Dysfunctional and Compensatory Prefrontal Cortical Systems, Genes and the Pathogenesis of Schizophrenia

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Cognitive deficits are critical determinants of schizophrenia morbidity. In this review, we offer a mechanistic perspective regarding schizophrenia-related changes observed in prefrontal cortical networks engaged in working memory. A body of earlier work converges on aberrations in putative macrocircuit stability and functional efficiency as the underlying pathophysiology of the cognitive deficits in schizophrenia. In parsing the dysfunctional prefrontal cortical dynamics of schizophrenia, recent functional magnetic resonance imaging and electoencephalography works suggest that in the context of reduced capacity for executive aspects of working memory, patients engage a larger network of cortical regions consistent with an interplay between reduced signal-to-noise components and the recruitment of compensatory networks. The genetic programming underlying these systems-level cortical interactions has been examined under the lens of certain schizophrenia susceptibility genes, especially catechol-*o*-methyltransferase (COMT) and GRM3. Variation in COMT, which presumably impacts on cortical dopamine signaling, translates into variable neural strategies for working memory and altering patterns of intracortical functional correlations. GRM3, which impacts on synaptic glutamate, interacts with COMT and exaggerates the genetic dissection of cortical processing strategies. These findings reveal novel insights into the modulation and parcellation of working memory processing in cortical assemblies and provide a mechanistic link between susceptibility genes and cortical pathophysiology related to schizophrenia.

Keywords: dopamine, fMRI, genetics, glutamate, psychosis, working memory

Introduction

Understanding the neurobiology of schizophrenia remains a significant challenge of public health importance. Cognitive dysfunction is a core feature of schizophrenia, and a key focus of investigation given its impact on functional outcome and chronic disease morbidity, largely unaffected by the present pharmacopoeia (Goldberg and Weinberger 1996; Green 1996). Working memory is a limited capacity system that enables us to temporarily hold, update, and work with relevant information; it underlies higher-order thinking, language, and goal-directed behavior (Baddeley 2003). It has been shown to be an important component underlying many cognitive deficits observed in schizophrenia (Goldberg et al. 1987; Goldman-Rakic 1994; Silver et al. 2003). There are several conceptual approaches to the study of working memory processes, though most agree that working memory involves a system of limited attentional capacity, peripheral information storage systems, and executive control processes (Baddeley 2003). In this

review, we will examine recent systems-level findings in the in vivo prefrontal cortical networks engaged by working memory and related cognitive processes in patients with schizophrenia, as well as in healthy individuals with susceptibility genes for schizophrenia. As we attempt to synthesize a coherent perspective on the interplay of cortical macrocircuits implicated in these processes, we will speculate on implications for the dynamic adaptations occurring in the brain in schizophrenia, and for future work on the neurodevelopmental pathophysiology of the disorder.

Prefrontal Cortex, Working Memory, and Schizophrenia

The prefrontal cortex is involved in working memory and related higher-cognitive processes like planning and goal-directed activity (Goldman-Rakic 1995, 1996; Fuster 2000). Seminal work on single-unit recording in nonhuman primates shows that neurons located around the principal sulcus in the dorsolateral prefrontal cortex exhibit delay-related activity during delay-match-to-sample paradigms (Goldman-Rakic 1987, 1990). Pharmacological manipulations of the dorsolateral prefrontal cortex, particularly involving the dopamine (DA) D1 receptor, also modulate working memory (Sawaguchi and Goldman-Rakic 1991, 1994; Williams and Goldman-Rakic 1995). Numerous functional neuroimaging studies have since elaborated the key role of the prefrontal cortex in human working memory. It is also clear that the neural system supporting working memory does not reside only in the prefrontal cortex, but extends beyond it to involve other distant cortical areas. These include the posterior parietal cortex, the inferotemporal cortex, the cingulate gyrus, and hippocampus—all of which have anatomical connections with the prefrontal cortex (Petrides and Pandya 1984; Selemon and Goldman-Rakic 1985; Goldman-Rakic 1988, 1999; Cavada and Goldman-Rakic 1989; Fuster 1997; Jonides et al. 1998).

There is abundant evidence that the prefrontal cortex and working memory are abnormal in schizophrenia. Postmortem studies have shown increased neuronal density in the dorsolateral prefrontal cortex of patients with schizophrenia (Garey et al. 1998; Harrison 1999; Selemon and Goldman-Rakic 1999; Glantz and Lewis 2000). Cognitive deficits, including working memory, may occur before the onset of psychosis (Jones et al. 1994; Davidson et al. 1999; Cannon et al. 2002; Fuller et al. 2002; Ang and Tan 2004), and are certainly present by the first-episode and thereafter (Goldberg and Weinberger 1988; Park and Holzman 1992; Keefe et al. 1995; Gold et al. 1997; Bilder et al. 2000; Weickert et al. 2000). An extensive body of functional imaging experiments is consistent with prefrontal cortical physiological dysfunction in schizophrenia (Weinberger

et al. 1986; Andreasen et al. 1992; Fletcher et al. 1998; Manoach et al. 1999, 2000; Callicott et al. 2000; Barch et al. 2001; Meyer-Lindenberg et al. 2001; Perlstein et al. 2001; Callicott, Mattay, et al. 2003; Manoach 2003; Schlosser, Gesierich, Kaufmann, Vucurevic, Hunsche, et al. 2003; Schlosser, Gesierich, Kaufmann, Vucurevic, Stoeter 2003; Tan et al. 2005, 2006). This is characterized by abnormal activation relative to healthy controls. As we will elaborate, emerging studies argue that the directionality of the findings (i.e., too much or too little prefrontal activity) depend on the specific task paradigm utilized, disease-related differences in behavioral performance, and capacity constraints of task load (Callicott et al. 1999, 2000; Ramsey et al. 2002; Callicott, Mattay, et al. 2003; Manoach 2003), and possibly the engagement of dysfunctional and compensatory macrocircuits (Tan et al. 2005, 2006). Contemporary functional neuroimaging therefore affords the opportunity to further elaborate the dynamics of these complex pathophysiological processes underlying what appears to be inefficient brain function in schizophrenia.

