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REVIEW

Executive Function, Neural Circuitry, and Genetic Mechanisms in Schizophrenia

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After decades of research aimed at elucidating the pathophysiology and etiology of schizophrenia, it has become increasingly apparent that it is an illness knowing few boundaries. Psychopathological manifestations extend across several domains, impacting multiple facets of real-world functioning for the affected individual. Even within one such domain, arguably the most enduring, difficult to treat, and devastating to long-term functioning—executive impairment—there are not only a host of disrupted component processes, but also a complex underlying dysfunctional neural architecture. Further, just as implicated brain structures (eg, dorsolateral prefrontal cortex) through postmortem and neuroimaging techniques continue to show alterations in multiple, interacting signaling pathways, so too does evolving understanding of genetic risk factors suggest multiple molecular entry points to illness liability. With this expansive network of interactions in mind, the present chapter takes a systems-level approach to executive dysfunction in schizophrenia, by identifying key regions both within and outside of the frontal lobes that show changes in schizophrenia and are important in cognitive control neural circuitry, summarizing current knowledge of their relevant functional interactions, and reviewing emerging links between schizophrenia risk genetics and characteristic executive circuit aberrancies observed with neuroimaging methods.

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INTRODUCTION

Psychiatry has long appreciated deficits in higher-order thought processes in schizophrenia, with relative sparing of many basic cognitive abilities (Kraepelin, 1909–1913), and indeed, the modern era of neuropsychological research has accumulated data from schizophrenic patients showing significant impairments in complex tasks requiring a range of advanced cognitive processes, collectively described as executive functions (Bozikas *et al*, 2006; Carter *et al*, 2001; Tan *et al*, 2006; Weinberger *et al*, 1986). Executive functions rely heavily on frontal lobe structures and include: directed attention and inhibition, task management, planning, monitoring, and coding of representations in working memory (Smith and Jonides, 1999). Subsets of these functions have shown a close relationship to both negative symptoms (O'Leary *et al*, 2000; Pantelis *et al*, 2001), thought disorder (Perlstein *et al*, 2001; Stirling *et al*, 2006), and functional outcomes in schizophrenia (Kurtz *et al*, 2005; Liddle, 2000), in line with the suggestion that frontal lobe dysfunction is crucially important in schizophrenic psychopathology (Elvevag and Goldberg, 2000; Weinberger *et al*, 1994). Accumulated evidence from over two decades of neuroimaging experiments has confirmed executive-task-related functional abnormalities of the prefrontal cortex in schizophrenia; however, despite the numerous replications of this finding, the precise nature of illness-related frontal local circuit aberrancies contributing to executive dysfunction remains incompletely defined and remains the focus of ongoing investigation. Furthermore, because (1) functional abnormalities in schizophrenia are not exclusive to the frontal cortex, and (2) executive processes, though heavily reliant on the frontal cortex, also require cooperation from structures outside of the frontal lobes, schizophrenia research has increasingly turned its eye toward discerning how extended neural circuit dynamics contribute to illness-related cognitive phenotypes. Ultimately, if both these local prefrontal and extended distributed network characteristics in schizophrenia are relevant to the neurobiology of this disorder, then it may be possible to examine these systems through the lens of genetics. As schizophrenia likely

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involves multiple molecular pathways, this approach is invaluable in clarifying the mechanistic steps between risk genes, neuronal cellular function, neural circuits, and clinical morbidity. This chapter reviews the contributions of regions implicated in both schizophrenia and executive processing to local and extended neural circuits as well as describes recent advances in understanding relationships between these circuits and schizophrenia risk genes. Emphasis is placed on seven interconnected brain regions that have each prominently shown: (1) neuropathological and/or neurophysiological abnormalities in schizophrenia, (2) relevance to executive functioning and aberrant activity during executive processing in schizophrenia, and (3) abnormal functional relationships with other included regions during executive processing in schizophrenia. Additionally, nine genes are highlighted, each with variation showing both (1) evidence for contribution to risk of schizophrenia and (2) association with schizophrenia executive neuroimaging phenotypes that include circuits involving the emphasized regions.

EXECUTIVE CIRCUITS WITHIN THE FRONTAL LOBES

Ever since seminal regional blood flow studies showing specific and replicable frontal lobe dysfunction during executive task challenge in schizophrenia (Berman *et al*, 1986; Weinberger *et al*, 1986), better characterization of executive control circuits within the frontal lobes has remained at the forefront of schizophrenia research efforts. Investigations of abstract rule inference (Berman *et al*, 1995; Buchsbaum *et al*, 2005; Monchi *et al*, 2001), conflict management and monitoring (Macdonald *et al*, 2000; Pardo *et al*, 1990), verbal fluency (Frith *et al*, 1991; Gourovitch *et al*, 2000), and working memory (Cohen *et al*, 1997; Tsuchida and Fellows, 2009) in healthy individuals consistently show reliance on key frontal regions, most notably, the dorsolateral, ventrolateral, and anterior cingulate cortices. Abnormal functional measures in each of these regions have been shown in schizophrenia during these same paradigms (Becker *et al*, 2008; Berman *et al*, 1986; Callicott *et al*, 2003b; Kerns *et al*, 2005; Spence *et al*, 2000; Weinberger *et al*, 1986), bolstering the hypothesis of frontal primacy in schizophrenic pathophysiology (Elvevag and Goldberg, 2000; Weinberger *et al*, 1994) but increasing the imperative to understand how these disparate frontal nodes interact in concert during illness.

Dorsolateral Prefrontal Cortex

Numerous lines of evidence converge to implicate abnormalities of the dorsolateral prefrontal cortex (DLPFC)—the prototypical center of higher-order cognitive processing—in schizophrenia pathophysiology. Though they have neither shown gross evidence of degeneration (eg, gliosis) nor a diagnostic lesion, postmortem studies of schizophrenia patient DLPFC tissue have nonetheless shown support for perturbations of excitatory cells: increased pyramidal cell density (Selemon *et al*, 1995, 1998), reduced pyramidal neuron dendritic spine density (Glantz and Lewis, 2000), altered NMDA receptor subunit expression (Akbarian *et al*, 1996); inhibitory cells: reduced GAD67 and GAT1 mRNA expression (Akbarian *et al*, 1995; Volk *et al*, 2000); and dopaminergic afferents: reduced tyrosine hydroxylase expressing afferent axons (Akil *et al*, 1999), reduced DARPP-32 concentrations (Albert *et al*, 2002; Ishikawa *et al*, 2007). To what degree each of these and other cellular pathological findings are primary effects or secondary to other local disturbances (eg, other cellular pathological changes) or more distant alterations (eg, abnormal afferents from other frontal lobe structures or extrafrontal structures, Wang and Deutch, 2007) requires dedicated future study.

