to provide background and rationale for an integrative cognitive control account of these seemingly unique and disparate findings. Finally, we will outline how this model can inform a critical research agenda that is focused on developing effective therapies to reduce disability associated with the illness.

A MODEL OF HIGHER COGNITIVE DEFICITS IN SCHIZOPHRENIA: IMPAIRED COGNITIVE CONTROL, DISORGANIZATION, AND THE PREFRONTAL CORTEX

In order to manage the complex set of demands that come with day-to-day life, the human brain has developed mechanisms to coordinate the multitude of incoming sensory and motor information with higher-level representations of internal goals or rules to determine appropriate behavioral responses. The adequate engagement of cognitive control requires the coordination of multiple brain regions, including the dorsolateral prefrontal cortex (DLPFC), medial frontal cortex (including the anterior cingulate cortex), and parietal regions (Botvinick *et al*, 2001; Carter *et al*, 1999; Cohen *et al*, 2000; Yarkoni *et al*, 2005). Owing to its interconnectivity with sensory and motor regions, the DLPFC is believed to have a central role in the maintenance of the rules for action as well as response selection (Asaad *et al*, 2000; Watanabe, 1990, 1992). In contrast, medial frontal regions, specifically the anterior cingulate cortex (ACC), are believed to detect response conflict as part of a 'control loop' and then signal the DLPFC when control-related activity should be increased to improve performance (Egner and Hirsch, 2005; Kerns *et al*, 2005; MacDonald *et al*, 2000). The activation of parietal regions provides the DLPFC with the ability to shift attentional focus and provides information on learned stimulus–response pairings (Bunge *et al*, 2002, 2003; Miller and Cohen, 2001; Posner and Petersen, 1990). When engaged in tasks requiring cognitive control, functional neuroimaging studies of healthy individuals have shown activation of a specific cortical network, including the DLPFC and anterior cingulate cortex (Brass and von Cramon, 2002; Braver *et al*, 2003; Dove *et al*, 2000; Dreher *et al*, 2002; Liston *et al*, 2006; Sohn *et al*, 2000; Yeung *et al*, 2006). When such prefrontal brain regions are damaged, affected individuals show predictable deficits in context maintenance and response inhibition (Miller, 2000).

Early studies of the prefrontal cortex (PFC) structure and function in non-human primates (Funahashi *et al*, 1993; Fuster, 1990; Goldman-Rakic, 1987; Jacobsen, 1936) suggested that the PFC serves as a temporary storage for incoming information, maintaining it 'online' for immediate use. However, more recent views of the PFC suggest that its role is much more complex (Braver *et al*, 2002; Bunge *et al*, 2002; D'Esposito and Postle, 2002; Fuster, 2002; Thompson-Schill *et al*, 2005). Although a complete discussion of this literature is beyond the scope of this review, it is important to summarize our current understanding of the PFC and its role in cognitive control. Given its extensive interconnections with sensory, motor, and subcortical regions, the PFC is believed to serve a primary role in integrating incoming information and providing 'top-down' processing to coordinate behavior (Miller, 2000; Miller and Cohen, 2001). Information processing in the brain is often competitive as different information is received from various pathways, leading to a competition for the selection of a behavioral response. In concordance with early theories of the PFC as 'online storage,' Miller and Cohen (2001) propose that the PFC actively maintains 'rules' online in order to evaluate incoming information as well as internal states to guide response selection toward a current goal. When we are confronted with conflicting behavioral responses, the PFC provides 'cognitive control' by maintaining the set of rules that are required to be successful in a new situation and constrains neural information processing across the brain in accordance with these rules and goals. By doing so, the PFC biases neural processing in the brain away from prepotent but incorrect responses and toward the appropriate response. Figure 1 illustrates this phenomenon using the Stroop task, in which the 'high control' condition of color naming requires greater engagement of the PFC to overcome the prepotent response of word reading. In this way, the PFC is responsible for maintaining goals and rules and binding them with incoming sensory and motor information to direct attention to task-relevant information.

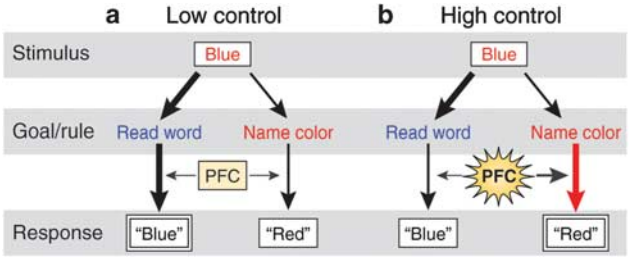

Figure 1. Simplified graphical depiction of the role of the prefrontal cortex (PFC) during the classic Stroop task, in which the stimulus is identical but the engagement of control processes is modulated by the rule. (a) Under low cognitive control demands (ie, word reading), the PFC is minimally engaged and the response is biased towards the prepotent word reading response, which is represented by relatively thicker black vertical arrows. (b) In contrast, under high cognitive control demands (ie, color naming), the PFC is strongly recruited to bias responding away from the prepotent response and toward the appropriate response represented by the large red vertical arrow.

This in turn biases information processing and response selection toward responses that are relevant for the goal at hand, and facilitates the updating of these rules and goals based on reward and ongoing experience (Miller and Cohen, 2001).

It is important to note that cognitive control processes encompass a broad class of mental operations, including goal or context representation and maintenance, strategic processes such as attention allocation and stimulus-response mapping, and performance monitoring (Carter *et al*, 1998; Cohen *et al*, 1990; Miyake and Shah, 1999; Shallice, 1988). Cognitive control is associated with a wide range of cognitive processes (Carter *et al*, 1998; Posner and Abdullaev, 1996) and is not restricted to a particular cognitive domain (Banich, 1997; Smith and Jonides, 1999). Therefore, cognitive control represents the overarching ability to maintain context for appropriate behavior in a given situation in the face of interference (such as through the activation of prepotent response tendencies) and impaired cognitive control would be expected to lead to a range of cognitive deficits across a broad range of 'domains' of higher cognition. The model of cognitive control deficits in schizophrenia described in this paper focuses on the contribution of the DLPFC in maintaining task context and guiding processing across the brain in a task appropriate manner.

COGNITIVE CONTROL DEFICITS IN SCHIZOPHRENIA: EVIDENCE FOR A PREFRONTALLY BASED DISORGANIZATION SYNDROME

Research on the role of the DLPFC has been a topic of interest to schizophrenia researchers for over three decades, as early studies of cerebral blood flow showed reductions in anterior to posterior resting gradients in patients (Ingvar and Franzen, 1974). Follow-up studies by Weinberger *et al* (1986) showed reduced activity in the DLPFC during the Wisconsin Card Sorting task for both medicated and unmedicated patients. Since those studies, many authors have reported decreased prefrontal activation (see Andreasen *et al* (1992) and Buchsbaum *et al* (1996) for early reviews or Glahn *et al* (2005) for a more recent review of activation studies). Such findings are not consistently reported across the literature (Glahn *et al*, 2005; Gur and Gur, 1995; Manoach *et al*, 1999), and this may be related to the selection of tasks that do not reliably activate the DLPFC in healthy controls (Carter *et al*, 1998; Taylor *et al*, 1994). Previous studies in our lab have consistently observed reduced DLPFC activity during cognitive control tasks in schizophrenia, which has been associated with impaired task performance and behavioral disorganization (Barch *et al*, 2001; Carter *et al*, 1998; MacDonald *et al*, 2005; Perlstein *et al*, 2001; Snitz *et al*, 2005; Yoon *et al*, 2008a) irrespective of patient medication status (MacDonald *et al*, 2005). Interestingly, although DLPFC activity has been reliably decreased in these studies,

posterior regions of VLPFC show normal activation patterns in patients (Barch *et al*, 2001; MacDonald *et al*, 2005; Perlstein *et al*, 2001), suggesting a pattern of reduced DLPFC activation with normal VLPFC functioning in schizophrenia (Glahn *et al*, 2005; Wolf *et al*, 2007). A meta-analysis of 41 neuroimaging studies of executive function in schizophrenia revealed similar findings of reduced activation in patients within bilateral DLPFC, ACC, and mediodorsal thalamus (Figure 2; Minzenberg *et al*, 2009).

Recently, Yoon *et al* (2008b) utilized fMRI and an abbreviated version of the AX-Continuous Performance Task (AX-CPT) to examine the relationship between DLPFC activation and cognitive and psychosocial functioning in the early phase of schizophrenia. In the AX-CPT, subjects make a target response to the probe letter X, *only* when it follows the cue letter A. All other stimuli require a non-target response, including trials in which X is preceded by any letter other than A (collectively referred to as cue B trials). Trials with target (AX) cue–probe pairings occur with high frequency (70%), setting up the tendency to make a target response to the X probe. The BX condition requires the highest cognitive control, as subjects must overcome the tendency to make a target response to X. First episode schizophrenia participants showed a pattern indicating poor cognitive control with increased BX relative to AY errors, which is consistent with previous findings of a specific deficit in first episode individuals (MacDonald and Carter, 2003a), and this impairment was associated with reduced activation of the DLPFC when compared with normal controls. Using the beta series correlation method (Rissman *et al*, 2004), whole-brain functional connectivity was measured by examining within-subjects correlations between the time series in the DLPFC seed region and the rest of the voxels in the brain. In control subjects, DLPFC activity during this task was correlated with the activation of a distributed frontoparietal network required to support optimal task performance. In contrast, first episode patients showed a significant reduction of DLPFC-related functional connectivity, as they did not engage the same frontoparietal network under conditions requiring high cognitive control. Importantly, the level of DLPFC connectivity was associated with increased symptoms of disorganization and poorer psychosocial functioning in the first episode sample. This pattern of results is strongly consistent with the notion that impaired PFC function is associated with an inability to exert top-down control over the task appropriate distributed network and suggests a basis for the association between a PFC-based disorganization syndrome in schizophrenia and functional impairment in the illness.