Dysfunctional Prefrontal Cortical Dynamics in Schizophrenia

Early functional imaging studies in schizophrenia have documented reduced frontal-lobe regional cerebral blood flow at rest and during complex tasks involving executive function (for review, see Callicott and Weinberger 1999). Recent work examining more specific processes involved in working memory and executive cognition have also often found reduced blood-oxygen-level–dependent activation in the prefrontal cortex in patients with schizophrenia (Callicott et al. 1998; Carter et al. 1998; Stevens et al. 1998; Barch et al. 2001, 2002, 2003; Perlstein et al. 2001, 2003). One important approach has been to examine the encoding, maintenance, and the application of contextual information in cognitive control (Braver et al. 1999; Barch et al. 2001). In one such study, patients with schizophrenia performed worse on such trials but did relatively better on trials where successful maintenance of contextual information interfered with subsequent task behavior. Both of these behavioral deficits were accompanied by reduced functional magnetic resonance imaging (fMRI) activation of the dorsolateral prefrontal cortex (Barch et al. 2001). Furthermore, the patients in this study were neuroleptic-naïve and at their first psychotic episode—thus potential confounds related to illness chronicity and treatment were not applicable to these findings. In neuroimaging studies using the N-back task, which engaged a number of storage and executive processes related to working memory, patients with schizophrenia also exhibited decreased performance accuracy and reaction time relative to healthy controls, along with decreased prefrontal activation (Callicott et al. 1998; Menon et al. 2001; Meyer-Lindenberg et al. 2001; Perlstein et al. 2001). This pattern of executive processing deficits appears to be relatively specific to schizophrenia, as suggested by comparisons between patients with schizophrenia and affective disorders, where the former were found to perform worse in executive function tasks and had more dorsolateral prefrontal cortical activation deficits (Berman et al. 1993; Barch et al. 2003; MacDonald et al. 2005).

A concern has often been raised regarding the impact of patients' poorer performance on cortical activation differences per se, as well as how this might reflect differences in the capacity limitation of working memory between patients and controls. Capacity limitation, a key feature of working memory,

is usually reflected in cognitive testing as decreasing performance in response to increasing working memory load (Shallice 1988; Just and Carpenter 1996; Fuster 1997). In addressing the dynamic range of physiological responses that presumably underlie variations in capacity during an N-back working memory task with increasing cognitive load, it was found that regions within the healthy dorsolateral prefrontal cortex evinced a nonlinear "inverted-U" shaped physiological response (Callicott et al. 1999; Mattay et al. 2003; Jansma et al. 2004). Thus, areas of prefrontal cortical activation increased with task load and difficulty, alongside decreased accuracy and slower reaction time. This occurred to an extent defined by the individual's working memory capacity, after which continued increase in task load resulted in decreased prefrontal cortical activation. This is analogous to findings with single-unit recordings in monkeys (Goldman-Rakic 1990) and with EEG evoked potentials in humans (Gevins et al. 1997), that is, that memory error is associated with failure of engagement of the appropriate cortical response network. It has been suggested that the working memory capacity of schizophrenia patients is relatively reduced to account for their deficits in cognitive performance and their tendency to disengage prefrontal cortical activation when their performance is failing (Fletcher et al. 1998; Callicott, Mattay, et al. 2003; Jansma et al. 2004). Patients therefore seem to fall off the information processing "treadmill" at a lower cognitive load, possibly as a reflection of underlying neuronal pathology (Weinberger et al. 2001).

These considerations, however, still leave unresolved the possibility that nonspecific factors like psychological disengagement or lack of effort could confound the finding of reduced working memory capacity and prefrontal activation in patients (Weinberger and Berman 1996). A complementary approach, therefore, has been to study patients whose working memory performance is at or near normal, or to account for performance deficits by analyzing only correct trials within an event-related study design. This approach often yielded the intriguing finding of regions with intact or relatively increased prefrontal cortical activation (Curtis et al. 1999; Manoach et al. 1999, 2000; Callicott et al. 2000; Ramsey et al. 2002; Callicott, Mattay, et al. 2003; Manoach 2003; MacDonald et al. 2005; Tan et al. 2005, 2006), which cannot easily be interpreted as reflecting nonspecific disengagement, lack of effort, or poor performance. Instead, the results of these studies suggest that when patients are able to keep up with the processing demands, they tend to do so less efficiently by engaging greater cerebral metabolic activity or a less focused cortical activity state. This might be analogous to the recruitment of extraneous neural activity in the early phases of a variety of learning paradigms, when the optimal cognitive strategy has not been arrived at, and when the task might conceivably be found to be more difficult (Andreasen et al. 1995; Shadmehr and Holcomb 1997; Petersen et al. 1998; Rypma and D'Esposito 1999; Ramsey et al. 2004). It might also parallel the reorganization in neural strategy following cortical injury with the redistribution of increased activity to functionally related healthy brain regions (Johansen-Berg et al. 2002). Indeed, if performance is preserved, then at least part of the increased or intact activation might serve to compensate for some underlying neural dysfunction, even as the overall network architecture might be inefficient. EEG evoked potential studies have suggested that this loss of an efficient or tuned response may represent a decrease in signal to noise or a failure of response stability within the cortical microcircuits that

support these cognitive operations (Winterer, Egan, et al. 2006). This concept has recently been extended in an fMRI study of simple choice reaction time in patients with schizophrenia, in which signal to noise and independent component analyses revealed greater noise and more independent components within medial prefrontal cortex during the establishment of even this simple response (Winterer, Musso, et al. 2006).