In vivo patient studies have further substantiated DLPFC pathological changes. Complimentary data from both region of interest (ROI) studies (Andreasen *et al*, 1994b; Nopoulos *et al*, 1995) and voxel-based morphometric studies (Cannon *et al*, 2002; Fornito *et al*, 2009; Giuliani *et al*, 2005) have reported statistically reduced DLPFC volumes in schizophrenia. Though not as consistently reported as reduced medial temporal lobe volumes (Honea *et al*, 2005), this finding, in concert with increased neuronal density, has been interpreted as a result of decreased DLPFC neuropil (Selemon *et al*, 1998). Importantly, reduced DLPFC gray matter volume is significantly more pronounced in patients with greater executive dysfunction, as measured by the Wisconsin Card Sorting Test (Rüsch *et al*, 2007). Neuronal measures of the DLPFC in schizophrenia have also shown abnormalities, particularly reduced *N*-acetylapartate (NAA), a measure of neuronal integrity, which has been repeatedly found in magnetic resonance spectroscopy studies (Abbott and Bustillo, 2006) and has shown relevance to cognitive function in schizophrenia: NAA levels in patients show a positive correlation with the degree of DLPFC working memory activation as measured by $[^{15}O]H_2O$ PET (Bertolino *et al*, 2000b). Notably, DLPFC D_1 receptor binding, measured by $[^{11}C]$NNC112 PET in medication-free schizophrenic patients, has been shown to be both increased and correlated with working memory impairment in schizophrenia (Abi-Dargham *et al*, 2002). When measured with $[^{11}C]$SCH23390, however, D_1 binding in the prefrontal cortex appears reduced (Okubo *et al*, 1997). Interestingly, these conflicting data actually correspond well with rodent models of subchronic dopaminergic depletion, which increases $[^{11}C]$NNC112 binding but paradoxically decreases $[^{11}C]$SCH23390 binding (Guo *et al*, 2003) and are hypothesized to reflect compensatory responses to reduced prefrontal dopaminergic input from the midbrain. White matter abnormalities of the DLPFC have also been described (Schlösser *et al*, 2007). Taken together, these cytopathological, structural, and neuroreceptor mapping findings predict both a prominent role for disrupted dorsolateral prefrontal cortical function and related aberrant interactions between this region and other brain structures contributing to executive dysfunction in schizophrenia.

In line with the former assertion, a plethora of functional imaging studies of schizophrenia have shown alterations in DLPFC physiology in response to executive cognitive demands. Replication of reduced relative frontal activity (Ingvar and Franzén, 1974), in the DLPFC during executive tasks, has been frequent in the past two decades, and has been observed in medicated, medication-free, and medication-naïve patients (Barch *et al*, 2001, 2003; Berman *et al*, 1986, 1992; Callicott *et al*, 1998; Camchong *et al*, 2006; Cannon *et al*, 2005; Cantor-Graae *et al*, 1991; Carter *et al*, 1998; Catafau *et al*, 1994; Curtis *et al*, 1998; Driesen *et al*, 2008; Fletcher *et al*, 1998; Glahn *et al*, 2005; Goldberg *et al*, 1990; Liu *et al*, 2002; Mcdowell *et al*, 2002; Meyer-Lindenberg *et al*, 2001, 2002; Parellada *et al*, 1994, 1998; Perlstein *et al*, 2001; 2003; Ragland *et al*, 1998; Rubia *et al*, 1994; 2001; Schlösser *et al*, 2007; Steinberg *et al*, 1996; Volz *et al*, 1997; Weinberger *et al*, 1986; Yurgelun-Todd *et al*, 1996). Furthermore, there is evidence that the DLPFC dysfunction as described in schizophrenia is not solely explained by attentional or global cognitive impairment (Berman *et al*, 1988), nor is it a result of neuropsychiatric illness, generally, as patients with major depression (Barch *et al*, 2003; Berman *et al*, 1993) and Huntington's (Goldberg *et al*, 1990) do not exhibit this finding. However, abnormally increased DLPFC activation has also been reported (Callicott *et al*, 2003b; Manoach *et al*, 1999; 2000; Potkin *et al*, 2009; Thermenos *et al*, 2005), often in fMRI studies of higher performing patient cohorts, and has been consequently labeled as inefficient prefrontal processing (Callicott *et al*, 2003b; Manoach *et al*, 1999; Potkin *et al*, 2009) because greater activation is required to achieve a given performance level. Notably, some studies have found that better performing patients show more hyperactivation in the DLPFC whereas poorer performing patients hypoactivate the DLPFC (Callicott *et al*, 2003b; Karlsgodt *et al*, 2007, 2009; Manoach *et al*, 2000); however, even this behavioral–physiological relationship shows variability, being susceptible to dopaminergic manipulation (Daniel *et al*, 1991) and may differ from healthy volunteers (Karlsgodt *et al*, 2009). Reconciliation of these findings remains a matter of debate, but several authors have proposed that they rest in part on variation in task demands and individual performance capacities. This hypothesis features an inverted U-shaped load–response curve, such that as task demands increase, activation initially rises until physiological capacity is reached, after which, activation falls (Fletcher *et al*, 1998). In schizophrenia, this curve may be shifted to the left (Jansma *et al*, 2004; Perlstein *et al*, 2003), resulting in hyperactivation (ie, inefficient signal) at lower relative task loads (where performance matching with healthy volunteers is more attainable) and hypoactivation (ie, inadequate signal) at higher relative task loads (where performance is likely to be significantly worse in schizophrenia) (Callicott *et al*, 2003b; Manoach 2003). This curve may also be flattened in patients, resulting in less neural response to varying load levels (Johnson *et al*, 2006). Thus, more activation is not always better; rather, its significance depends on individual capacity and task load. Other investigations have emphasized the impact of greater morphological variability in schizophrenia. Such variability can affect the topographical distribution of activation patterns, which, in turn, can weaken group-averaged data for a given region, despite potentially equivalent or stronger activations at the individual level (Manoach, 2003; Park *et al*, 2004). Additional factors, such as specific task paradigm characteristics (Barbalat *et al*, 2009; Curtis *et al*, 1999; Holmes *et al*, 2005; Macdonald *et al*, 2005; Quintana *et al*, 2003), clinical heterogeneity, and medication status (see Weiss *et al*, 2003 versus Weiss *et al*, 2007, showing greater activation during a modified Stroop paradigm when medicated patients were studied, but the opposite finding when a separate cohort of unmedicated patients was studied), may also have a role. Regardless of the cause of directional discrepancies, because most studies of DLPFC connectivity (covariance with activity in other brain regions) show abnormal disconnection with other neocortical structures important for executive function (Bassett *et al*, 2008; Kim *et al*, 2003; Schlösser *et al*, 2003; Spence *et al*, 2000; Tan *et al*, 2006; Whitfield-Gabrieli *et al*, 2009; Wolf *et al*, 2007; Woodward *et al*, 2009; Yasuno *et al*, 2005) and because even patients who overactivate the DLPFC still often do not achieve a higher performance on executive tasks than their healthy control comparators, it is clear that DLPFC is dysfunctional in schizophrenia. In the context of the cellular pathological, structural, and neuroreceptor imaging DLPFC findings, such altered DLPFC physiology seems to be an expected and robust illness-related phenotype reflecting reduced neurophysiological resources in which microcircuits are either overtaxed or overwhelmed.

Ventrolateral Prefrontal Cortex

Though less well studied in schizophrenia than the DLPFC, the ventrolateral prefrontal cortex (VLPFC), judged to be preferentially involved in working memory storage and rehearsal processes rather than information manipulation (Wager and Smith, 2003), may show less cellular abnormalities. For instance, the increased density of pyramidal neurons in DLPFC does not seem to exist in the VLPFC (Selemon *et al*, 2003). Nonetheless, activation differences have been reported in schizophrenia during executive tasks including working memory (Callicott *et al*, 2003b; Scheuerecker *et al*, 2008; Schneider *et al*, 2007; Stevens *et al*, 1998; Tan *et al*, 2005), motor response inhibition (Kaladjian *et al*, 2007), and attentional tasks (Schneider *et al*, 2007), raising the question of exactly how this region contributes to executive processing networks in psychotic illness. In line with the theory that VLPFC is recruited in a compensatory fashion during DLPFC-taxing tasks in schizophrenia, patients have shown increased VLPFC activation in conjunction with reduced DLPFC activation during manipulation in a verbal working memory task (Tan *et al*, 2005).