As noted previously, individuals with schizophrenia show cognitive impairment in other domains, such as episodic memory (Aleman *et al*, 1999). Structural abnormalities in medial temporal regions found in individuals with schizophrenia (Shenton *et al*, 2001; Steen *et al*, 2005), specifically the hippocampal region (Heckers, 2001), may contribute to the observed impairment in memory functioning. However, recent meta-analyses (Ragland *et al*, 2009; Ranganath *et al*, 2008) suggest that episodic memory impairment in schizophrenia may be, in part, the result of impaired prefrontal cognitive control mechanisms, which help to guide encoding and retrieval processes. Specifically, Ragland *et al* (2009) examined 18 functional neuroimaging studies of episodic memory encoding and retrieval in individuals with schizophrenia and healthy controls. Results showed decreased activation of prefrontal regions, including the dorsolateral and ventrolateral prefrontal cortices, but not medial temporal regions during encoding and retrieval when compared with healthy controls. When the participants were provided with an encoding strategy, decreased activation was still observed in the dorsolateral prefrontal region, with no difference observed in the ventrolateral prefrontal region, suggesting that this area may serve to compensate for continued impairment in dorsolateral prefrontal functioning. In contrast to expectation, no reliable findings were found in the hippocampus, whereas increased activation was observed in the parahippocampal gyrus during encoding and retrieval, which was again interpreted as serving a potential compensatory role. Taken together, these findings suggest that prefrontal cognitive control deficits may be related to many aspects of cognitive impairment that are associated with schizophrenia.

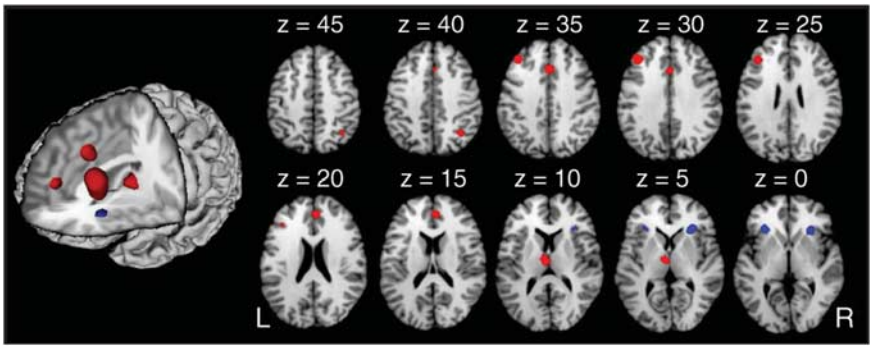

Figure 2. Regions in which patients with schizophrenia showed co-occurring hypoactivation compared with controls across a full set of executive function studies (reprinted with permission from Minzenberg *et al*, 2009).

COGNITION AS A MARKER OF RISK FOR SCHIZOPHRENIA AND THE RELATIONSHIP TO COGNITIVE CONTROL

In addition to its role as a predictor of clinical and psychosocial functioning for those individuals diagnosed with schizophrenia, impaired cognition may also represent an endophenotype, or intermediate trait that lies between an underlying genetic vulnerability and expression of the clinical phenotype that can be used to identify individuals at greatest risk for the illness. Unaffected first-degree relatives of individuals with schizophrenia consistently show deficits on measures of executive function and processing speed (Egan *et al*, 2001a; Faraone *et al*, 1995; Franke *et al*, 1993; Keefe *et al*, 1994; Kuha *et al*, 2007), attention (Faraone *et al*, 1995, 1999; Finkelstein *et al*, 1997; Mulet *et al*, 2007), and verbal memory (Faraone *et al*, 1995, 1999; Habets *et al*, 2008). Cannon *et al* (2000b) showed that frontally mediated deficits on neuropsychological measures of attention and working memory were associated with increasing genetic liability to schizophrenia and were equally impaired in affected and unaffected monozygotic (MZ) co-twins, whereas deficits in temporally mediated verbal episodic memory were significantly more pronounced in the affected members of discordant MZ pairs. This finding supported previous work by Harris *et al* (1996), who showed that a subset of relatives in multiply affected families showed deficits on a measure of set shifting and processing speed when compared with normal controls.

A recent meta-analysis by Snitz *et al* (2006) showed that first-degree relatives showed a wide range of effect sizes across tasks, with the largest effect sizes seen on Trails B, CPT-X d-prime, and CPT-AX/-IP d-prime and false alarms. The authors concluded that cognitive deficits, particularly those involving executive control, working memory, and inhibition, may be the most likely to yield positive results in the search for genes conferring risk for schizophrenia. These data, along with evidence of cognitive dysfunction early in childhood (Cannon *et al*, 2000a; Cornblatt *et al*, 1999; Erlenmeyer-Kimling *et al*, 2000; Jones *et al*, 1994; Niendam *et al*, 2003; Russell *et al*, 1997) and impaired cognition at the onset of the illness, implicate a neurodevelopmental pathophysiological mechanism that leads to illness onset.

EVIDENCE FOR COGNITIVE CONTROL DEFICITS IN GENETIC HIGH-RISK SAMPLES

Given strong evidence of morphometric, functional, and behavioral dysfunction of the PFC and associated cognitive control tasks in patients, a body of work has examined whether cognitive control deficits are associated with a genetic liability for the disorder. Many studies have highlighted impairment in frontally mediated executive functions in both adult (Cannon *et al*, 2000b; Egan *et al*, 2001a; Faraone *et al*, 1995; Finkelstein *et al*, 1997; Franke *et al*, 1993; Keefe *et al*, 1994) and child genetic high-risk samples (Cornblatt, 2002; Cosway *et al*, 2000; Johnstone *et al*, 2002; Wolf *et al*, 2002). More specifically, deficits in cognitive control have also been shown in first-degree relatives of individuals with schizophrenia. MacDonald *et al* (2003b) used the expectancy version of the AX-CPT task to show a specific deficit in context processing that was associated with genetic liability. Specifically, they found that patients and siblings performed better on AY relative to BX trials, which implied worse context processing, compared with controls who performed better on BX relative to AY trials. A follow-up study utilizing the expectancy variant of the AX-CPT revealed significantly greater BX errors in siblings as well as increased activity throughout the cognitive control network compared with controls (Delawalla *et al*, 2008). Other measures of cognitive control, such as the Stroop (Filbey *et al*, 2008) and antisaccade task (Calkins *et al*, 2004), have also been shown to be associated with genetic liability. Becker *et al* (2008) used fMRI to evaluate relatives' performance and neural activity on a single-trial version of the Stroop task. Although behavioral performance was similar for relatives and controls, relatives showed increased activity in right dorsal and ventral PFC and left parietal cortex, as well as significantly decreased activity in the left dorsal PFC. In contrast, Thermenos *et al* (2004) showed increased activity in the left DLPFC in relatives compared with controls on the Q3A-INT task, which is a variant of the AX-CPT, in which subjects maintained the context of an auditory cue while being presented with distracting auditory information.

Converging evidence from structural neuroimaging studies also highlights the association between reduced gray matter volume and density in the PFC and genetic liability. Specifically, gray matter volume reductions have been noted in the DLPFC (Diwadkar *et al*, 2006) and anterior cingulate cortex (Job *et al*, 2003), as well as decreased cortical thickness in the anterior cingulate (Goghari *et al*, 2007) in unaffected first-degree relatives. Cannon *et al* (2002) utilized a twin design to show significantly decreased prefrontal gray matter volume (including DLPFC and polar PFC) that was associated with increasing genetic risk for schizophrenia.

The search for predictors of the development of schizophrenia has revealed a similar set of cognitive, neurofunctional, and structural brain abnormalities in individuals at genetic high risk. Although few genetic high-risk studies have employed longitudinal follow-up designs, the development of psychosis in adulthood in the offspring of individuals with schizophrenia has been associated with impairment in cognitive control as measured by the Stroop task (Johnstone *et al*, 2002). In addition, lower gray matter density in the left inferior temporal gyrus, uncus, and right cerebellum was found over follow-up in individuals who subsequently developed schizophrenia (Job *et al*, 2005). Increased prefrontal cortical folding has also been associated with subsequent development of psychosis (Harris *et al*, 2004a, b, 2007), providing evidence that abnormal development of prefrontal gray matter may contribute to later illness onset. Functionally, increased

parietal activation and reduced anterior cingulate activation was associated with the later development of schizophrenia in the Edinburgh High Risk sample (Whalley *et al*, 2004, 2006). These findings highlight the potential role of genes as a contributor to structural changes in prefrontal and parietal regions, which lead to observed deficits in cognitive control for both affected and unaffected risk groups.