Dysfunctional and Compensatory Cortical Networks in Schizophrenia

The conceptualization that there might be an interplay of dysfunctional and compensatory cortical regions or networks in schizophrenia gains traction in view of recent trends to examine specific working memory subprocesses that engage combinations of prefrontal subregions and associated nodes in the extended working memory network. As alluded to by previous behavioral (Goldberg et al. 1998; Kim et al. 2004) and imaging (Barch et al. 2001; MacDonald et al. 2005; Tan et al. 2005, 2006) studies, the executive aspects of working memory (e.g. the application of appropriate contextual information, or manipulation of information within working memory) appear selectively vulnerable in schizophrenia, relative to the maintenance of information. Executive processes hierarchically engage more dorsal (Brodmann Areas BAs 9, 10, and 46) than ventral regions (BAs 44, 45, 47) in the prefrontal cortex, whereby higher-order processes in the dorsolateral prefrontal cortex are suggested to exert control on more ventrolateral regions responsible for less complex processes (Fuster 1997; D'Esposito et al. 1999; Koechlin et al. 2003), such as rehearsal of information within working memory (Paulesu et al. 1993; Awh et al. 1996). Correspondingly, for patients with schizophrenia who have working memory deficits, regions of decreased activation (Barch et al. 2001; Callicott, Mattay, et al. 2003; MacDonald et al. 2005; Tan et al. 2005) or reduced functional connectivity (Kim et al. 2003; Meyer-Lindenberg, Olsen, et al. 2005; Tan et al. 2006) have often been localized to the dorsolateral prefrontal cortex in tasks engaging executive aspects of working memory that seem to exceed capacity in patients at reduced loads.

Conversely, schizophrenia patients with near normal working memory performance sometimes have shown activation patterns in the ventrolateral prefrontal cortex that were either intact (Barch et al. 2001; Perlstein et al. 2001; Kim et al. 2003; Meyer-Lindenberg, Olsen, et al. 2005), or increased (Callicott, Mattay, et al. 2003; Glahn et al. 2005; MacDonald et al. 2005; Tan et al. 2005, 2006), possibly in compensation for the dysfunctional dorsolateral prefrontal response. A series of recent fMRI findings examining brain–behavior correlations and frontoparietal functional connectivity support this interpretation (Tan et al. 2006): working memory performance was correlated with dorsolateral prefrontal cortical activation in healthy controls, but this relationship occurred at the ventrolateral prefrontal cortex in patients; and although healthy controls had relatively greater frontoparietal functional connectivity with the dorsolateral prefrontal cortex, schizophrenia patients evinced increased ventrolateral frontoparietal functional connectivity that was reciprocally related to deficits in the dorsal regions (Fig. 1). Thus, although healthy controls optimally utilized the dorsolateral prefrontal cortex in executive working memory tasks, schizophrenia patients were unable to do so but engaged greater ventrolateral prefrontal cortex involvement instead. Furthermore, poorer performing patients activated another
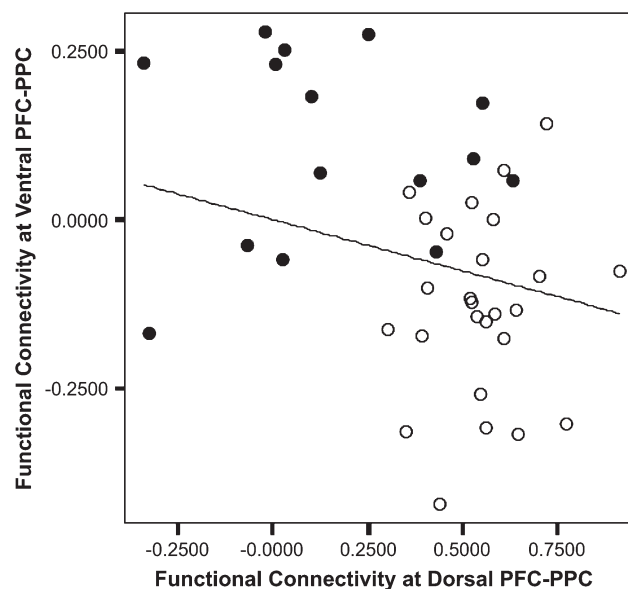
Figure 1. Functional connectivity of the ventral prefrontal cortex (PFC)—posterior parietal cortex (PPC) plotted against that of the dorsal PFC–PPC for all subjects. Functional connectivity of the left ventral PFC and right dorsal PFC regions of interest with the respective PPC regions had an inverse relationship ($P < 0.01$). Lower connectivity at the dorsal PFC–PPC predicted higher compensatory connectivity at the ventral PFC–PPC. Patients are represented by filled circles ($n = 15$) and normal controls by open circles ($n = 26$). (Adapted from Tan et al. 2006.)

region in the ventrolateral prefrontal cortex more than better performing patients, suggesting that this compensatory strategy might not always result in improved performance (Tan et al. 2006). The compensatory response may thus reflect a *relative* loss of hierarchical functional specialization in the diseased prefrontal cortex, where optimum dorsolateral prefrontal function is compromised and accompanied by a greater reliance on less efficient ventrolateral prefrontal engagement. Although resulting in a limited restoration of performance through a reweighting of the distributed neuronal architecture, the overall neural circuitry is likely to be unstable, may have a more limited functional capacity, and may eventually fail to maintain cognitive performance (i.e., reach capacity at lower levels of cognitive complexity). Still, how might these systems-level prefrontal cortical interactions relate to the core biology of schizophrenia in terms of key neurotransmitter complexes and the genes that program the wiring of this circuitry?