More recent data examining functional connectivity suggest that this potential compensatory mechanism cannot simply be described as increased relative activation, but rather, increased dominance and assumption of DLPFC's nodal role in extended executive circuitry. Tan *et al* (2006), for instance, used the n-back working memory fMRI paradigm to show that high-performing healthy control subjects evidenced greater DLPFC relative to VLPFC activation with greater working memory load, whereas volunteers with schizophrenia showed the opposite pattern. Remarkably, in control subjects, DLPFC showed more robust functional connectivity with a posterior parietal region, whereas in patients, the VLPFC showed greater parietal functional connectivity (Tan *et al*, 2006). Of note, this echoes report of abnormally increased 'structural connectivity' (the correlation between gray matter volumes of two or more brain structures across individuals) between ventral prefrontal cortex and inferior parietal lobule (IPL) in schizophrenia (Buchanan *et al*, 2004). Likewise, these results are similar to findings from a word-encoding fMRI paradigm, in which schizophrenic patients showed reduced DLPFC-temporal and increased VLPFC-temporal functional connectivity (Wolf *et al*, 2007). Thus, increased VLPFC relative to DLPFC prominence in executive neural networks may characterize altered and often inadequate (by behavioral performance measures) circuit-level strategies in schizophrenia during DLPFC-activating executive tasks.

Anterior Cingulate

As in DLPFC, postmortem experiments in schizophrenia have identified alterations in the neurons of the anterior cingulate cortex (ACC), a paralimbic structure also within the frontal lobes. These include abnormalities in a wide range of proteins (Clark *et al*, 2006), increased glutamatergic vertical fibers—presumably associative afferents—in layers II and IIIa (Benes *et al*, 1992b), reduced layer IV pyramidal cell density (Benes *et al*, 2001), and a number of findings related to GABAergic neurons (Torrey *et al*, 2005), such as reduced concentration of neurons expressing GAD67 mRNA (Woo *et al*, 2004) but increased superficial layer $GABA_A$ receptor binding (Benes *et al*, 1992a), though this last finding was not seen in receptor imaging studies *in vivo* (Verhoeff *et al*, 1999). Corroborating experiments using structural and spectroscopic MRI have further documented reductions in anterior cingulate volume (Baiano *et al*, 2007; Goldstein *et al*, 1999), gray matter concentration (Kubicki *et al*, 2002; Meda *et al*, 2008; Rüsch *et al*, 2007), and NAA levels (Wood *et al*, 2007), as well as increased glutamine (Theberge *et al*, 2002). Additionally, PET studies have shown reduced $D_{2/3}$ binding in this region (Buchsbaum *et al*, 2006; Suhara *et al*, 2002; Yasuno *et al*, 2005). Many of these volumetric (Szeszko *et al*, 2000), morphometric (Eack *et al*, 2008), spectroscopic (Ohrmann *et al*, 2008), and neuroreceptor (Ko *et al*, 2009; Lumme *et al*, 2007) indices have shown robust relationships with executive functioning in healthy control subjects.

In light of these findings, it is perhaps not surprising that executive functions reliant on anterior cingulate activity elicit abnormal ACC responses in schizophrenia. For example, during tasks that include conflict and error monitoring, subjects with schizophrenia show both worse performance (in select, but not all, studies: less error-related reaction time slowing, posterror behavioral adjustments and more errors) and less anterior cingulate activation (Andreasen *et al*, 1992; Carter *et al*, 1997, 2001; Dolan *et al*, 1995; Ford *et al*, 2004; Kerns *et al*, 2005; Krabbendam *et al*, 2009; Laurens *et al*, 2003; Polli *et al*, 2008; Rubia *et al*, 2001; Salgado-Pineda *et al*, 2004; Volz *et al*, 1999; Weiss *et al*, 2007; Yucel *et al*, 2002; but see Weiss *et al*, 2003), suggesting a deficit in self-monitoring processes required to signal conflicts between response and maintained rule representations (Macdonald *et al*, 2000). Similar reductions in anterior cingulate activation during verbal fluency tasks have also been reported in several (Boksman *et al*, 2005; Broome *et al*, 2009; Fletcher *et al*, 1996; Fu *et al*, 2005), but not all (Ragland *et al*, 2008), investigations. It is notable that dopamine agonist administration results in marked augmentation of ACC activation during verbal fluency in schizophrenia, but not healthy volunteers (Dolan *et al*, 1995), implicating either aberrant modulatory mesencephalic input to this region and/or postsynaptic dopaminergic signaling dysregulation in this region. Robust evidence for augmented basal ganglia sensitivity to dopamine agonists in schizophrenia (Abi-Dargham *et al*, 1998; Laruelle *et al*, 1996) offers circumstantial support for the former hypothesis. As the anterior cingulate shows heterogeneous functional topography, it is important to note that the majority of the above-cited findings localize to the dorsal anterior cingulate, consistent with a more cognitive specialization of this region (Drevets and Raichle, 1998), though a few reports also feature rostral anterior cingulate findings (Laurens *et al*, 2003; Polli *et al*, 2008), perhaps reflecting motivational components of task performance and monitoring (Polli *et al*, 2008). The absence of subgenual anterior cingulate cortical findings suggest that this region likely does not have an important function in executive task performance, in line with its predominantly affective role (Drevets and Raichle, 1998).

Given the above-cited cellular, structural, and functional abnormalities in ACC and DLPFC, effective neural cooperation between these structures in the service of executive processing in schizophrenia is critical but unlikely. Indeed, preclinical and clinical studies are both suggestive of disrupted DLPFC–ACC communication. Efferent projections from the anterior cingulate (BA32) synapse both on excitatory and inhibitory target cells in the supragranular layers of DLPFC (BA9), the latter being predominantly calbindin-positive GABAergic neurons (Medalla and Barbas, 2009) that inhibit distal pyramidal spines in the theorized service of dampening distracting stimuli (Wang *et al*, 2004). This is in contrast to projections within DLPFC regions (BA46→BA9), in which inhibitory targets are less

robust and more frequently calretinin-positive cells that synapse on inhibitory interneurons, thereby promoting disinhibitory effects on DLPFC pyramidal cells (Medalla and Barbas, 2009). Notably, the density of calbindin-positive, but not calretinin-positive, GABAergic neurons may be reduced in the superficial layers of the DLPFC in schizophrenia (Beasley *et al*, 2002; Sakai *et al*, 2008) but see (Daviss and Lewis, 1995; Tooney and Chahl, 2004), suggesting one potential basis for disrupted ACC–DLPFC neural transmission, resulting in increased noise at the level of higher-order cognitive representations (Winterer *et al*, 2004). Likewise, reciprocal connections from DLPFC and other cortical regions to the ACC may also be affected as suggested indirectly by superficial cortical layer abnormalities within the ACC (Benes *et al*, 1992a, b). Reduced white matter integrity (fractional anisotropy measured by DTI) in the cingulum bundle, which shows a relationship with impaired Wisconsin Card Sorting Task performance (Kubicki *et al*, 2003), offers another reason to predict altered communication between the anterior cingulate and prefrontal regions. In any case, frontocingulate functional dysconnectivity has been explicitly described during verbal fluency (Spence *et al*, 2000) and modified continuous performance tasks (Honey *et al*, 2005) in schizophrenia. Further, structural equation modeling of regional $D_{2/3}$ receptor binding has shown altered connectivity from other frontal cortical regions (as well as thalamus and parietal cortex) to the anterior cingulate (Yasuno *et al*, 2005).