APPLYING PREFRONTAL ENDOPHENOTYPES TO THE GENETIC STUDY OF SCHIZOPHRENIA

Family, twin, and adoption studies indicate that schizophrenia has a large genetic component, on the order of 65–85% (Cannon *et al*, 1998; Cardno *et al*, 1999; Kendler and Diehl, 1993; Sullivan *et al*, 2003). Given that transmission of the disorder has not been linked to a major gene, schizophrenia is generally thought to be associated with multiple genes of small effect, including both common variants and rare but highly penetrant copy number variants or CNVs (Karayiorgou and Gogos, 1997). Identification of the molecular genetic basis of the disorder has been challenging owing to this polygenic inheritance as well as to genetic heterogeneity and a non-trivial environmental component, which is show by incomplete concordance for schizophrenia in MZ co-twins (Cannon *et al*, 1998). In addition, the phenotypic presentation of the disorder is markedly heterogeneous, with varying expression of core features of positive, negative, and cognitive symptoms. Given the phenotypic and genetic complexity of schizophrenia, the utilization of neural and cognitive endophenotypes may offer additional power to detect susceptibility loci by examining traits closer to the mechanism of abnormal gene action. In addition, the quantitative nature of these data allows for examination of the trait in unaffected relatives, as well as offering greater resolution in mapping genes of small effect. Although the use of cognitive or neuroimaging endophenotypes has often been highlighted as a way to facilitate the identification of genes associated with the pathophysiology of schizophrenia, the identification of functional variants remains, to date, somewhat elusive. Therefore, we will discuss current findings on two potential genetic linkages that have shown consistent relationships with prefrontally mediated cognition.

Two genes, *DTNBP1* (ie, *dysbindin*) and *catechol-o-methyltransferase* (*COMT*), have arguably garnered the most support as potential contributors to impaired PFC cognition in schizophrenia (for a review, see Joyce and Roiser, 2007). *Dysbindin* codes for a protein that is expressed within the forebrain glutamatergic neurons and interacts with proteins involved in vesicular transport and glutamate release. Using a mouse model, Jentsch *et al* (2009) showed that mice carrying a null mutation in the *dysbindin* gene showed impairments of spatial working memory in a gene dose-dependent manner. These data provide support for a putative mechanism for prefrontal dysfunction in schizophrenia, suggesting that altered regulation of glutamatergic circuits in the PFC may play a role in the cognitive phenotype of the disorder. Generally, the *dysbindin* high-risk haplotype has been associated with cognitive decline, as measured by a decrease in IQ of 10 points (Burdick *et al*, 2007), although the *dysbindin* genotype only accounted for 2.2% of the variance in cognitive decline. Donohoe *et al* (2007) found lower spatial working memory performance in patients carrying the *dysbindin* risk haplotype, in which the *dysbindin* haplotype explained 12% of the variation in working memory performance. In agreement with animal studies mentioned previously (Jentsch *et al*, 2009), *dysbindin* has been associated with altered activation within the DLPFC during working memory (Markov *et al*, 2010). Specifically, the authors found that healthy subjects who carried the risk allele showed greater activation in DLPFC compared with non-carriers. In patients with schizophrenia, the high-risk allele has been associated with reduced gray matter volume in the PFC (Donohoe *et al*, 2010).

COMT is an enzyme involved in synaptic dopamine (DA) catabolism that has an important role in the PFC, in which there are relatively fewer DA transporters (Sesack *et al*, 1998). The majority of studies investigating cognitive performance and *COMT* have focused on the $val^{158}met$ polymorphism (for a recent review, see Tan *et al*, 2009). In patients with schizophrenia, loading of the *COMT met* allele conferred enhanced cognitive performance on the Wisconsin Card Sorting Test, a measure of executive function, and a more efficient physiological response in the PFC during an N-back working memory task (Egan *et al*, 2001b). Other complementary studies identified an association between the *val* allele and impaired performance on working memory (Wirgenes *et al*, 2010; Woodward *et al*, 2007) and attention (Bilder *et al*, 2002). However, others have either been unable to replicate these findings (Ho *et al*, 2005; Szoke *et al*, 2006) or have even found incongruent results. For example, Neuhaus *et al* (2009) found that poor performance on the signal discrimination index of the CPT-IP was associated with the *met* variant in a gene dose-dependent manner. The presence of the $val^{158}met$ genotype in patients has also been associated with opposite effects in brain activation compared with controls, such that control subjects with the homozygous *met* genotype showed greater activity on a verbal fluency task in the frontal operculum, parietal operculum, and middle temporal gyrus than those with the homozygous *val* genotype (Prata *et al*, 2009). These findings were reversed for the patient group, such that patients with the homozygous *met* genotype showed less activity in these regions compared with patients with the homozygous *val* genotype. Moreover, a similar genotype by group interaction was found on behavioral performance measures, as the loading of the *met* allele in patients and the *val* allele in controls was associated with better performance. These data have prompted the development of an altered efficiency model, which posits that loading of the *met* allele in patients, and higher availability of DA in the PFC, is associated with better performance,

whereas loading of the *met* allele in healthy subjects may push DA availability and cortical function beyond the optimal range. Such a discrepancy between healthy controls and patients was also illustrated in a meta-analysis of *COMT* genotype and WCST performance, in which genotype was associated with perseverative errors in healthy controls but not in patients with schizophrenia (Barnett *et al*, 2007). Although there is evidence for an association with *COMT* and prefrontally biased cognition, the effect on risk for schizophrenia is small and inconsistent based on recent meta-analyses (Allen *et al*, 2008; Fan *et al*, 2005; Munafo *et al*, 2005; Okochi *et al*, 2009).

In addition to *COMT* and *dysbindin*, a number of other candidate genes have been identified by linkage and targeted association studies, including *neuregulin 1* (*NRG1*), *disrupted in schizophrenia 1*, and *d*-amino-acid oxidase. *NRG1* in particular codes for a trophic factor with a range of functions that includes the modulation of γ-aminobutyric acid (GABA)-ergic transmission, which is critical for PFC-mediated cognition and will be described in greater detail later in the review (Mei and Xiong, 2008).

Although a comprehensive analysis of this literature is outside the scope of this review (for a review, see Eisenberg and Berman, 2010), it is important to note that there is substantial disagreement as to how to interpret the existing genetic association data (O'Donovan *et al*, 2009). Some researchers may place more emphasis on genes with more modest empirical support but with strong pathophysiological relevance to the disorder, whereas others may be more agnostic to the mechanism of gene action and primarily concerned with a strong, reliable association. Although the candidate genes mentioned above all have putatively strong pathophysiological mechanisms relevant to schizophrenia, given that they impinge upon prefrontal systems, none of the genes yet identified remain unchallenged and all await further study. Moreover, our ability to elucidate the genetic underpinnings of the disorder may increase as genetic association studies move towards tasks generated from the cognitive neuroscience literature that tap specific cognitive control processes.

EVIDENCE FOR COGNITIVE CONTROL DEFICITS IN CLINICAL HIGH RISK

Although most individuals with schizophrenia experience the onset of clinical symptoms during late adolescence and early adulthood, deficits in cognition are evident years before the development of psychotic symptoms, during childhood and adolescence (Cannon *et al*, 2000a; Cornblatt *et al*, 1999; Erlenmeyer-Kimling *et al*, 2000; Jones *et al*, 1994; Niendam *et al*, 2003; Russell *et al*, 1997). These cognitive deficits are hypothesized to accelerate during the prodromal period in association with changes in brain functioning that lead to the development of psychotic symptoms (Feinberg, 1982; McGlashan and Hoffman, 2000). Such neurological changes may also lead to functional decline in a variety of domains (Cosway *et al*, 2000). Therefore, deficits in cognition in high-risk samples not only serve as markers of risk, but changes in such deficits over time may differentiate those individuals who convert to psychosis or experience functional disability from those who do not.

Impairment in multiple cognitive domains are reported in clinical high risk (CHR) samples (McGlashan, 2001; Miller *et al*, 2002), with the most pronounced deficits observed on measures of frontal and temporal lobe functions, including attention, working memory, processing speed, executive functioning, and verbal learning and memory (Bartok *et al*, 2005; Brewer *et al*, 2005; Eastvold *et al*, 2007; Francey *et al*, 2005; Gschwandtner *et al*, 2003, 2006; Hambrecht *et al*, 2002; Hawkins *et al*, 2004; Keefe *et al*, 2006; Lencz *et al*, 2006; Niendam *et al*, 2006, 2007; Pukrop *et al*, 2007, 2006; Silverstein *et al*, 2006; Simon *et al*, 2007; Smith *et al*, 2006; Wood *et al*, 2003b). Evidence of impairment on computerized measures of prefrontal cognitive functioning in CHR youth when compared with normal controls has also been reported (Francey *et al*, 2005; Gschwandtner *et al*, 2003, 2006; Hambrecht *et al*, 2002; Hawkins *et al*, 2004; Keefe *et al*, 2006; Lencz *et al*, 2006), although CHR individuals showed better performance than individuals with first-episode schizophrenia (Hambrecht *et al*, 2002; Hawkins *et al*, 2004; Keefe *et al*, 2006). Overall, impairments on measures of prefrontal cognitive functioning, including spatial working memory (Wood *et al*, 2003b), antisaccade eye movements (Nieman *et al*, 2007), olfactory identification (Brewer *et al*, 2003), and rapid information processing (Brewer *et al*, 2005; Lencz *et al*, 2006), are associated with conversion to psychosis.