Imaging Genetics of Working Memory and Risk for Schizophrenia

DA-ergic and glutamatergic abnormalities have long served as major theoretical frameworks for understanding the pathophysiology as well as pharmacology of schizophrenia and its cognitive deficits, particularly working memory (Weinberger et al. 1988; Lisman et al. 1998; Carlsson et al. 2001; Egan, Goldberg, Kolachana, et al. 2001; Coyle et al. 2003; Laruelle et al. 2003; Moghaddam 2003; Sesack et al. 2003; Tamminga et al. 2003; Egan et al. 2004; Honey et al. 2004; Seamans and Yang 2004; Harrison and Weinberger 2005; Krystal et al. 2005). DA-ergic, glutamatergic, and GABAergic (gamma-amino-butyric acidergic) receptor systems are also central in the prefrontal neural dynamics mediating working memory (Sawaguchi and Goldman-Rakic 1991; Williams and Goldman-Rakic 1995; Lisman et al. 1998; Wang 1999; Durstewitz and Seamans 2002;

Seamans and Yang 2004). Locally sustained activity of prefrontal neurons that are crucial in the maintenance of relevant information during the delay period of working memory tasks (Goldman-Rakic 1987, 1990) appear to be protected against distracters and instability by DA-mediated mechanisms (Durstewitz et al. 2000), which likely act by stabilizing the inhibitory architecture (Winterer and Weinberger 2004). This is likely to be critically dependent on DA D1-receptors (Williams and Goldman-Rakic 1995) and their role in enhancing N-methyl-D-aspartic acid (NMDA) receptor–mediated postsynaptic currents in prefrontal pyramidal and GABAergic neurons active during the delay period (Seamans, Durstewitz, et al. 2001; Wang and O'Donnell 2001). Concurrently, the D1-receptor appears to cause a tonic increase in the firing of GABAergic inhibitory interneurons, allowing a relative exaggeration of task-relevant activity compared with nontask related activity, thus increasing signal-to-noise (Seamans, Gorelova, et al. 2001). Of significance to the series of functional neuroimaging studies examining this process described below, the dose–response signature of prefrontal DA upon related signaling appears to follow an inverted-U curve (Williams and Goldman-Rakic 1995; Seamans and Yang 2004; Vijayraghavan et al. 2007).

These molecular and single-neuron paradigms resonate with suggestions that the functional architecture of the lateral prefrontal cortex could be hierarchically organized, whereby the more anterior and dorsal regions are thought to be engaged in higher-order executive processing (D'Esposito et al. 1999; Koechlin et al. 2003), wherein manipulation of information in memory has recently been modeled in integrate-and-fire networks to engage more inhibitory processing (Deco et al. 2004; Deco and Rolls 2005). Thus, it would be conceivable that changes in signal-to-noise processing through the DA-ergic D1-receptor or related NMDA or GABA receptor systems in the prefrontal cortex would tend to enhance or to degrade working memory predictably along the inverted-U shaped tuning curve (Williams and Goldman-Rakic 1995; Seamans and Yang 2004), and that executive aspects of working memory would be more sensitive to these variable effects.

Indeed, extensions of these hypotheses to the more complex in vivo human cortex have, in recent years, supported these possibilities (Egan, Goldberg, Kolachana, et al. 2001; Weinberger et al. 2001; Mattay et al. 2003; Egan et al. 2004; Bertolino et al. 2004; Blasi et al. 2005; Meyer-Lindenberg, Kohn, et al. 2005). This has been facilitated by examining the effects of an increasing set of putative schizophrenia candidate genes (particularly COMT and GRM3) using neuroimaging of working memory. Although these genes by themselves have modest effects on schizophrenia risk per se (Harrison and Weinberger 2005), their influence on key DA-ergic and glutamatergic neurotransmitter signaling pathways implicated in more constrained intermediate phenotypes such as working memory provides a powerful approach to examine the relationships between the biology of schizophrenia risk and specific brain function in vivo (Meyer-Lindenberg and Weinberger 2006).

The study of catechol-o-methyltransferase (COMT) is an important example of recent studies linking genes to cortical physiologic organization. COMT is a major enzyme in synaptic DA catabolism with a critical role in prefrontal cortical DA signaling because of the relative lack of DA transporters in this region (Seasack et al. 1998; Lewis et al. 2001; Chen et al. 2004). A common polymorphism in the COMT gene resulting from a valine-to-methionine Val(108/158)Met substitution gives rise

to a significant reduction in its enzymatic activity in the prefrontal cortex and in peripheral tissues (Lotta et al. 1995; Lachman et al. 1996; Chen et al. 2004). This is thought to correspond to reduced prefrontal DA in proportion to Val-allele load—the allele that has been weakly associated with risk for schizophrenia and psychosis. Located on chromosome 22q11, this susceptibility locus has been implicated in meta-analyses of linkage to schizophrenia (Badner and Gershon 2002; Lewis et al. 2003). COMT is also deleted in velocardiofacial syndrome, a condition that has a 20 times increased risk for schizophrenia (Murphy 2002). However, the effect on risk for schizophrenia of the specific COMT Val(108/158)Met polymorphism is small and inconsistent (Glatt et al. 2003; Fan et al. 2005). This is not surprising given the manifold factors associated with schizophrenia pathogenesis, such as the interaction of genes and environmental conditions (Caspi et al. 2005).