EXTENDED EXECUTIVE CIRCUITS

Despite historical emphasis on frontal circuits in investigations aimed at understanding cognitive pathophysiology in schizophrenia, recent studies have amassed considerable evidence that a systems-level disruption, including but not limited to frontal cortical dysfunction, is at play. During executive tasks, functional neuroimaging of patients shows abnormal activation not only in the frontal lobes, but also similarly in other distributed brain regions typically recruited by executive task demands (Jansma *et al*, 2004). Several of these regions have also shown cellular, structural, or neurochemical abnormalities in schizophrenia and include (1) the IPL, which has consistently shown significant contributions to a range of executive functions in neurophysiological experiments and may be a particularly important support to frontal executive circuits as a working memory storage buffer (Jonides *et al*, 1998); (2) the medial temporal cortex/hippocampus, which may provide specific contextual/stimulus–stimulus association consolidation for abstract rule establishment during select executive tasks, such as the Wisconsin Card Sort (Graham *et al*, 2009), but is normally suppressed during other executive functions (eg, working memory); (3) the basal ganglia/caudate, which is important for cognitive flexibility (Eslinger and Grattan, 1993), and along with the thalamus, may provide a gating function for prefrontal-bound information during working memory (Frank *et al*, 2001; Landau *et al*, 2009); and (4) the thalamus, which is an essential pathway within cortico-striatal-thalamic-cortical loops and shows prefrontal-like participation in working-memory-related neural transmission (Tanibuchi and Goldman-Rakic, 2003). Furthermore, particular disturbances of communication among these and frontal regions, often measured through fMRI or PET functional connectivity methodologies, suggest inefficient circuit dynamics that may underlie executive dysfunction. Thus, studies in recent years have increasingly attended to extrafrontal regions both to show novel cellular and molecular biological markers of disease, and to understand the critical contributions of extrafrontal regions to these circuits.

Inferior Parietal Lobule

Though preclinical data implicating the IPL in schizophrenia are scarce, structural imaging findings in this region are not. Reductions in parietal gray matter volume in schizophrenia relative to healthy individuals have been reported in a handful of studies (Buchanan *et al*, 2004; Frederikse *et al*, 2000; Goldstein *et al*, 1999; Hulshoff Pol *et al*, 2001; Kubicki *et al*, 2002; Nierenberg *et al*, 2005; Schlaepfer *et al*, 1994; Wolf *et al*, 2008; Zhou *et al*, 2007) and are more pronounced in patients with passivity delusions (Maruff *et al*, 2005) and greater cognitive impairment (Wolf *et al*, 2008). Schizophrenia patients also show significantly greater structural variability (Yoon *et al*, 2006) and reversed or absent hemispheric asymmetry (Buchanan *et al*, 2004; Niznikiewicz *et al*, 2000; Zhou *et al*, 2007) in this region. Reductions in parietal white matter have also been found in patients with prominent negative symptoms (Zetzsche *et al*, 2008). It is notable that child onset schizophrenia patients show early and accelerated parietal volume loss over time (Thompson *et al*, 2001).

Regions in the IPL (BA 40), in addition to lateral prefrontal cortices and anterior cingulate, show reliable activation during prototypical executive function tasks, such as the Wisconsin Card Sorting Test, as well as during component executive processes, such as response inhibition and set shifting (Buchsbaum *et al*, 2005). In conjunction with structural imaging evidence for abnormalities in this area and executive dysfunction in schizophrenia, this would predict parietal functional deficits detectible during executive task performance. Indeed, akin to findings in the prefrontal cortex, reductions in parietal activation during working memory (Barch and Csernansky, 2007; Broome *et al*, 2009; Jansma *et al*, 2004; Kindermann *et al*, 2004; Schlagenhauf *et al*, 2008; Schlösser *et al*, 2007; Schneider *et al*, 2007), semantic integration (Kuperberg *et al*, 2008), and selective attention (modified Stroop) (Weiss *et al*, 2007) have been commonly observed in schizophrenia subjects (but see Lee *et al*, 2008; Ragland *et al*, 2008; Thermenos *et al*, 2005, showing increases). Recent data also suggest the possibility that hallucinating patients may have less

working-memory-associated parietal activation than non-hallucinating patients (Wible *et al*, 2009).

The inferior parietal and prefrontal cortices share key involvement in executive processing and important anatomical connections. In view of both of these regions' structural and functional abnormalities in schizophrenia, it is likely that communication between these structures, particularly during executive tasks, is abnormal as well in patients. The superior longitudinal fasciculus, which links parietal and prefrontal cortical areas, shows reduced fractional anisotropy, a measure of white matter integrity, in schizophrenia (Shergill *et al*, 2007) suggestive of impaired prefrontal–parietal interactions. This notion has been advanced by several functional connectivity studies as well: for instance, DLPFC–IPL connectivity during the n-back working memory task is reduced in schizophrenia (Kim *et al*, 2003; Tan *et al*, 2006), though the results of two other studies have been mixed (Barch and Csernansky, 2007; Schlosser *et al*, 2003). Similarly, during a choice reaction-time test (Woodward *et al*, 2009) and the AX version of the continuous performance task (Yoon *et al*, 2008), both of which require less executive resources than the n-back working memory test, prefrontal–IPL connectivity is also reduced in schizophrenia. Even resting state regional glucose metabolism shows this pattern (Mallet *et al*, 1998), substantiating the pervasive nature of this functional disconnection.

Temporal Cortex/Hippocampus

The medial temporal cortex has been the focus of a large number of investigations and findings of regional pathological changes in schizophrenia. Postmortem examination of the hippocampal formation has shown a number of abnormalities in schizophrenia, including reduced pyramidal cell size (Arnold *et al*, 1995; Benes *et al*, 1991; Zaidel *et al*, 1997) (but see Highley *et al*, 2003), reduced dendritic spine density (Rosoklija *et al*, 2000), reduced spinophilin mRNA expression (Law *et al*, 2004), reduced microtubule-associated proteins (Arnold *et al*, 1991), reduced BDNF (Durany *et al*, 2001), reduced mossy fiber terminal density (Kolomeets *et al*, 2007), reduced synaptic protein levels (Browning *et al*, 1993; Sawada *et al*, 2005; Young *et al*, 1998), alterations in NMDA receptor subtypes (reduced NR1 and increased NR2B) (Gao *et al*, 2000) and reduced non-NMDA ionotropic glutamate receptors (Harrison *et al*, 1991), as well as reduced mRNA expression of DISC1 binding partners (*FEZ1*, *NUDEL*, and *LIS1)* (Lipska *et al*, 2006b), among others.

Hippocampal volume reductions in schizophrenia have been shown by both voxel-based and ROI methodologies (Honea *et al*, 2005; Nelson *et al*, 1998; Weiss *et al*, 2005; Wright *et al*, 2000) are seen even when compared with patients' unaffected monozygotic twins, implicating non-genetic contributions to this finding (Suddath *et al*, 1990), and are present at the onset of psychosis (Bogerts *et al*, 1990). Furthermore, in patients, but not healthy individuals, hippocampal volume predicts the degree of prefrontal hypoactivation during the Wisconsin Card Sorting Test (Weinberger *et al*, 1992), leading to the hypothesis that fronto-limbic circuits may be particularly central to schizophrenia pathophysiology linked to cognitive dysfunction. Compelling rodent models have elaborated on this interaction: neonatal ventral hippocampal lesions in rodents disrupt medial temporal–prefrontal afferentation and produce numerous schizophrenia-like phenotypes after adolescence (Lipska and Weinberger, 2000) including working memory deficits (Lipska *et al*, 2002) and reduced prefrontal NAA (Bertolino *et al*, 2002), suggesting that, in fact, medial temporal lobe afferentation is critical to prefrontal cortical development and subsequent executive processing. Additionally, reductions in fractional anisotropy of temporal white matter, including the fornix (Fitzsimmons *et al*, 2009) and inferior longitudinal fasciculus (Ashtari *et al*, 2007), suggest compromised integrity of key bidirectional white matter tracts of the hippocampus, including those that communicate with the prefrontal cortex.