When compared with healthy controls, CHR individuals also show a variety of structural and functional abnormalities, including reduced gray matter density in frontal, temporal, and subcortical brain regions (Borgwardt *et al*, 2007b; Hurlemann *et al*, 2008; Jung *et al*, 2009; Phillips *et al*, 2002; Witthaus *et al*, 2008; Wood *et al*, 2005), as well as reduced *N*-acetylaspartate (NAA) in frontal regions (Jessen *et al*, 2006; Wood *et al*, 2003a). The frequency of neurodevelopmentally associated abnormalities was also higher in CHR samples when compared with healthy controls (Choi *et al*, 2008; Takahashi *et al*, 2008a, b; Yucel *et al*, 2003).

Few neuroimaging studies focused on frontal functioning in CHR samples have been published to date. Morey *et al* (2005) examined frontal and striatal functions during a visual oddball paradigm in CHR, first episode, chronic schizophrenia, and healthy control samples. Behaviorally, the CHR individuals' performance was intermediate between the healthy control and first episode samples. In addition, the CHR group showed significantly smaller differential activation between task-relevant and task-irrelevant stimuli in the frontal regions (ACC, inferior frontal gyrus, middle frontal gyrus) than the control group. Similarly, CHR individuals have shown intermediate activation relative to controls and schizophrenia patients during a working memory task (N-back) in the DLPFC, inferior frontal, and parietal cortices (Broome *et al*, 2009).

Fusar-Poli *et al* (2010) replicated this finding of reduced DLPFC and parietal activation in response to the N-back in combination with fluorine 18-labeled fluorodopa PET. The authors revealed that, within the at-risk group, the degree of abnormality in the PFC (ie, attenuated DLPFC activation) was associated with the severity of striatal DA dysfunction (ie, elevated Ki value). This relationship was reversed in the control group, such that prefrontal activation during working memory was positively correlated with the level of striatal DA function. This pattern of results was presented as evidence of an inverted U relationship compatible with models of working memory that suggest there is an optimal level of DA activity associated with maximal efficiency of working memory performance (Williams and Castner, 2006). Taken together, these studies show that CHR individuals have difficulty activating the cortical network that underlies effective cognitive control processes and provide important evidence supporting the potential role of abnormalities in this network as a marker of risk for psychosis.

A recent review of this literature by Wood *et al* (2008) noted that impairments in prefrontal cognitive functioning, and the underlying neurobiological abnormalities, provide the most likely marker of conversion risk. In CHR samples, conversion to psychosis was associated with reduced gray matter density in frontal, temporal, and parietal regions (Borgwardt *et al*, 2007a, b, 2008; Fornito *et al*, 2008; Pantelis *et al*, 2003, 2005), although such findings were not consistent for analyses of the hippocampus (Phillips *et al*, 2002). Reductions in NAA in the anterior cingulate cortex (Jessen *et al*, 2006), thickness of the anterior genu of the corpus callosum (Walterfang *et al*, 2008b), and reduced serotonin receptor density in frontotemporal gray matter (Hurlemann *et al*, 2008) were also associated with conversion. Frontal white matter tracts, specifically the fronto-occipital fasciculus and left superior longitudinal fasciculus, were also reduced in size for CHR individuals who subsequently developed psychosis (Walterfang *et al*, 2008a). Taken together, these findings suggest that investigations of frontally mediated cognitive functions through functional neuroimaging hold the most promise as markers of risk for clinical, and potentially functional, deterioration in at-risk samples.

IMPLICATIONS OF HIGHER COGNITIVE DYSFUNCTION AND THE DEVELOPMENTAL PATHWAY PRECEDING SCHIZOPHRENIA

As noted above, cognitive deficits are present at the onset of the psychotic phase of the illness, during the prodromal phase, and even in those at risk for the illness. Consequently, schizophrenia has been conceptualized as a neurodevelopmental disorder in which genetic and environmental etiological factors affect processes related to brain development that in turn result in the clinical expression of the disorder during adolescence, itself a time of rapid brain development. According to the neurodevelopmental hypothesis of schizophrenia originally proposed by Feinberg (1982), abnormal pruning of synaptic connections in the cortex during adolescence leads to the onset of psychotic symptoms. In normal development, the pruning of superfluous synaptic connections during normal brain development results in increased efficiency and specialization of cortical and subcortical areas; however, in schizophrenia it is hypothesized that environmental stress and/or genetic liability could alter the pruning process and cause an abnormal rate or pattern of synaptic elimination, resulting in the development of psychotic symptoms.

Using a computer simulation of the pruning process, McGlashan and Hoffman (2000) showed how the pruning of connections above a particular threshold resulted in cognitive impairment as well as the appearance of 'hallucinations' during tasks of speech perception. In their model, the pruning process can advance at varying levels of intensity, with the most aggressive pruning leading to the earliest onset of psychosis and reduced opportunity for later recovery. Conversely, by decreasing the baseline level of available connections, it was shown that early brain insult could reduce the neuronal reserve, in which case a normal pruning process would be sufficient to cross the threshold into psychotic symptoms. Therefore, early brain injury in the form of prenatal insult (eg, Brown and Derkits, 2010; Cannon *et al*, 2000c), postnatal environmental stress (eg, van Winkel *et al*, 2008), and/or abnormal rates of synaptic pruning during adolescence could work alone or in conjunction to push an individual past the threshold into psychosis.

Empirical evidence has accumulated to support this notion. In a post-mortem study of individuals with schizophrenia, Selemon *et al* (1995) showed abnormally high neuronal density in the prefrontal and occipital cortices. A previous hypothesis attributed decreased cortical gray matter volume to the effects of widespread neuronal cell death (Weinberger, 1987). However, Selemon and Goldman-Rakic (1999) associated the increased density of cells, in the context of reduced volume, with the loss of neuropil, or interconnections between the neurons, which could be the result of excessive pruning. Glantz and Lewis (2000) provided additional support for this hypothesis by showing decreased dendritic spine density in the layer 3 pyramidal neurons of the DLPFC. Therefore, whereas the process of synaptic pruning in normal development serves to increase the efficiency of brain functioning, the observed deficits in schizophrenia may be related to an overly aggressive pruning process that reduces neuronal interconnection to a detrimental level, leading to the development of psychotic symptoms and related cognitive dysfunction that may become manifest during the prodromal period. Alternatively, an initially depleted neuronal connectivity, which may be associated with early brain insult, could lead to symptoms of schizophrenia if subsequent normal pruning processes decrease that connectivity further, crossing a hypothetical threshold beyond which the capacity for integrated cognitive and emotional

activity is severely compromised. Recently, Reichenberg *et al* (2010) used long-term follow-up data to examine cognitive development between the ages of 7 and 13 in the Dunedin birth cohort. Examination of cognitive variables revealed that individuals who later develop schizophrenia showed deficits in verbal and visual knowledge, comprehension and reasoning at age 7, as well as a slowing in the development of processing speed, working memory, and visual–spatial reasoning as they progress through puberty. These findings support an integrated model of aberrant cognitive development in schizophrenia, incorporating both a static cognitive deficit that is apparent early in childhood as well as a developmental lag in cognitive domains supporting attention and working memory as they grow through adolescence.