In contrast, investigations of the effect of the COMT Val(108/158)Met polymorphism on working memory have converged with that predicted by cellular models of prefrontal DA previously described. Reduced prefrontal DA in COMT Val-carriers, presumably through decreased tonic D1-receptor activation, would be expected to result in firstly, reduced cortical signal-to-noise; secondly, a relatively inefficient and detuned prefrontal cortical activation map if performance accuracy is still maintained; and ultimately, reduced working memory and executive function. Each of these predictions have been borne out, and COMT genotypes were found to account for about 3–4% of the variance in performance on frontal-lobe tests, with poorer performance in subjects carrying the Val- rather than the Met-allele, even in normal subjects (Egan, Goldberg, Kolachana, et al. 2001; Malhotra et al. 2002; Goldberg et al. 2003; Nolan et al. 2004; de Frias et al. 2006). Analogous results were obtained in normal children (Diamond et al. 2004). Correspondingly, using fMRI to study cortical activity, healthy Val-allele carriers engaged relatively greater N-back prefrontal cortical activation, consistent with the conclusion that Val carriers are relatively less efficient (Egan, Goldberg, Kolachana, et al. 2001; Mattay et al. 2003; Meyer-Lindenberg et al. 2006). As might be predicted by the greater dependence on dorsolateral prefrontal cortical processing of higher-executive tasks (D'Esposito et al. 1999; Koechlin et al. 2003; Deco et al. 2004; Deco and Rolls 2005), these COMT effects in dorsolateral prefrontal cortex were more prominent at higher working memory loads (Mattay et al. 2003). The study by Mattay et al. (2003) also showed that the putatively inefficient prefrontal cortical activation in Val-homozygotes could be improved by the dopamimetic amphetamine, resulting in a more focused reduction of dorsolateral prefrontal activation as it became more optimally modulated, or closer to its peak on the inverted-U prefrontal DA tuning curve (Mattay et al. 2003). Conversely, Met-homozygotes, who were presumably already at the peak at baseline, appeared to be pushed off the peak of the curve by amphetamine, resulting in the adoption of a relatively inefficient (increased) cortical activation pattern (Fig. 2). Using an EEG evoked potential analysis based on signal-to-noise during the P300 oddball paradigm, it was recently demonstrated that COMT Val-allele load was associated with poorer signal-to-noise during this paradigm in prefrontal cortex, in patients with schizophrenia, in their healthy siblings, and also in normal subjects (Winterer, Egan, et al. 2006). These studies strongly indicate that this functional polymorphism in COMT impacts on the stability and tuning of cortical circuitry during working memory processing.
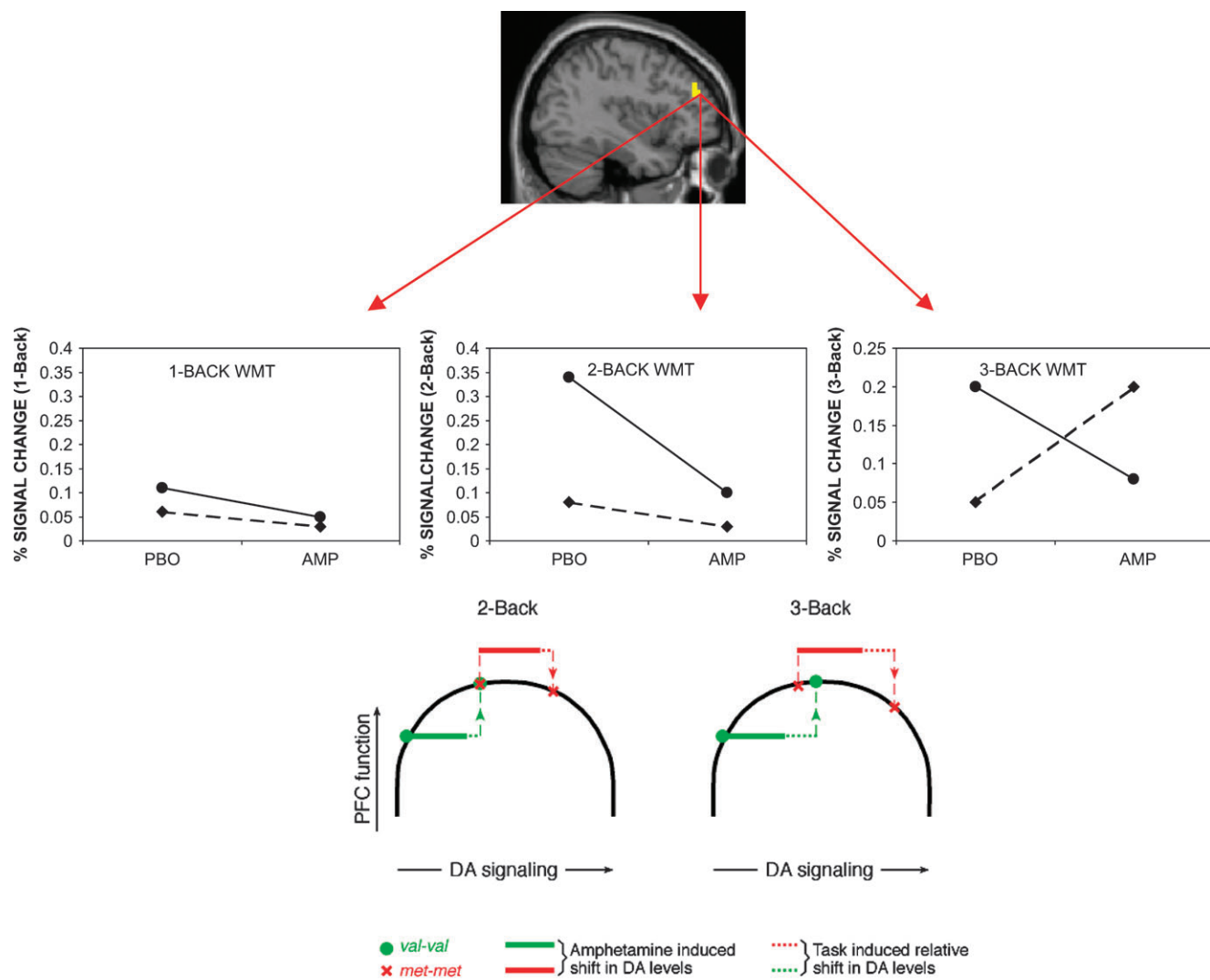
Figure 2. fMRI activation signal was extracted from the dorsal prefrontal cortex (top panel) in the presence of amphetamine (AMP) or placebo (PBO) administration at differing working memory task (WMT) loads as a function of COMT genotype (middle panel). In COMT Val-homozygote individuals (who have relatively lower cortical DA; solid lines, middle panel), AMP improved prefrontal cortical efficiency (lower activation). In contrast, individuals homozygous for the *met* allele (who have relatively greater cortical DA; dashed lines, middle panel), AMP had deleterious effects on PFC efficiency (greater activation) at 3-back WMT load (rightmost graph in middle panel). These results suggest that individuals homozygous for the COMT-*val* allele have PFC functional efficiency on the up slope of the normal range, whereby AMP could increase DA signaling to more optimal levels nearer the peak (bottom panel). On the other hand, individuals homozygous for the COMT-*met* allele appear already near peak PFC functional efficiency, and so increased DA signaling from AMP shifted PFC function onto the down slope of the inverted-U efficiency curve (bottom panel; adapted from Mattay et al. 2003).