On the framework of these observations, recent functional imaging experiments have uncovered abnormalities of hippocampal–prefrontal interactions during executive tasks, particularly working memory, in schizophrenia. During the n-back working memory task, which is not thought to rely substantially on hippocampal processing, the hippocampus is deactivated and disengaged from prefrontal and inferior parietal regions (Meyer-Lindenberg *et al*, 2005b). However, patients with schizophrenia show impaired suppression of this region in the contexts of hypoactivated DLPFC (Meyer-Lindenberg *et al*, 2001), hyperactivated VLPFC (Thermenos *et al*, 2005), or hyperactivated basal ganglia (Kawasaki *et al*, 1992). Precise examination of hippocampal–DLPFC interactions during the 0-back sensorimotor task in health and in schizophrenia shows an inverse correlation between these regions; however, in patients, but not healthy volunteers, this relationship remains inappropriately robust and regionally specific during the 2-back working memory condition (Meyer-Lindenberg *et al*, 2005b). As noted by Meyer-Lindenberg *et al*, impairment in modulating fronto-limbic circuitry in response to executive challenge could be predicted by an etiological model (Lipska *et al*, 2002) centered on early abnormal hippocampal physiology and connectivity resulting in subsequent retarded maturation of DLPFC and aberrant reciprocal innervation back to the hippocampus. Continued investigation of this hypothesis will require more direct studies of frontohippocampal circuitry during executive task challenge and will need to address other aspects of executive circuit abnormalities, including the role of medial temporal and prefrontal dopaminergic signaling (Aalto *et al*, 2005) in relation to basal ganglia function (Saunders *et al*, 1998).

Basal Ganglia

Postmortem examinations of the neostriatum implicating its involvement in schizophrenia have reported several

findings, including: increased corticostriatal dendritic spine density (Kung *et al*, 1998; Roberts *et al*, 2005, 2008), reduced axonic mitochondria (Kung and Roberts, 1999), reduced GABA and glutamate uptake sites (Simpson *et al*, 1992), reduced cholinergic interneurons (Holt *et al*, 1999), increased dopamine concentrations (Mackay *et al*, 1982), and increased $D_{2/3}$ and more robustly D_4 receptors (Mackay *et al*, 1982; Murray *et al*, 1995; Seeman *et al*, 1993).

In vivo PET imaging studies have found upregulation of striatal D_2 receptors as well, even in medication-naïve patients (Wong *et al*, 1986). Though there have been several negative studies, the weight of the literature supports an effect (Kestler *et al*, 2001; Laruelle, 1998). Striatal presynaptic dopamine synthesis and storage, measured by PET L-DOPA radiotracers, is increased in the schizophrenia prodrome (Howes *et al*, 2009) and in patients who fulfill full diagnostic criteria regardless of medication status (medicated, medication free, and neuroleptic naïve) (Hietala *et al*, 1995, 1999; Lindström *et al*, 1999; Mcgowan *et al*, 2004; Meyer-Lindenberg *et al*, 2002; Nozaki *et al*, 2009; Reith *et al*, 1994) (but see Dao-Castellana *et al*, 1997, showing only greater variability in patients and Elkashef *et al*, 2000 showing decreases in ventral striatum). Greater amphetamine-induced striatal dopamine release (D_2 receptor radioligand displacement) in schizophrenia, measured by PET and SPECT, has also been well documented (Abi-Dargham *et al*, 1998; Breier *et al*, 1997; Laruelle *et al*, 1996). Taken together, these results establish abnormally heightened dopaminergic signaling in the striatum in schizophrenia.

As functional imaging studies have outlined a role for the striatum, and the caudate in particular, in spatial working memory (Postle and D'Esposito, 1999), planning (Owen *et al*, 1996), interference management (Vernaleken *et al*, 2007), and verbal working memory (Chang *et al*, 2007; Koch *et al*, 2008; Landau *et al*, 2009; Lewis *et al*, 2004; Rypma *et al*, 1999), striatal disinhibition may contribute to executive dysfunction in schizophrenia. This is in accord with the anatomy of basal ganglia-thalamo-cortical tracts, which features significant innervation of the above-discussed prefrontal regions (Middleton and Strick, 2002), and with the working memory deficits that arise from anterior neostriatal lesions in nonhuman primates, which can be remarkably similar to deficits seen with prefrontal lesions (Goldman and Rosvold, 1972). Conversely, striatal disinhibition in schizophrenia may be compensatory for or directly result from prefrontal dysfunction, as reciprocal corticostriatal modulation of the basal ganglia is also robust in the healthy individual. Bolstering prefrontal dopaminergic signaling with locally administered dopamine agonists results in reduced striatal dopamine release (Jaskiw *et al*, 1991; Kolachana *et al*, 1995). Likewise, frontal lesions result in exaggerated striatal dopamine release (Flores *et al*, 1996; Jaskiw *et al*, 1990a, b; Pycock *et al*, 1980), and surgical disconnection of frontostriatal circuitry impairs delayed alternation task performance in rats (Dunnett *et al*, 2005). Thus, to what degree abnormal neural activity in the striatum during executive functioning in schizophrenia is a primary or secondary phenomenon remains an unresolved question.

Nonetheless, hypothesizing that frontostriatal circuits are dominant (Pantelis *et al*, 1997) and specific (Badcock *et al*, 2005) contributors to schizophrenic cognitive impairments, a number of investigations have elucidated frontostriatal circuit abnormalities relevant to executive dysfunction in schizophrenia. Indirect evidence from functional imaging studies has been suggestive of striatal dysfunction (hyperactivation) in schizophrenia during inhibition tasks (Rubia *et al*, 2001), verbal fluency (Ragland *et al*, 2008), numeric working memory (Manoach *et al*, 2000), and the Wisconsin Card Sort Task (Kawasaki *et al*, 1992; Rubin *et al*, 1991, 1994). Perhaps the strongest evidence for the frontostriatal hypothesis comes from multimodal imaging approaches. Reduced DLPFC NAA shows an inverse relationship with amphetamine-induced striatal dopamine release, measured with [^{11}C]raclopride PET, in patients with schizophrenia but not control subjects (Bertolino *et al*, 2000a). Though DLPFC NAA has been related to executive functioning in schizophrenia (Bertolino *et al*, 2000b), better characterization of striatal dysregulation and disturbed prefrontal physiology requires *in vivo* examination of both of these factors. This was recently achieved by Meyer-Lindenberg *et al* who studied schizophrenia patients and healthy volunteers with both [^{15}O]H_2O PET during the Wisconsin Card Sorting Task and [^{18}F]DOPA PET. Patients showed greater striatal presynaptic dopamine synthesis and storage and reduced prefrontal activation during the Card Sort compared with healthy individuals, and moreover, in patients these two abnormalities were highly correlated (Meyer-Lindenberg *et al*, 2002). These remarkable and predicted associations invite speculation that breakdowns in prefrontal neuronal integrity and function result in impaired restraint on striatal circuits, yielding an inflexible, dysregulated circuit. However, given the correlative nature of these findings, further testing is needed to establish causality.