THE ROLE OF MICRO- AND MACRO-CIRCUIT DYSFUNCTION IN IMPAIRED COGNITIVE CONTROL IN SCHIZOPHRENIA

Given convergent findings from structural and functional neuroimaging studies, post-mortem data, and genetic association studies that implicate the PFC as a region associated with the cognitive deficits that characterize schizophrenia, a large body of work has led to a search for pathophysiological mechanisms associated with interneuron connectivity within the PFC (micro-circuits) as well as regional connectivity (macro-circuits). Sustained firing of pyramidal neurons within the DLPFC during engagement in a working memory task has been shown to be crucial to successful task performance (Goldman-Rakic, 1995; Wilson *et al*, 1994). Changes in local circuit function in the PFC may contribute to failure of this region to recruit task appropriate networks across the brain and lead to disorganized brain function and behavior in schizophrenia. Although such a hypothesis can only be directly tested at this time in animal models, functional neuroimaging findings of altered BOLD signal within DLPFC have generally been the closest proxy. Relevant to this, Logothetis and others (Logothetis *et al*, 2001; Murayama *et al*, 2010; Niessing *et al*, 2005) recorded directly from neuronal populations during fMRI to show that the BOLD signal is most strongly related to population neuronal activity, as reflected in field potentials, and specifically to synchronous neuronal activity in the high-frequency gamma (30–80 Hz) range. This is particularly significant in view of the results of post-mortem studies in schizophrenia. Reduced GABA release by the parvalbumin subclass of GABA-ergic interneurons in the PFC and other regions of the brain is suggested by a range of post-mortem findings reported across a number of laboratories (for a review, see Gonzalez-Burgos and Lewis, 2008; Lewis *et al*, 2005). Other studies, including those cited above, suggest that there is altered thalamocortical connectivity, including possibly decreased neuronal numbers in the thalamus as well as reduced dendritic spines on pyramidal cells in the thalamic recipient zones of Brodmann area (BA) 9. Projections from medial dorsal thalamus to DLPFC are critical for initiating and maintaining gamma band activity (Jones, 1997), whereas chandelier cells gate the timing of synchronous activation of populations of pyramidal neurons by targeting the axon initial segment of pyramidal cells through membrane receptors with fast spiking calcium channels. These post-mortem disturbances would be predicted, in life, to be associated with impairments in prefrontal gamma activity and an associated reduction in cognition-related BOLD activity.

Oscillatory activity in the gamma range is readily recorded from the human EEG and there has been increasing interest in both normal cognitive neuroscience and in the study of schizophrenia in recent years. Oscillatory activity can be *evoked* or *induced* (Galambos, 1992). *Evoked* gamma responses are temporally locked to stimuli and typically thought to reflect perceptual processes; *induced* gamma band responses represent signals independent of evoked ones, typically appearing later during a trial of a task, with a jittered latency across trials, and are thought to be associated primarily with higher cognitive processes (for a review, see Tallon-Baudry and Bertrand, 1999a). For example, in studies of visual working memory, many investigators (Howard *et al*, 2003; Tallon-Baudry and Bertrand, 1999a; Tallon-Baudry *et al*, 1998, 1999b) have reported *induced* gamma band responses over frontal leads during delay periods of working memory tasks. Although these data are often interpreted as being related to the maintenance of information in working memory, a substantial literature in cognitive neuroscience suggests that the DLPFC maintains *context representation* during working memory tasks, in support of task appropriate responding (Miller and Cohen, 2001) based on items stored in ventral PFC and posterior areas. This raises the possibility that alterations in PFC gamma band oscillatory functions related to forming and maintaining a context representation might be impaired in schizophrenia and related to impaired cognitive control. Disturbances in local micro-circuits in the PFC and an inability to generate sustained oscillatory activity in this region may form the basis for disrupted top-down support to task-relevant circuits across the brain at a macro-circuit level, leading to impaired task-related cognitive activity and behavioral disorganization in the illness. Cho *et al* (2006) reported a reduction in PFC-related gamma activity in schizophrenia during cognitive control, a finding that was also related to impaired task performance and behavioral disorganization in the patient group. Figure 3 summarizes an integrated model in which altered local micro-circuit function disrupts high-frequency oscillations in the PFC, leading to a failure of top-down support for the recruitment of task appropriate macro-circuits or distributed networks in the brain, resulting in impaired task appropriate behavior, clinical disorganization, and impaired functioning in schizophrenia. This model integrates decades of research that has focused on DLPFC dysfunction in schizophrenia, while providing detailed links between cellular mechanisms, altered neurophysiology, and the clinical phenotype of

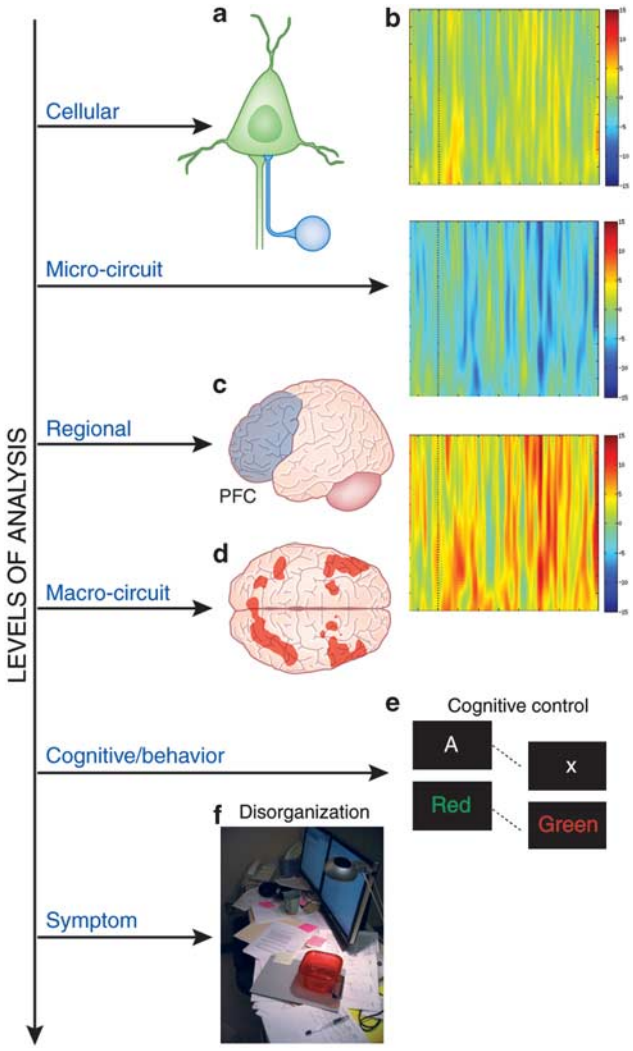

Figure 3. From cells to circumstantiality: a unified model outlining (a) γ-aminobutyric acid (GABA)-ergic cellular abnormalities, (b) 'micro-circuit' gamma oscillatory function, (c) regional recruitment of the prefrontal cortex (PFC) in mediating cognitive control, (d) engagement of the 'macro-circuit', the coordinated activation of frontal and parietal regions as a neural system, (e) cognitive/behavioral performance on cognitive control tasks (eg, AX-Continuous Performance Task (AX-CPT) and Stroop), and (f) disorganization symptoms.

schizophrenia. This specific pathophysiological conceptualization can help guide future genetic studies by providing specific cognitive and neural endophenotypes. In addition, this model has the potential of enhancing the identification and development of novel treatment targets, such as partial agonists at the α_2-subunit of the GABA-A receptor (Lewis *et al*, 2008a), as well as aiding the development of new biomarkers for use in the future for diagnosis and risk identification.

IMPLICATIONS FOR PHARMACOLOGY OF HIGHER COGNITION IN SCHIZOPHRENIA

Current consensus supports cognitive dysfunction as a critical treatment target in schizophrenia. The FDA has recently agreed to consider cognitive dysfunction as a discrete indication for approval of new pharmacological agents in schizophrenia (Buchanan *et al*, 2005). Among the existing FDA-approved pharmacopoeia, considerable recent research has addressed the potential of atypical antipsychotic medication for remediation of cognitive dysfunction. It has been proposed that this advantage may arise from unique pharmacological actions of the atypical antipsychotics as these medications elevate catecholamines and glutamate in the cortex, particularly the PFC (Meltzer and Huang, 2008; Stip *et al*, 2005). These effects would likely be owing to direct antagonism of serotonergic and adrenergic receptors, which are located on catecholamine and glutamatergic terminals, and serve to inhibit neurotransmitter release. Nonetheless, the clinical literature addressing effects of atypical antipsychotics on cognition in schizophrenia is plagued by several important methodological problems (Goldberg *et al*, 2007); (Carpenter and Gold, 2002; Carter, 2005; Harvey and Keefe, 2001; Montgomery *et al*, 2004; Weiss *et al*, 2002), contributing to considerable heterogeneity in existing findings with regard to the effects of these medications on cognition. As a result, there is an emerging consensus that there is no strong evidence for atypical antipsychotic remediation of cognition in schizophrenia and there remains a great need to identify and develop truly novel agents for this indication.