Cortical information processing, especially in prefrontal cortex, impacts on the regulation of DA activity in the mesencephalon (Winterer and Weinberger 2004). This is probably important in learning as it is reasonable to assume that reward signals emanating from brainstem DA neuronal firing must correspond to prefrontal cortical executive action for learning to take place. COMT, presumably via its actions at the cortical level, appears to impact on DA activity in the brainstem. In a study of normal postmortem human brainstem, individuals with a COMT Val/Val genotype had twice the expression of the messenger RNA for tyrosine hydroxylase, the rate limiting biosynthetic enzyme for DA (Akil et al. 2003). Remarkably, this relationship has been confirmed in a positron emission tomography imaging study of normal living subjects. COMT Val-carriers were shown to have relatively increased midbrain DA synthesis (measured with f-18 flurodopa uptake) that correlated negatively with N-back dorsolateral prefrontal cortical activation (measured with O-15 H2O regional cerebral blood flow), whereas prefrontal activation in Met-homozygotes positively correlated with midbrain DA synthesis (Meyer-Lindenberg, Kohn, et al. 2005). These reciprocal relationships fit tightly to the inverted-U tuning curve of prefrontal DA whereby increased midbrain DA synthesis in COMT Val-carriers with lower prefrontal DA tends to help restore more efficient cortical activation, whereas COMT Met-homozygotes are at risk to become less efficient with increased midbrain DA synthesis.

Like DA, glutamatergic abnormalities are important in schizophrenia and working memory function, and it follows that disease-related mutations in glutamate signaling could similarly impair its function. This has been found to be the case for GRM3 (Egan et al. 2004), a heteroceptor modulating NMDA-receptor transmission, and located on chromosome 7q21–22 (Moghaddam and Adams 1998; Egan et al. 2004; Harrison and Weinberger 2005). A polymorphism in intron 2 and related haplotypes were
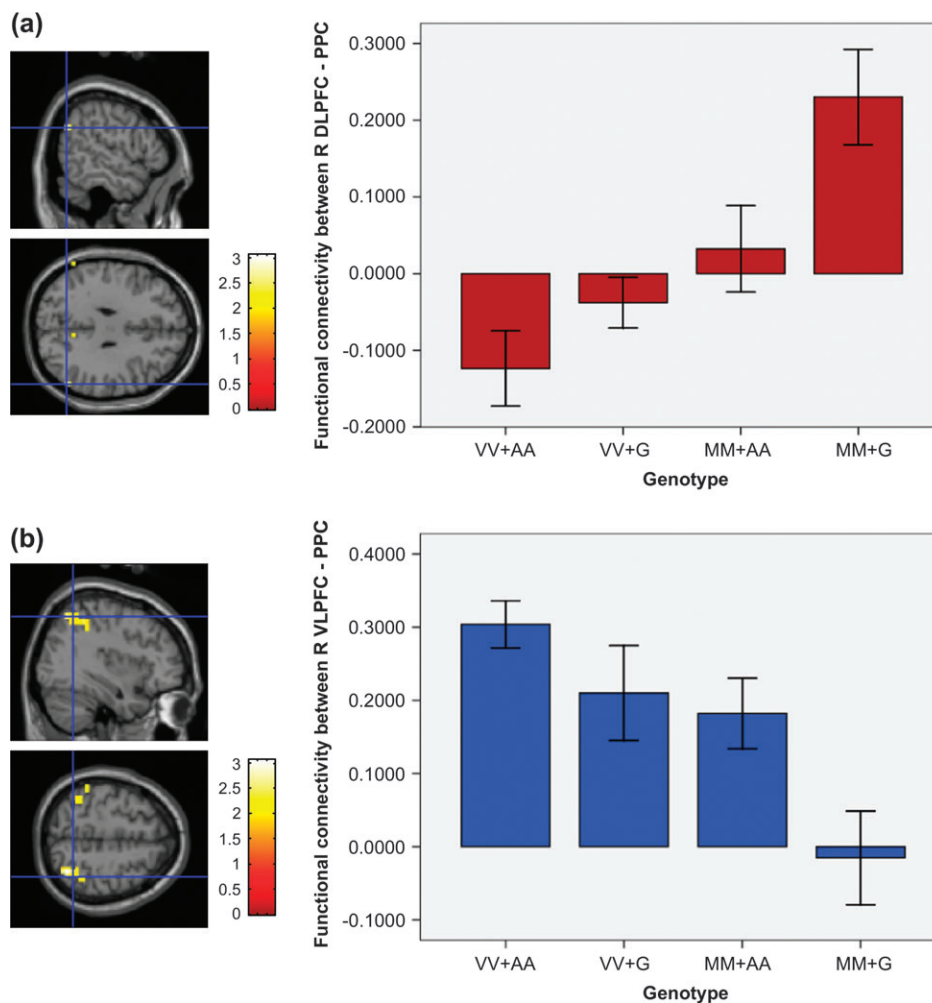
Figure 3. (a) Regions in the bilateral posterior parietal cortex (PPC) where functional connectivity with the dorsolateral prefrontal cortex (DLPFC) occurred in the conjunction contrast of COMT Met-homozygote > Val homozygote and GRM3 G-carrier > A-homozygote ($P < 0.001$ uncorrected). (b) Regions in the bilateral PPC where functional connectivity with the ventrolateral prefrontal cortex (VLPFC) occurred in the opposite conjunction contrast of COMT Val-homozygote > Met homozygote and GRM3 A-homozygote > G-carriers ($P < 0.001$ uncorrected). There was a reciprocal relationship whereby decreased DLPFC–PPC functional connectivity with relatively deleterious COMT Val (Egan, Goldberg, Kolachana, et al. 2001) and GRM A alleles (Egan et al. 2004) was associated with increased VLPFC–PPC functional connectivity and vice versa. (Adapted from Tan et al. 2007)