Thalamus

As the thalamus is a central entry point for frontal cortex-bound projections, including those from the striatum, there has been great interest in investigating this region for pathology in schizophrenia. Reductions in mediodorsal nucleus volume (Byne *et al*, 2002), neuronal number (Pakkenberg, 1990; Popken *et al*, 2000), and multiple ionotropic glutamatergic receptor types (NMDA, AMPA, Kainate) exist in thalamic nuclei (most prominently, mediodorsal and centromedial) of schizophrenia postmortem tissue (Ibrahim *et al*, 2000). Upregulation of exitatory amino-acid transporter (types 1 and 2) (Smith *et al*, 2001a) and vesicular glutamate transporter (Smith *et al*, 2001b) has also been reported in the same regions.

In vivo data showing illness-associated thalamic volume reductions (Andreasen *et al*, 1994a; Gur *et al*, 1998; Hulshoff Pol *et al*, 2001; Konick and Friedman, 2001) and reduced NAA measured by magnetic resonance techniques

(Auer *et al*, 2001; Deicken *et al*, 2000; Ende *et al*, 2001) align well with reports of cellular neuropathological findings in the mediodorsal nuclei of schizophrenic patients. Reductions in $D_{2/3}$ receptor binding in the mediodorsal and pulvinar thalamic nuclei have also recently been documented (Buchsbaum *et al*, 2006; Talvik *et al*, 2003).

As thalamic activity is associated with the working memory (Callicott *et al*, 1999; Rypma *et al*, 1999), the Wisconsin Card Sorting Task (Goldberg *et al*, 1998), and the verbal fluency (Basho *et al*, 2007), pathological changes in this region in schizophrenia predict abnormal physiological responses to executive challenge. Indeed, hypoactivation of this region during working memory tasks (Andrews *et al*, 2006; Camchong *et al*, 2006; Mendrek *et al*, 2004; Schlösser *et al*, 2008) has been well replicated (though, see Manoach *et al*, 2000 showing hyperactivation). The mediodorsal nucleus of the thalamus shows reduced glucose metabolism in patients performing a modified California Verbal Learning Test (Hazlett *et al*, 2004) and manifests reduced connectivity with both regions in the DLPFC and medial temporal lobe (Mitelman *et al*, 2005). This agrees well with the possibility of structural derangement of prefrontal- and anterior cingulate-thalamic connections, as suggested by recent DTI studies using tractography (Kunimatsu *et al*, 2008) and fractional anisotropy measurements (Zou *et al*, 2008). In contrast, schizophrenia patients have shown increased thalamo-ventrolateral prefrontal and thalamo-dorsolateral prefrontal connectivity by structural equation modeling during an fMRI n-back paradigm (Schlösser *et al*, 2003). Though Schlosser and Mitelman used very different methodologies, it remains unclear how to reconcile their opposing results without additional experimentation.

THE INFLUENCE OF SCHIZOPHRENIA RISK GENES ON EXECUTIVE CIRCUITRY

As schizophrenia is highly heritable (Cardno and Gottesman, 2000), and healthy relatives of patients show executive task impairments and associated neuroimaging phenotypes, which are qualitatively similar to their affected family member but attenuated (Callicott *et al*, 2003a; Macdonald *et al*, 2008), and given a core role for executive dysfunction in schizophrenia, it is likely that functional variation in specific schizophrenia risk genes will impact aspects of the above-reviewed neurocircuit dynamics in predictable ways. Building on the endophenotype approach originally proposed by Gottesman and Sheilds (1972), recent advances in imaging genetics have begun to provide remarkably convergent evidence supporting this hypothesis, as delineated below (see Table 1). Such advances are crucial, in part, because among the multitude of molecular pathways impacting the interacting neural systems relevant to schizophrenia, any one candidate risk gene variant is likely to contribute only a nominal effect to the complex behavioral phenotype that establishes the clinical diagnosis, and the gene variants discussed here are no exception. However, the experiments reviewed below have nonetheless been able to detect robust genetic effects by using neuroimaging techniques to assay 'intermediate' phenotypes at the neural systems level—a level of organization that is closer to the actual impact of a single gene variation—rather than measuring diagnosis itself (Mier *et al*, 2009). One particular strength of this approach is the ability to examine risk gene effects in healthy individuals that do not possess many of the confounds inherent in studying patients, such as medication exposure and psychotic symptoms, which has resulted in the majority of studies employing healthy populations; but by the same token, much work is still needed to better understand the effects of these genetic variants in the complex clinical and genetic context of schizophrenia.

COMT

Variation in the gene coding for catechol-O-methyltransferase (*COMT*), an enzyme central to cortical synaptic dopamine catabolism modestly influences risk of illness and has garnered significant attention for providing insight into the biological underpinnings of the imaging phenotype of schizophrenia. The rs4680 single nucleotide polymorphism (SNP) has been best studied, and the valine risk allele confers thermostability, permitting greater enzymatic activity and thereby reduced dopaminergic tone in cortical synapses. In a seminal paper by Egan *et al* and subsequent replications, the valine risk allele reliably predicts worse performance but increased dorsolateral prefrontal and anterior cingulate physiological response to the n-back task in both schizophrenic individuals and their unaffected siblings (Egan *et al*, 2001). This work has been extended to show that predicted prefrontal dopaminergic tone by combined genotype and pharmacological condition follow an inverted U-shaped response during working memory, such that risk allele homozygotes have improved and protective allele homozygotes have worse prefrontal efficiency in response to amphetamine (Mattay *et al*, 2003). Notably, functional variation in the *COMT* gene is not limited to the rs4680 SNP, but rather includes other polymorphisms, including a P2 promoter region SNP and a 3′ region SNP. These three SNPs show nonlinear interacting effects on prefrontal efficiency during working memory task performance, in agreement with predictions of resultant cortical dopaminergic catabolic rates, and highlight the complexity of genetic contributions to functional neuroimaging phenotypes, even within a single gene (Meyer-Lindenberg *et al*, 2006). To add to this complexity, the ability of COMT to regulate cortical dopamine relies on other genetically determined cellular resources, as suggested by studies of *MTHFR* by Roffman *et al* (2008). Variation in *MTHFR* (rs1801133), which also shows association with schizophrenia risk (Gilbody *et al*, 2007), regulates the availability of methyl groups for use by COMT and, in combination with rs4680, predicts DLPFC activation during working memory in a manner consistent with the

Table 1 Selected Executive Function Circuit Findings in Schizophrenia

Circuit	Functional connectivity findings during executive function in schizophrenia	Additional findings	Putative involved risk genes	Risk-variant-associated circuit findings
Frontocingulate	Reduced	*Reduced frontocingulate D2-binding correlation*	*NRG1*	*Reduced anterior cingulate, inferior frontal activation during sentence completion*
		Reduced cingulum bundle fractional anisotropy		
Frontoparietal	Reduced (dorsal prefrontal–parietal)	*Reduced frontoparietal resting glucose metabolism correlation*	*COMT*	Reduced dorsal prefrontal–parietal connectivity during working memory
	Increased (ventral prefrontal–parietal)			
		Reduced superior longitudinal fasciculus fractional anisotropy		Increased ventral prefrontal–parietal connectivity during working memory
			RGS4	Reduced dorsal prefrontal–parietal connectivity during working memory
			GRM3	Reduced dorsal prefrontal–parietal connectivity during working memory
				Increased ventral prefrontal–parietal connectivity during working memory
Frontotemporal	Increased	*Reduced fornix fractional anisotropy*	*COMT*	Increased frontotemporal connectivity during recognition memory
		Reduced cingulum bundle fractional anisotropy		
			ZNF804A	Increased frontotemporal connectivity during working memory
			DISC1	*Increased hippocampal activation during working memory*
				Increased prefrontal activation during working memory
Frontostriatal	Increased	*Reduced anterior limb of internal capsule fractional anisotropy*	*PPP1R1B*	Increased frontostriatal connectivity during working memory
		Dorsolateral prefrontal N-acetylaspartate reductions correlate with exaggerated amphetamine-induced striatal dopamine release		
			PRODH	Increased frontostriatal connectivity during working memory
			AKT1	*Reduced prefrontal and caudate volumes*
			NRG1	*Reduced anterior limb of internal capsule fractional anisotropy*
Thalamofrontal	Mixed	*Reduced superior occipitofrontal fasciculus fractional anisotropy*	*NRG1*	*Reduced anterior limb of internal capsule fractional anisotropy*
		Reduced anterior limb of internal capsule fractional anisotropy		

Italicized findings indicate indirect evidence (ie, not executive functional connectivity data).

above-mentioned inverted U-shaped curve. Taken together, these data provide further support for the proposition that suboptimal prefrontal dopamine signaling contributes to the prefrontal imaging phenotypes of executive dysfunction in schizophrenia.