Several neurotransmitter systems in the brain have critical roles in supporting the neural networks believed to be impaired in schizophrenia, including the PFC, and offer potential treatment targets for cognition. Perhaps, the most well established are the two primary catecholamine systems, DA and norepinephrine (NE). The DA hypothesis of schizophrenia has been an enduring framework for investigation of the pathophysiology of this illness, and recent evidence has elaborated the role of this neurotransmitter system (Carlsson and Carlsson, 2006). Seamans and Yang (2004) outlined an elegant theory of DA modulatory function in the PFC, such that breadth and salience of information in working memory is controlled by DA PFC inputs. This model has relevance to schizophrenia as a chronic state of hypodopaminergia has been implicated in the PFC of schizophrenia patients, with decreased tyrosine hydroxylase binding (Akil *et al*, 1999) and increased D1 binding, which may represent a compensatory upregulation in response to a chronic deficit of synaptic DA (Abi-Dargham *et al*, 2002). This could contribute to PFC-dependent cognitive deficits, as research shows that 6-OHDA lesions in the DLPFC disrupt working memory in monkeys (Brozoski *et al*, 1979). The D1 receptor appears critical in delineating PFC DA effects, as microinjection of D1 antagonists (but not D2 antagonists) into the DLPFC disrupts working memory-guided saccades (Sawaguchi and Goldman-Rakic, 1994). In studies of healthy adult humans as well as patients with schizophrenia, amphetamine improves working memory (Barch and Carter, 2005), with associated changes in DLPFC activity measured by fMRI (Mattay *et al*, 2000). The D1/D2 agonist pergolide shows

specific benefits for working memory, in contrast to other cognitive functions (Kimberg and D'Esposito, 2003). D1 receptors also modulate both long-term potentiation and long-term depression in the rodent PFC, probably through interactions with NMDA receptors, providing a cellular mechanism for DA effects on PFC plasticity (Jay, 2003; Otani *et al*, 2003). Chronic treatment of monkeys with typical or atypical antipsychotics (at clinically relevant doses) also leads to spatial working memory deficits (Castner *et al*, 2000), along with D1 receptor downregulation in PFC (Lidow *et al*, 1997). The potential exacerbation of pre-existing DA dysfunction could partly explain the lack of efficacy of existing medications for PFC-dependent cognition in schizophrenia. D4 receptors have also been targeted in schizophrenia. However, D4 antagonists do not appear to have efficacy for the symptoms of schizophrenia, and enhancements in working and episodic memory have been observed in animal models after both D4 agonists and antagonists, suggesting that the role of D4 receptor in cognition is complex and possibly multiphasic (Gray and Roth, 2007).

The ascending NE system is also implicated in PFC-dependent cognition. This relates in part to the observation that the NE transporter (NET) is largely responsible for the termination of DA action in the PFC, owing to a paucity of DA transporter protein (Moron *et al*, 2002). However, NE itself strongly modulates PFC neurons and associated cognitive processes. For instance, α_2-receptor agonists improve working memory performance in monkeys when administered either systemically or directly into the PFC (Franowicz and Arnsten, 1998). Clonidine reverses the working memory deficit induced in rats by PCP (Marrs *et al*, 2005). α_2-Receptor antagonists can reverse the benefit of α_2-agonists when co-administered, and impair memory performance when given alone (Li and Mei, 1994). These effects appear to occur at post-synaptic sites. Guanfacine also improves spatial working memory in healthy humans (Jakala *et al*, 1999). Furthermore, there is considerable evidence for NE modulation of plasticity-dependent processes, such as long-term memory consolidation, via β-adrenergic receptors in PFC and elsewhere (Tronel *et al*, 2004).

To date, agents that have adequate brain penetration and direct agonist activity at specific catecholamine receptor subtypes remain generally unavailable to test this mechanism for remediation of cognition in schizophrenia. However, a number of catecholamine transporter inhibitors are in use for other neuropsychiatric indications, particularly for attention-deficit disorder. Among these, there is evidence that low-dose amphetamine improves PFC-dependent cognitive function in schizophrenia (Barch and Carter, 2005; Daniel *et al*, 1991), and more recent evidence that modafinil improves PFC-dependent cognition in schizophrenia patients (Turner *et al*, 2004; for a review, see Minzenberg and Carter, 2008a), which may be a function of modulation of locus coeruleus neuronal activity (Minzenberg *et al*, 2008b). In addition, a small study found atomoxetine to improve working memory-related PFC activity in schizophrenia (Friedman *et al*, 2008), and inhibition of COMT with tolcapone improves cortical activity and working memory performance in healthy adults, dependent on COMT genotype (Apud *et al*, 2007). This evidence, while preliminary, suggests that the modulation of catecholamine neuronal activity, and augmentation of these neurotransmitters in the cortex, may be a safe and effective therapeutic strategy for cognition in schizophrenia.

More recently, neurons that use GABA as a neurotransmitter have become a major focus for models of pathophysiology in schizophrenia (Gonzalez-Burgos and Lewis, 2008). Post-mortem studies have found consistent evidence of reduced mRNA for the 67-kDa isoform of the enzyme that synthesizes GABA, glutamic acid decarboxylase (GAD-67), as well as reduced mRNA coding for the GABA membrane transporter (GAT1). These changes are both observed in the DLPFC in a subpopulation of GABA-ergic neurons that express the calcium-binding protein parvalbumin (Gonzalez-Burgos and Lewis, 2008). These fast-spiking interneurons exert a strong influence on the timing of cortical pyramidal cell activity as well as subthreshold membrane potentials in these cells, and are major determinants of high-frequency cortical oscillations, such as those in the gamma range (30–80 Hz). As described previously, gamma oscillations are associated with a range of higher-order cognitive processes, and are consistently impaired in schizophrenia. Interestingly, a recent study found that a partial agonist at the α_2-subunit of the GABA-A receptor remediates this oscillatory deficit in schizophrenia (Lewis *et al*, 2008a). The predominant medications currently available that act at the GABA-A receptor are the benzodiazepines, which lack pharmacological or anatomical specificity, and probably disrupt the finely tuned temporal dynamics of GABA-ergic (and thus pyramidal cell) activity. In contrast, agents that inhibit GAT1 (eg, tiagabine), for instance, may augment neurotransmission at GABA synapses while largely preserving the temporal pattern of signaling that is necessary to establish or maintain cortical oscillations. These remain to be studied for effects on cognition in schizophrenia.

Glutamate is another neurotransmitter that has been considered as a potential target for cognitive remediation in schizophrenia. There is evidence of impaired glutamatergic function in schizophrenia (Coyle, 2006), including impaired plasticity processes (Lewis and Gonzalez-Burgos, 2008b), and the clinical and biological effects of non-competitive NMDA receptor antagonists (such as ketamine and phencyclidine) suggest a role in the treatment of cognitive impairment in schizophrenia. Accordingly, enhancement of NMDA receptor function has been an emerging line of research, particularly targeting the glycine modulatory site on the NMDAR. Although initial small pilot studies suggested clinical improvement with the administration of glycine, D-serine and D-alanine, a large multi-center study found no effects on MATRICS neuropsychological measures among schizophrenia patients treated with glycine or

D-cycloserine (Buchanan *et al*, 2007). Glycine transporter inhibitors that have shown promise in pre-clinical studies, however, have not been tested to date for effects on cognition in schizophrenia patients. Allosteric potentiators of AMPA receptor function (AMPAkines) also improve cognition in animal models; however, a large multi-center study failed to show cognitive benefits with the AMPAkine CX-516 added on to existing atypical antipsychotic treatment (Goff *et al*, 2008). A study of a new agonist at the metabotropic 2/3 subtype glutamate receptor has shown promise for symptoms of schizophrenia in a phase II clinical trial; however, it remains unknown whether this is accompanied by cognitive improvement (Patil *et al*, 2007).

The central cholinergic system has also been targeted for cognitive remediation in schizophrenia. Earlier work focused on acetylcholinesterase inhibition as a mechanism to enhance synaptic acetylcholine. Although an initial pilot study showed enhanced PFC activity in schizophrenia patients on donepezil (Nahas *et al*, 2003), repeated clinical trials of AChE inhibitors failed to show improvements in cognition (Ferreri *et al*, 2006). More recently, direct nicotinic receptor agents have been tested, with an emphasis on the α7-subunit of the nicotinic receptor. A partial agonist drug with selectivity for the α7-subunit (DMXB-A) initially showed promise for cognition, with single-dose benefits on the RBANS summary score (Olincy *et al*, 2006); however, a larger phase 2 trial generally failed to show improvement in the MATRICS neuropsychological battery (Freedman *et al*, 2008). It remains unclear whether this is owing to tachyphylaxis of the nicotinic receptor in response to sustained exposure to the drug, inadequacy of the cognitive measures, some aspect of the clinical sample, or other issues. Muscarinic ACh receptors have been investigated as well. The antimuscarinic activity of the antiparkinsonian agents, as well as intrinsic antimuscarinic activity found in medications such as olanzapine, appears to exacerbate cognitive dysfunction in schizophrenia (Minzenberg *et al*, 2004; Vinogradov *et al*, 2009). More specifically, the M1 receptor subtype has been implicated in schizophrenia post-mortem studies (Crook *et al*, 2000, 2001), M1 receptor knockout mice exhibit working and long-term memory deficits (Anagnostaras *et al*, 2003), and this receptor strongly modulates cortical gamma oscillatory activity (Whittington *et al*, 2000). Although a major clozapine metabolite (NMDC) appears to be a potent M1 agonist (Sur *et al*, 2003), there is no available agent yet with sufficient selectivity for this receptor to provide an adequate test of M1 agonism in cognitive remediation.