significantly associated with schizophrenia in several samples (Martí et al. 2002; Egan et al. 2004; Fallin et al. 2005; Chen et al. 2005), though negative studies also have been reported (Norton et al. 2005). GRM3 regulates synaptic glutamate via a presynaptic mechanism and by regulating the expression of the glial glutamate transporter, which inactivates synaptic glutamate. Risk variants in GRM3 may be a factor influencing alternative splicing of the GRM3-receptor (Sartorius et al. 2006). In postmortem brain, the risk allele is associated with reduced prefrontal glial glutamate transporter EAAT2, a protein modulating synaptic glutamate (Egan et al. 2004). Consistent with the role of the glutamatergic system in schizophrenia and working memory, the risk allele was associated with inefficient prefrontal cortical fMRI activation and reduced working memory performance even in normal subjects (Egan et al. 2004).

Critically, given the tight relationships governing DA-ergic, and glutamatergic (and GABAergic) dynamics in the biology of working memory (Sawaguchi and Goldman-Rakic 1991; Williams and Goldman-Rakic 1995; Lisman et al. 1998; Wang 1999; Durstewitz and Seamans 2002; Seamans and Yang 2004), and their putatively greater involvement in executive aspects

of working memory at the dorsolateral prefrontal cortex (D'Esposito et al. 1999; Koechlin et al. 2003; Mattay et al. 2003; Deco et al. 2004; Deco and Rolls 2005), we would expect that higher-order working memory processes taxing dorsolateral prefrontal cortex might be more vulnerable to the combined effect of suboptimal DA-ergic and glutamatergic influence. If these processes were related to the prefrontal deficits associated with schizophrenia, a similar pattern of inefficiently increased dorsolateral prefrontal cortical activation might occur in the context of relatively preserved cognitive performance (Curtis et al. 1999; Manoach et al. 1999, 2000; Callicott et al. 2000; Ramsey et al. 2002; Callicott, Mattay, et al. 2003; Manoach 2003; Tan et al. 2005, 2006). Moreover, this pattern of relatively increased activation predicted during suboptimal DA-ergic and glutamatergic function might also be associated with reduced frontoparietal functional connectivity as found in schizophrenia (Tan et al. 2006). Correspondingly, putative compensatory activation from the ventrolateral prefrontal cortical regions (Barch et al. 2001; Perlstein et al. 2001; Callicott, Mattay, et al. 2003; Kim et al. 2003; Glahn et al. 2005; MacDonald et al. 2005; Meyer-Lindenberg, Olsen, et al. 2005; Tan et al. 2005, 2006)

would be engaged with reciprocal increased activation and frontoparietal functional connectivity. Consistent with the interplay of cortical macrocircuits suggested by these possibilities, a recent fMRI study revealed that the integrity of higher-executive areas in the dorsolateral prefrontal cortex could be disproportionately compromised and inefficient in the presence of combined deleterious COMT and GRM3 genotypes in normal subjects, with a reweighting of activity to the ventrolateral prefrontal cortex if performance was maintained (Fig. 3) (Tan et al., 2007).

If confirmed, these findings could extend putative brain DA-ergic and glutamatergic cross-talk to the level of in-vivo neural systems interactions in cortical circuits implicated in working memory dysfunction and in schizophrenia. To the extent that these complex genetic associations mimic biological phenomena related to schizophrenia, they suggest that the neurobiology of schizophrenia involves dynamic changes to cortical systems as they adapt to these adverse neurobiological environments through the additional engagement of related cortical networks—possibly those usually engaged by processes lower in the cognitive processing hierarchy such as the ventrolateral prefrontal cortex. This example of putative disease-related functional plasticity appears at least in part genetically driven, and dissociable. The disproportionately inefficient prefrontal response associated with the combined deleterious genotypes of COMT and GRM3 also underlies an important concept in complex genetic diseases—that of epistatic interactions between genes, each of small individual effect. Thus, COMT, GRM3, and/or closely related downstream molecular events could play leading roles in human working memory and the pathogenesis of schizophrenia and could provide a foothold for other clinically relevant investigations.