Importantly, recent investigations have expanded this line of inquiry to assess the impact of genetically defined cortical dopamine tone on distributed circuitry relevant to executive function, and a number of results have emerged that are consistent with the data and putative mechanisms regarding schizophrenia itself, reviewed above. For instance, during the n-back working memory task, valine carriers show increased ventrolateral relative to dorsolateral prefrontal engagement and increased ventrolateral relative to

dorsolateral connectivity with parietal regions, as had been seen in schizophrenia earlier (Tan *et al*, 2007). Additionally, just as inappropriate prefrontal–hippocampal coupling persists during working memory in schizophrenia patients (Meyer-Lindenberg *et al*, 2005b), during a recognition memory task that activates the hippocampus, carriers of *COMT* rs4680 valine alleles show disadvantageous increased prefrontal–hippocampal connectivity (Bertolino *et al*, 2006). Finally, in agreement with the above-highlighted frontostriatal circuit abnormalities in schizophrenia, particularly disinhibited presynaptic striatal dopaminergic signaling in association with DLPFC hypofunction, postmortem data show that *COMT* valine alleles predict increased tyrosine hydroxylase mRNA expression in the midbrain (Akil *et al*, 2003), origin of dopaminergic projections to the striatum. Corroborating this effect are *in vivo* data describing *COMT* genotype effects on the relationship between midbrain dopamine storage and prefrontal activation during the n-back task: in met homozygotes, this relationship was negative, but in val carriers, it was positive (Meyer-Lindenberg *et al*, 2005a). This has been interpreted as a downstream effect of genetically conferred variation of prefrontal dopaminergic neurotransmission, as midbrain relative to cortical COMT expression is weak (Kastner *et al*, 1994), such that suboptimal prefrontal output to mesencephalic inhibitory cells results in exaggerated activity of dopamine neurons projecting to the striatum.

RGS4

RGS4 is an important modulator of central dopamine, glutamate, and neuregulin G-protein receptor systems, and transcript expression in the DLPFC of schizophrenia patients has been shown to be reduced (Mirnics *et al*, 2001). An SNP (rs951436 C→A) in the gene coding for this protein is associated with both schizophrenia (Chowdari *et al*, 2002) and reductions in DLPFC volumes (Prasad *et al*, 2005). Buckholtz *et al* (2007a, b) studied this risk SNP in a large group of healthy individuals undergoing functional MRI scans during the n-back task and found that individuals carrying more risk alleles evidenced greater activation in the left ventrolateral PFC, but less activation in the right lateral PFC, temporal cortex, and caudate (Buckholtz *et al*, 2007a). Similar to investigations in *COMT* (Tan *et al*, 2007) and schizophrenia itself (Tan *et al*, 2006), examination of functional connectivity between these differentially activated nodes showed that risk alleles impaired cooperativity between right hemispheric nodes activated by the task (eg, DLPFC, PPC) but exaggerated cooperativity between VLPFC and nodes deactivated by task (eg, mPFC, superior temporal cortex, posterior cingulate, and parahippocampal gyrus) (Buckholtz *et al*, 2007a). Notably, when regional brain activations during the n-back task are examined with consideration of both *COMT* and *RGS4* genotypes, there exists an epistatic interaction, such that *RGS4* risk allele-associated greater DLPFC and midbrain activation occurs only in the context of *COMT* risk allele carriers (Buckholtz *et al*, 2007b). Regardless of whether this interaction occurs biologically at the molecular (eg, *COMT* regulating *RGS4* gene expression, Lipska *et al*, 2006a) or systems level (eg, inefficient executive circuits being more susceptible to *RGS4* effects) (Buckholtz *et al*, 2007b), these data highlight the complex contribution of schizophrenia risk gene networks to executive processing.

GRM3

An SNP in the gene coding for the metabotropic type II glutamate receptor mGluR3, *GRM3* (rs6465084), results in weakly increased risk for schizophrenia, reduced prefrontal excitatory amino-acid transporter 2 mRNA expression (EEAT2), worse verbal fluency performance, and reduced DLPFC neuronal integrity as measured by magnetic resonance spectroscopy (Egan *et al*, 2004; Marenco *et al*, 2006). As in *COMT*, during the n-back working memory task, greater DLPFC BOLD signal activation for the same performance level ('prefrontal inefficiency') is seen in carriers of the risk SNP (Egan *et al*, 2004). However, this finding of *GRM3* risk allele-associated prefrontal inefficiency during working memory, as in *RGS4*, has been replicated in *COMT* rs4680 risk allele carriers but not in methionine homozygotes, suggesting an epistatic interaction between these two risk genes. Furthermore, carriers of both *COMT* and *GRM3* risk alleles show disproportionately greater VLPFC over DLPFC connectivity with parietal regions activated by this task (Tan *et al*, 2007), similar to the schizophrenia phenotype (Tan *et al*, 2006).

PPP1R1B

Dopamine- and cAMP-regulated phosphoprotein of molecular weight 32 kDa (DARPP-32) is abundant in the striatum and has a key function in modulating dopaminergic postsynaptic intracellular signaling through multifaceted effects on protein kinases (Svenningsson *et al*, 2004). One common haplotype in the *PPP1R1B* gene coding for DARPP-32 shows an association with schizophrenia, with worse IQ, verbal fluency, working memory, and Wisconsin Card Sorting performance, with reduced striatal volumes, with reduced striatal BOLD activation during the n-back, and with increased frontostriatal connectivity. Notably, both the activation and connectivity findings were replicated in a separate cohort during performance of an emotional face-matching task (Meyer-Lindenberg *et al*, 2007).

PRODH

A functional haplotype (rs4819756 and rs2870983 and rs450046 minor alleles) in the proline oxydase gene, *PRODH*, shows increased enzymatic activity, risk for schizophrenia, diminished striatal volumes, reduced striatal BOLD activation, and increased frontostriatal connectivity during the n-back task (Kempf *et al*, 2008). Despite

significant differences between the functions of proline oxydase and DARPP-32, these results are remarkably similar to those of *PPP1R1B* and converge on circuitry (prefrontal-neostriatal) that is dysregulated in schizophrenia (Meyer-Lindenberg *et al*, 2002).

AKT-1

AKT-1 is an intracellular signaling protein that has an important function in dopamine-mediated neurotransmission (Beaulieu *et al*, 2005; Wei *et al*, 2007) and has shown reduced expression in schizophrenic brains (Emamian *et al*, 2004) and lymphocytes (Tan *et al*, 2008). Further, several reports have found an association between a functional *AKT-1* genetic variations and schizophrenia (Emamian *et al*, 2004; Tan *et al*, 2008). One such variation, an SNP, rs1130233, additionally shows a relationship with neuropsychological assessments of executive function as well as n-back-related prefrontal activation. The risk allele also imparts reduced prefrontal and caudate volumes, in agreement with its hypothesized impact on frontostriatal circuitry, though formal testing of functional connectivity has not been performed at this date (Tan *et al*, 2008).