The role of the central histaminergic (HA) neurotransmitter system in systems neuroscience and cognition has been elaborated recently. The major focus has been on the recently discovered H3 receptor, which acts as both an autoreceptor on histaminergic terminals, but importantly also as an inhibitory heteroreceptor on the terminals of several other neurochemically defined cell types (Esbenshade *et al*, 2006). These include catecholamines, and cholinergic and serotonin neurons. The central HA system serves an information-processing role quite similar to that of the cholinergic system, directly modulating various forms of attention and memory. Non-selective antihistamine medications that penetrate the brain are well known to impair a range of cognitive processes, and antagonism of the H3 terminal autoreceptor could improve cognition in part by enhancing synaptic HA. In addition, however, the indirect effects of HA antagonism (or *H3* gene knockout) at the H3 terminal heteroreceptor serve to amplify catecholamine and cholinergic modulatory effects on cortical function. This includes PFC function subserving working and long-term memory, attention, and executive functions (Esbenshade *et al*, 2006). Although it remains unknown whether there is any underlying disturbance in the HA system in schizophrenia, these HA modulatory effects on other transmitter systems and cortical function suggest a very novel target with a potentially excellent cost–benefit profile in clinical terms. Accordingly, several pharmaceutical firms have H3 antagonists in development for cognition in schizophrenia.

Finally, the endocannibinoid system has been implicated in schizophrenia, and may serve as a highly novel treatment target for both cognitive and clinical symptomatology. Epidemiological studies indicate a strong association of high levels of cannabis use and psychosis (Henquet *et al*, 2008), and acute intoxication can produce symptoms (D'Souza *et al*, 2004). There is also evidence of alterations in this system in schizophrenia, such as increased binding at the CB1 receptor, the primary cannabinoid receptor in the brain (Dean *et al*, 2001; Newell *et al*, 2006; Zavitsanou *et al*, 2004), and increased CSF levels of anandamide, the primary endogenous ligand in the brain (Giuffrida *et al*, 2004; Leweke *et al*, 1999), in schizophrenia patients. Variation in the *CNR1* gene (which codes for the CB1 receptor) is associated with both risk for schizophrenia (Ujike *et al*, 2002) and variation in clinical response to atypical antipsychotics (Hamdani *et al*, 2008). CB1 receptors function primarily to mediate retrograde signals from post-synaptic to pre-synaptic neurons and, via this mechanism, influence a range of plasticity processes (Heifets and Castillo, 2009; Lovinger, 2008). The cell types regulated by CB1 receptors include DA, glutamate, and GABA. In animal models of cognition, CB1-active agents modify various forms of memory, with antagonists remediating the adverse effects of endogenous or exogenous CB1 agonists to normalize cognition (Egerton *et al*, 2006). This suggests that CB1 antagonists may remediate the cognitive deficits inherent to schizophrenia, the adverse effects of cannabis use on cognition and clinical state, or even modify a major risk factor for the onset of this illness. Rimonabant is a CB1 antagonist that was initially tested to treat cardiovascular risk factors associated with obesity, but was withdrawn owing to safety concerns. However, this class of agents remains of interest for various clinical indications in medicine, and a test of their potential for cognitive and clinical remediation in schizophrenia is warranted.

PFC-BASED COGNITIVE CONTROL AS A TREATMENT TARGET IN SCHIZOPHRENIA

As observed above, there are varied effects of pharmacological intervention on PFC function and the range of cognitive processes supported by the PFC. This heterogeneity may arise from the diverse roles of different neurotransmitter systems in the support of these processes, and from numerous methodological factors in the existing empirical literature in both animal models and in clinical trials. Nonetheless, the construct of cognitive control may offer an integrative framework to specify a novel target for treatment development.

This warrants the consideration of pharmacology studies that use explicit cognitive control measures. This is a small literature to date and the majority of studies focused on catecholamine systems. Single-dose *d*-amphetamine (*d*-AMP) 0.25 mg/kg orally has been found to enhance speed on a classic Stroop task, both in healthy subjects and in stable schizophrenia patients (Barch and Carter, 2005), and improved accuracy in healthy subjects on the conflict condition of the Eriksen Flanker task (Servan-Schreiber *et al*, 1998). A study of healthy subjects using a lateralized version of the classic Stroop found bromocriptine to modestly improve conflict-related RT, whereas pergolide (a mixed D1/D2 agonist) was ineffective (Roesch-Ely *et al*, 2005). These findings suggest that D2 receptors may mediate the major effect of DA on control processes, possibly by modulating the rate or pattern of DA cell firing via the cell-body D2 autoreceptor. Using the AX-CPT task, a 4-week double-blind course of treatment of schizotypal personality disorder subjects with guanfacine, a specific α-2 adrenergic agonist, was associated with improved performance, as BX errors were significantly reduced and AY errors were more modestly increased, a pattern approaching that of healthy subjects (McClure *et al*, 2007). In contrast, a parenteral dose of *d*-AMP administered to rats (0.5 mg/kg subcutaneously) led to increased BX errors (but not AY errors) on an AX-CPT analog task (Maes *et al*, 2001). This may occur at higher AMP doses that push subjects to the descending limb of an inverted-U curve relating cognition to neurotransmission. Studies using electrophysiology during Flanker performance by healthy subjects have found haloperidol to attenuate both performance and the error-related negativity (ERN) (Zirnheld *et al*, 2004), whereas yohimbine augmented both the performance and the ERN (Riba *et al*, 2005). As an α-2 antagonist, yohimbine may have exerted its major effect either at the cell body, to increase action potential activity (potentially in a task-related manner), and/or to augment NE release by inhibiting the terminal autoreceptor. The effect of modafinil, a mixed DAT/NET inhibitor, on neural activity measured by fMRI during cognitive control performance suggests that modulation of LC cell-body activity may be a strong determinant of PFC-based control processes (Minzenberg *et al*, 2008b). The role of DA in performance monitoring, specifically in modulating the ERN (Holroyd and Coles, 2002) is proposed to arise from the reward prediction error. This is observed in reinforcement learning paradigms and mediated by a transient decrease in midbrain DA cell firing in response to errors or negative feedback (Schultz *et al*, 1997), disinhibiting pyramidal cells in the ACC as one result. Although this model remains to be adequately tested, it does provide a useful heuristic to guide pharmacological studies.

The role of other neurotransmitter systems in modulating cognitive control processes has been much less well studied. A few studies have found that decreased serotonin activity during Stroop performance (achieved by orally induced transient depletion of tryoptophan, a precursor to serotonin) is associated with increased neural activity in ACC and DLPFC (Horacek *et al*, 2005) and improved performance (Scholes *et al*, 2007). Given the opponent interactions between DA and serotonin (Daw *et al*, 2002), probably mediated primarily via inhibitory serotonin (5-HT2) receptors on DA neurons, an advantageous feature of candidate pro-control agents for schizophrenia may combine pro-catecholamine and serotonin antagonist activity, analogous to the combination of DA antagonist and serotonin antagonist activity for the symptomatology of schizophrenia. Another important consideration arising from this relatively small but provocative literature is that agents that alter the firing patterns of monoamine cells may have a unique potential, compared with direct post-synaptic receptor-active agents, in modulating these systems and their effects on the distributed cortical–subcortical networks that support complex cognitive processes. The potential of other neurotransmitter systems as targets to enhance cognitive control processes awaits further basic science research, both in animal models and in humans.

ALTERNATIVE MODELS FOR HIGHER COGNITIVE DEFICITS IN SCHIZOPHRENIA

Although the cognitive control model we propose here seeks to unify a number of discrete findings of deficits within the domain of higher cognitive dysfunction in schizophrenia, several alternative views have been articulated. One such view is that the range of cognitive deficits noted in schizophrenia, in fact, represents multiple distinct impairments that are each linked to individual neural systems that together produce the syndrome. In this 'multiple endophenotype' view, cognitive control processes would simply represent one of the many discrete deficits that compose schizophrenia. This view is reinforced by findings that particular morphometric features (eg, hippocampal size) and cognitive performance (eg, verbal declarative memory) may be associated with increasing genetic liability to the disorder (for a review, see Cannon and Keller, 2006; van Erp *et al*, 2004). As mentioned previously, other candidate cognitive endophenotypes have been proposed and investigated, including early sensory processing (eg, mismatch negativity, prepulse inhibition), executive dysfunction, and language dysfunction (Bertisch *et al*, 2010; Braff and Light, 2005; Calkins *et al*, 2004; Freedman *et al*, 2003;

Glahn *et al*, 2003; Gottesman and Gould, 2003; Hasenkamp *et al*, 2010; Winterer *et al*, 2003). The 'multiple endophenotype' approach has developed and maintained strength owing to the idea that each specific cognitive endophenotype may be more tightly linked to a particular functional gene that may be causal for schizophrenia. However, this drive toward cognitive and genetic specificity may have narrowed our focus too sharply and led the field away from a broader, more integrative perspective. Just as some medical illnesses can manifest with a variety of disparate physical symptoms (eg, systemic lupus erythematosis), a piecemeal approach to cognition in schizophrenia may obscure the fact that the failure of a singular overarching cognitive domain could yield a substantial proportion of the varied pattern of cognitive deficits that are observed in the disorder. Future investigations should systematically investigate the interplay between diverse cognitive systems to address the question as to whether impairment in one overarching domain, such as cognitive control, is the most parsimonious explanation for the array of higher cognitive deficits that are observed in the disorder.