Future Directions

Future work will need to elaborate on these early leads in several major areas—particularly in elaborating the related molecular events, and the developmental pathophysiology of schizophrenia. It would be critical to improve upon the resolution of how genetic variation (and indeed haplotypic variation; The International HapMap Consortium 2005) in COMT and GRM3, and other related schizophrenia susceptibility genes impacting neurotransmission (such as neuregulin, dysbindin, DISC1, RGS4, and G72) translate to molecular mechanisms that could account for these systems-level blood-oxygen-level–dependent observations in fMRI. We speculate that higher synaptic DA in COMT Met-homozygotes favorably enables the engagement of frontoparietal networks to handle the executive demands of complex working memory tasks, possibly with optimal D1 and NMDA-receptor–mediated signal-to-noise processing (Sawaguchi and Goldman-Rakic 1991; Moghaddam and Adams 1998; Durstewitz and Seamans 2002; Seamans and Yang 2004), and associated increased neural firing synchronicity (Wang 2001; Spencer et al. 2004) indexed by functional connectivity. Conversely, less efficient and noisier processing in the context of lower synaptic DA in COMT Val-homozygotes and more deleterious glutamatergic states, as well as in disease states, could require the additional recruitment of parallel inhibitory networks from the ventrolateral prefrontal cortex. These might have computational properties required to supplement dysfunctional dorsolateral prefrontal cortical executive processes. However, a mechanistic explanation for how the

engagement of additional networks occurs in response to the relative loss of function of others is unknown. Clearly, not all brain regions are affected to the same degree in schizophrenia. But beyond the important finding that cellular abnormalities may occur at the dorsolateral prefrontal cortex but not at more ventrolateral regions (Selemon et al. 2003), relatively little is known about how some of these network changes could be grounded in terms of its neuropathology. Promising ideas along the lines of neural modeling (Deco et al. 2004; Deco and Rolls 2005), and other paradigms related to cortical plasticity and response to injury (Corbetta et al. 2005; Serrien et al. 2006) could be helpful in future investigational efforts to further resolve the critical molecular events influencing macrocircuitry changes in schizophrenia.

Another major avenue of future work is to consider these networks in terms of their neurodevelopmental phases. Core cognitive deficits, in which working memory plays a leading role, are likely to have begun before the first psychotic episode (Jones et al. 1994; Davidson et al. 1999; Cannon et al. 2002; Fuller et al. 2002; Ang and Tan 2004). Healthy siblings of schizophrenia patients have working memory deficits (Egan, Goldberg, Gscheidle, et al. 2001), as well as prefrontal cortical activation abnormalities (Callicott, Egan, et al. 2003). The prefrontal cortex is one of the last structures to mature in humans, and key changes occur in prefrontal cortical neurons around adolescence, particularly in terms of the enhanced inhibition critical for executive function (Lewis et al. 2004). These developmental changes might therefore be both temporally and causally related to the onset of prodromal symptoms and the first psychotic episode, which tend to occur at late adolescence and early adulthood (Weinberger 1987; McGlashan and Hoffman 2000; Lewis et al. 2004). However, relatively little is understood about how the functional architecture of working memory, genes, and brain developmental trajectories interact, and how this might lead to a decompensation in those destined to develop psychosis, although some data on language deficits are emerging from longitudinal studies of high-risk subjects (Whalley et al. 2004, 2006). It might be conceivable that subtle cortical network physiological differences exist vis-à-vis recent findings of cortical thickness changes during longitudinal neurodevelopmental studies in schizophrenia, velocardiofacial syndrome, Williams syndrome, and attention-deficit-hyperactivity disorder (Thompson et al. 2001; Toga et al. 2006).

Finally, understanding how schizophrenia susceptibility alleles influence working memory in the brain could provide clues about biomarkers and targets for novel treatment and preventative strategies. The COMT genotype was recently demonstrated to influence improvement in working memory following antipsychotic treatment. Individuals homozygous for the COMT Met-allele improved more in working memory after antipsychotic treatment (Bertolino et al. 2004; Weickert et al. 2004). Notably, this was reflected by a more efficient dorsolateral prefrontal cortical function following treatment (Bertolino et al. 2004). Better understanding of how COMT and other factors associated with disease neurodevelopment and medication response intersect as a function of brain DA could serve as a starting point in identifying novel treatment targets. Indeed, a study of tolcapone, a central nervous system penetrant COMT inhibitor, has found a salutary effect of this drug on working memory performance in healthy volunteer subjects, especially in COMT Val-allele carriers, and also an improvement in prefrontal cortical efficiency measured with fMRI (Apud et al.

2007). The results of tolcapone in patients with schizophrenia are eagerly anticipated. The emerging data also suggest that dynamic changes in cortical systems occur as they adapt to adverse neurobiological conditions, perhaps through the engagement of additional cortical networks, and resulting in an overall less efficient neural architecture that is ultimately dysfunctional (Callicott, Mattay, et al. 2003; Corbetta et al. 2005; Tan et al. 2005, 2006, unpublished manuscript). Further evaluation of the effects of treatments on these processes should be warranted through the study of disease susceptibility genes, in combination with longitudinal follow-up, advances in experimental task design, and the use of multimodal neuroimaging. There are potentially powerful synergies in linking fMRI with the temporal resolution of megnetoencephalography or EEG (Horwitz and Poeppel 2002) and the enhanced structural connectivity measurements of diffusion-tensor imaging (Kim DS and Kim M 2005). These developments will herald an era of rapid bidirectional dataflow between cellular molecular models, and the in-vivo human brain in health and disease, leading perhaps toward cures and prevention (Insel and Scolnick 2006).

Notes

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