DISC-1

The *disrupted in schizophrenia* (*DISC-1*) gene codes for a protein abundant in the hippocampus, which partners with Nudel and other dynein complex proteins to impact centrosomal function, neurite outgrowth, and neuronal migration (Kamiya *et al*, 2005). Variations in *DISC-1* are associated with schizophrenia (Callicott *et al*, 2005; Ekelund *et al*, 2004; Hennah *et al*, 2003; Hodgkinson *et al*, 2004), and recent multimodal imaging data have evidenced an effect of the *DISC-1* Ser704Cys polymorphism on hippocampal structure and function in healthy adults (Callicott *et al*, 2005). Specifically, serine homozygotes showed reduced hippocampal gray matter volume, lower hippocampal *N*-acetyl aspartate, and during the n-back working memory task, abnormally greater hippocampal activation (Callicott *et al*, 2005). These results align well with the impaired suppression of medial temporal lobe activity during executive processing seen in schizophrenia (Meyer-Lindenberg *et al*, 2001). Furthermore, during verbal fluency task performance, serine homozygotes show increased prefrontal activation (Prata *et al*, 2008), though to what degree frontotemporal connectivity is directly influenced by this polymorphism remains to be tested.

ZNF804A

In a recent genome-wide association study, an SNP (rs1344706) in *ZNF804A*, a gene coding for a protein of unclear function but potential gene regulatory ability, showed independent, significant association with schizophrenia (O'Donovan *et al*, 2008). Comparing healthy individuals with either no, one, or two risk alleles, Esslinger *et al* (2009) have found that the number of risk alleles predicted greater prefrontal–hippocampal functional connectivity during the n-back working memory task, just as had been described earlier in patients (Meyer-Lindenberg *et al*, 2005b), reinforcing the fact that greater functional connectivity (especially with a dysfunctional prefrontal cortex, as in schizophrenia), not only less, can be the risk phenotype. Better understanding of the biology of *ZNF804A* is needed to clarify the nature of this observation, but it is nonetheless remarkable that a risk gene without *a priori* evidence for either prefrontal or hippocampal involvement can so clearly show a predicted illness circuit phenotype in this way.

NRG-1

Neuregulin1 (NRG-1) isoforms and its receptor ErbB4 have important functions in potentially illness-relevant neural processes, including neuronal migration, axonal guidance and myelination, synaptic plasticity, and glutamatergic dendritic spine maturation (Barros *et al*, 2009; Mei and Xiong, 2008). Variation in the *NRG-1* gene has shown association with schizophrenia diagnosis, behavioral abnormalities in mouse models responsive to antipsychotic medication (Li *et al*, 2006; Stefansson *et al*, 2002), and altered neuregulin isoform expression (Law *et al*, 2006).

In a group of individuals at high risk of developing schizophrenia by virtue of strong family history, carrier status of an NRG1 risk allele (SNP8NRG243177 polymorphism, which influences neuregulin transcript expression, Law *et al*, 2006) predicted development of psychotic symptoms as well as reduced activation in medial prefrontal and temporo-occipital regions during a sentence completion task (Hall *et al*, 2006).

The number of *NRG-1* risk alleles carried in healthy adults correlates with reduced semantic verbal fluency performance and reduced anterior cingulate, inferior frontal, and middle temporal activation measured by fMRI BOLD signal (Kircher *et al*, 2009). Disrupted microstructural connectivity in association with the risk allele of this same polymorphism is evidence by reduced white matter density and fractional anisotropy in the anterior limb of the internal capsule (Mcintosh *et al*, 2007), which contains important axonal fibers linking the prefrontal cortex with other nodes in the extended executive network. Future work is needed to confirm these findings and determine to what degree these abnormalities explain functional differences in individuals with different allelic risk loads.

SUMMARY AND FUTURE DIRECTIONS

Key brain regions that show postmortem and *in vivo* evidence for disarray in schizophrenia are important in executive functioning, and are physiologically abnormal during executive challenge in patients, evidence characteristically aberrant interactions and remarkable susceptibility to variation in putative schizophrenia risk genes.

DLPFC dysfunction and aberrant functional connectivity, relatively increased VLPFC involvement in executive circuitry, ACC, and IPL dysfunction and reduced coupling with DLPFC, impairment in suppression of medial temporal activity during certain executive challenges, prefrontal disinhibition of mesostriatal dopaminergic signaling, and reduced thalamofrontal cooperativity not only form a complex landscape of circuit changes in schizophrenia, but also, in selected subsets of these, create quantifiable links to emerging molecular footprints of genetic predisposition to psychosis. Systematic work is needed to better characterize the dynamics of these systems-level abnormalities in response to particular executive task demands, pharmacological interventions, and genetic environments.

Specifically, several avenues of research promise to provide invaluable insights into pathophysiology and ultimately targeted treatment of this devastating illness.

To address accumulating evidence of genetic heterogeneity underlying the disorder and concomitant variability in psychopathological and neuropsychological profiles, all of which may have contributed to apparent inconsistencies in the literature, more extensive genetically, clinically, and cognitively stratified studies are necessary. Likewise, longitudinal studies directed at understanding both naturalistic and pharmacologically induced fluctuations in executive network function are essential to assess the stability of circuit perturbations in schizophrenia over the course of illness and treatment. Additionally, developing advanced methodologies to bridge molecular and physiological data and fuel both candidate risk gene discovery and biological validation has become increasingly important. One such approach is to use neurocircuit risk phenotypes as quantitative trait variables to identify genetic factors contributing to executive dysfunction in psychotic disorders. Potkin *et al* (2008) have begun to implement this strategy with DLPFC activation alone as the quantitative trait variable, yielding novel results. As efforts to characterize and quantify the above-outlined systems-level circuitry disruptions in schizophrenia advance, bringing greater predictive power for diagnosis and treatment response to nuanced functional imaging phenotypes, this reverse mapping—from imaging to genes—may become increasingly valuable for understanding illness pathophysiology and for developing pharmacogenetic models. Similarly, development of robust data-driven analytical techniques, such as parallel independent components analysis (Liu *et al*, 2009) to meaningfully combine highly dimensional genetic and imaging datasets in a coordinated and comprehensive fashion may eventually help shed light on the underlying structures of each. Finally, because inherited variation in DNA sequences, though incredibly useful for identifying key molecular pathways to schizophrenia as illustrated above, is likely only a partial contributor to illness brain phenotypes, it will be progressively more important to explore connections between executive circuit dynamics and *de novo* mutations (Stefansson *et al*, 2008), epigenetics (Huang and Akbarian, 2007), and gene–environment interactions (Caspi *et al*, 2005; Nicodemus *et al*, 2008) associated with schizophrenia.

In summary, schizophrenia patients show a remarkable number of characteristic abnormalities of executive circuitry, evident *in vivo* with functional neuroimaging techniques, the topography of which corresponds well to other pathological findings in postmortem tissue and *in vivo* neurochemical (magnetic resonance spectroscopy, neuroreceptor mapping) assays. A growing list of candidate schizophrenia risk genes show variation in executive circuit dynamics, akin to that in illness, suggesting that increasing attention to genetic and genetic–environmental interactions yields promise for better understanding the biology of executive dysfunction in schizophrenia.

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DISCLOSURE

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