Deficits have also been reported on perceptual tasks in schizophrenia, including those measuring perceptual thresholds, perceptual context effects and sensory gating, such as mismatch negativity, p50 suppression, and prepulse inhibition. There should be little doubt that perception is altered in schizophrenia given the prominence of hallucinatory behavior in the symptomatology of the illness. However, the relationship between performance on perceptual tasks and higher cognitive deficits in schizophrenia is unknown, as indeed is the relationship between different perceptual tasks themselves. Some of the tasks involving perceptual discrimination would be conceptualized by cognitive neuroscientists as perceptual decision-making tasks (Heekeren *et al*, 2004; Wendelken *et al*, 2009) and these have been shown to engage a distributed brain circuitry that includes the PFC, which is strongly engaged when subjects are pushed to their limit of perceptual discrimination. Others, such as mismatch paradigms, typically include a distractor task that involves reading or watching a movie. Functional imaging studies of these paradigms show that they also engage frontal networks (Molholm *et al*, 2005). Interestingly, in a study of perceptual organization, Silverstein *et al* (1996) showed a full recovery in performance to the normal range in patients simply by removing several conditions of the task to reduce strategy-shifting demands, suggesting a role for altered cognitive control processes in these deficits. Other work showing intact subliminal priming in the context of lowered backward masking performance also suggests that low-level visual processes may be preserved, while top-down attentional and control mechanisms may be associated with impaired performance (Del Cul *et al*, 2006). Finally, psychophysical tasks involving staircasing methods for threshold discrimination are highly sensitive to attention lapses and, whereas some studies have controlled for this (Dakin *et al*, 2005), many such studies in schizophrenia have not. Hence, it is unclear as to what degree impaired performance on some tasks involving perceptual thresholds and discrimination might also reflect a generalized performance deficit.

Finally, it could be hypothesized that altered perceptual processing could result in higher cognitive deficits related to attention, executive functions, memory, and language processing in schizophrenia in a bottom-up manner. This is unlikely, however, because many studies have shown that stimuli such as words or images are processed quite normally in schizophrenia, fully to the semantic level, where they elicit normal or even increased priming effects. The opposite pattern, reduced priming, is seen when patients are required to rely on strategic processing (Barch *et al*, 1996b; Kerns and Berenbaum, 2002; Kreher *et al*, 2009). Using a degraded stimulus version of the AX CPT, Barch *et al* (1997) showed that, unlike the pattern typically seen in schizophrenia, healthy subjects working with degraded perceptual input show a general increase in error rates (generalized deficit pattern) and did not change the level of DLPFC activation during fMRI rather than the selective increase in BX errors and decrease in PFC activation that characterizes patients with schizophrenia. Understanding the relationship between deficits on the performance of tasks engaging higher cognitive functions such as attention, executive functions, memory and language process, which can readily be accounted for by the prefrontally mediated cognitive control model, and performance on measures of different aspects of perceptual processing would bring increased coherence to our understanding of the mechanisms of impaired brain function and behavior in schizophrenia, and should be an increased focus of future research.

CONCLUSION

A large body of evidence has accumulated implicating higher cognitive dysfunction as a core feature of schizophrenia that is associated with clinical features of the disorder (eg, disorganization, negative symptoms) and functional outcome. In addition, higher cognitive deficits are present in childhood, in various risk states (eg, genetic high risk, CHR), at the onset of the illness, and stably persist throughout the course of the disorder. Given the pervasive nature of these deficits, a great deal of effort has been put forth to characterize cognitive impairment and use these data to inform our understanding of the pathophysiology of schizophrenia as well as identify treatment targets. There has also been some progress using these methods to identify functional susceptibility genes.

In this review, we have described a model of impaired cognitive control that seeks to account for a notable proportion of higher cognitive deficits that have been discussed in the schizophrenia literature. Cognitive control regulates a wide array of cognitive systems (Carter *et al*, 1998; Posner and Abdullaev, 1996) and is not restricted to a particular cognitive domain (Banich, 1997; Smith and

Jonides, 1999). For example, in addition to accounting for deficits in attention and working memory, the cognitive control model posits that episodic memory deficits may be driven primarily by frontally mediated encoding and retrieval failures rather than a hippocampally mediated inability to learn (Ragland *et al*, 2009). In addition, we outlined data that might indicate the pathophysiological basis of impaired cognitive control, starting at the 'micro-circuit' cellular level where functional alterations of the chandelier subtype of GABA-ergic interneurons in the DLPFC may result in reduced neuronal synchrony followed by subsequent prefrontal cortical dysfunction (for a review see, Lewis *et al*, 2005) and associated BOLD response reductions. Dysfunctional prefrontal recruitment of task appropriate networks during cognitive control represents 'macro-circuit' systems-level abnormalities that in turn lead to the impaired cognitive performance and behavioral disorganization.

Although we are focusing on a model of prefrontally based cognitive deficits, it is important to note that we are in no way implying that only the PFC is impaired in schizophrenia. Abnormalities in post-mortem tissue as well as morphometric and functional imaging changes have been reported in a wide range of brain regions, including the hippocampus, thalamus, superior temporal gyrus, and visual cortex (Benes *et al*, 2001; Dorph-Petersen *et al*, 2007; Ellison-Wright *et al*, 2008; Glahn *et al*, 2008; Honea *et al*, 2005; Wright *et al*, 2000). By formulating this model based on the evidence presented above, we propose that altered PFC function is likely to be a central driver in impaired cognition in schizophrenia and that a detailed understanding of the nature of impaired function in this neural system can inform our understanding not only of cognitive deficits in schizophrenia but also key targets for intervention. Importantly, our model, which attempts to link impaired local circuit dysfunction in the DLPFC to impaired distributed network dysfunction and a broad range of cognitive and functional impairments, has implications far beyond the simple notion that the DLPFC is affected in schizophrenia. The developmental, cellular, and molecular processes underlying local circuit function in the DLPFC should and are receiving a great deal of attention in research that seeks to understand pathophysiology and treatment targets. Cognitive neuroscience tasks implemented in imaging and cognitive EEG are providing a new generation of phenotypic measures that can help clarify the boundaries and overlap between schizophrenia and other serious mental disorders as well as to understand the functional significance of schizophrenia-related genetic variation. Furthermore, an understanding of the role of cognitive control can inform the development of cognitive training technologies, which to date are the only viable treatment approaches to impaired cognition in schizophrenia.

To this end, cognition is an important emerging treatment target in schizophrenia. The role of neurotransmitter systems in modulating prefrontal cortical function has become increasingly well understood and these systems have been identified as important treatment targets. Accordingly, there is preliminary evidence that catecholamine and other agents improve PFC function and cognition, including in schizophrenia patients. Although there have been variable outcomes among recent clinical trials of novel agents that act on catecholamine, glutamate, and cholinergic systems, these studies are complex and must overcome methodological challenges. Nonetheless, monoamine and amino-acid transmitter systems remain promising targets.

FUTURE RESEARCH DIRECTIONS

Although we have accumulated a large body of knowledge with regard to the course of the disorder after onset and factors influencing outcome, one of the most rapidly expanding areas of research is investigating how to accurately identify those individuals who will go on to develop schizophrenia. This area of research is particularly important as these findings promote early intervention, which has the potential to alter the trajectory of the illness for those at highest risk and reduce the burden on individuals, their families, and the health-care system. As discussed previously, there is evidence of cognitive deficits before the onset of the illness; however, there is limited knowledge as to when cognitive dysfunction emerges and how these deficits progress throughout childhood and adolescence. In addition, it remains unclear whether deficits at the population level in pre-adolescent samples are uniform across the sample or whether they reflect a subgroup with developmental pathology. These types of questions require prospective, most likely multicenter, studies that examine at-risk individuals in youth and continue through years after the disorder may manifest. Although the majority of current studies of at-risk youth measure clinical factors associated with transition to psychosis, future studies would benefit from examining cognitive predictors of conversion as well.

Treatment research may benefit substantially from the use of measures and methods that are linked to the function of neural systems, including behavioral and imaging measures from cognitive neuroscience, which might not have traditionally been included in the treatment development process. Such methods offer unique advantages for translational research, as many cognitive processes and their associated neural systems are preserved across species. Substantial interest in optimizing research in this way has led to recent initiatives such as CNTRICS (Carter and Barch, 2007; Carter *et al*, 2008; www.cntrics.ucdavis.edu). However, it is challenging to optimize the measurement properties of these sorts of tools and substantial work remains to be carried out before valid reliable imaging biomarkers will be developed and optimized for the purpose of enhancing translational research.

Finally, ongoing research into pharmacotherapy for impaired cognition in schizophrenia will also need to address patient heterogeneity by developing tailored treatment based on phenotypic (eg, cognitive symptoms,

disorganization) and possibly genotypic variability. Such a personalized approach may allow us to get greater traction on the elusive problem of developing a successful treatment for the cognitive deficits that form a functional 'glass ceiling' for many people with schizophrenia.

DISCLOSURE

Drs Lesh, Niendam, and Minzenberg have no disclosures to report. Dr Carter has served as a consultant for Pfizer, Lilly, Merck, and Servier, and receives research funding from Glaxo-Smith Kline.

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