

THE COGNITIVE NEUROSCIENCE OF SCHIZOPHRENIA

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■ **Abstract** Individuals with schizophrenia experience a range of cognitive deficits and associated dysfunctions in the neural systems that support cognitive processes. This chapter reviews the literature on disturbances in working memory, executive control, and episodic memory in schizophrenia. Advances in basic cognitive neuroscience are described to help explain the cognitive neuroscience of schizophrenia. For working memory in schizophrenia, evidence is reviewed regarding deficits in the verbal (phonological loop) and nonverbal (visual-spatial scratch pad) buffer systems as well as in the central executive function. In the domain of episodic memory, evidence is reviewed for deficits in recollection versus familiarity processes in episodic memory. Also discussed are conceptual issues and potential confounds relevant to understanding the cognitive neuroscience of schizophrenia, including the role that cognitive deficits play in the developmental course of schizophrenia, relationships to specific symptom domains, behavioral performance confounds, and medication influences on behavioral performance and brain function.

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INTRODUCTION

Researchers and theorists have long recognized that abnormalities in cognitive function are a key component of schizophrenia, one of the most debilitating psychiatric disorders. Nonetheless, the past two decades have witnessed a relative explosion of research on cognition in schizophrenia, much of it couched within the framework of understanding the cognitive neuroscience of schizophrenia. This emphasis on cognition in schizophrenia is in part due to the growing body of research that suggests cognitive function in schizophrenia is one of the most critical determinants of quality of life in schizophrenia, potentially more so than the severity of other aspects/symptoms of schizophrenia such as hallucinations, delusions, or even negative symptoms (Green et al. 2000). Such findings have led even the most applied researchers and clinicians to become more invested in understanding the nature and source of cognitive deficits in schizophrenia, as such information may help to identify the treatment approaches that may be most effective in ameliorating such cognitive deficits in schizophrenia.

The research on cognitive function in individuals already suffering from manifest illness has identified deficits in many different cognitive domains, and it is beyond the scope of this chapter to review the literature relevant to all possible cognitive deficits and associated neural dysfunctions in schizophrenia. However, three cognitive domains in schizophrenia arguably have received the vast majority of research attention and consistent evidence suggesting impairment: working memory (WM), executive control, and episodic memory (EM). In reviewing and summarizing the large literature on each of these cognitive domains in schizophrenia, I apply the advances made in basic cognitive neuroscience to help us understand the clinical cognitive neuroscience of schizophrenia.

CONCEPTUAL AND METHODOLOGICAL ISSUES

A number of conceptual and methodological issues have implications for interpreting the empirical literature across a range of cognitive domains thought to be impaired in schizophrenia. These issues include (a) the relationship between cognitive deficits and either vulnerability to schizophrenia, manifest illness as a whole, or specific symptoms; (b) the potential influences of medications used to treat schizophrenia on behavioral performance, brain function, or even brain structure; and (c) the influence of behavioral performance on brain function.

Cognition, Schizotypy, and Schizophrenia

At least some of the cognitive-neural system dysfunctions present in individuals with schizophrenia may be dissociable from each other, in that different etiological mechanisms may cause them, and thus the dysfunctions may be differentially related to manifest symptoms and/or vulnerability to this disorder. For example, some deficits are present only in ill individuals or in those at risk for the disorder. The predominant view of the genetics of schizophrenia is that it is polygenic, with the manifest illness resulting from the combined action of multiple genes. As such, some individuals will have genes that put them at risk for the development of schizophrenia, but they will never develop manifest illness (Meehl 1962). If at least some of these genes also contribute to cognitive-neural dysfunction, then such individuals may share common cognitive deficits with individuals who have the manifest illness. As an example, Cannon et al. (2002) have argued that prefrontally mediated WM deficits are one such vulnerability factor in schizophrenia that does not vary with clinical state. Other cognitive-neural system dysfunctions may be present only in individuals with either schizophrenia itself, or at least some subclinical symptoms of the disorder (e.g., schizotypal symptoms). These types of cognitive-neural system dysfunctions may also have a genetic contribution, but to manifest may require either a large set of "schizophrenia" genes or the additional contribution of some environmental event. For example, Cannon and colleagues have argued that the occurrence of medial temporal lobe and EM deficits in schizophrenia reflect the combined contribution of genes and an environmental event such as fetal hypoxia that is itself biologically disruptive (Cannon et al. 2002).

A second characterization is whether the cognitive-neural system dysfunction plays a specific role in the development of other symptoms of schizophrenia, such as hallucinations, delusions, thought disorder, or negative symptoms. Some cognitive-neural disturbances may be necessary for the development of specific types of symptoms in schizophrenia (though not necessarily sufficient), and thus may be a key mechanism in the pathway to symptom formation. For example, it has been argued that deficits in WM in schizophrenia play a causal role in disorganized speech (e.g., Melinder & Barch 2003). If so, then the severity of such cognitive deficits across individuals should be correlated with the severity of the symptoms to which they contribute. However, other cognitive-neural system disturbances may not be causally related to any specific symptoms, but may still serve to constrain and modify overall life function in individuals with schizophrenia. For example, deficits in EM in schizophrenia have not been linked clearly to the development of a specific type of symptom in schizophrenia, but the deficits may be critically important in determining the ability of patients to function well in their everyday lives. The severity of this type of cognitive deficit would not be expected to correlate across individuals with the severity of any particular symptom, though it may be correlated with a variety of indices of life function.

Medication Influences on Cognition and Brain Function

Individuals with schizophrenia typically are treated with a range of medications, which can include either typical or atypical antipsychotics, anticholinergic agents (benzotropine), and even mood stabilizers or antidepressants. These medications influence a range of neurotransmitter systems with known importance to cognition, including dopamine, norepinephrine, and acetylcholine, and can have detrimental influences on cognition (and potentially even beneficial effects). For example, several studies have suggested that anticholinergic medications can impair both WM and EM in individuals with schizophrenia (e.g., Strauss et al. 1990). Fortunately, a relatively large number of behavioral studies demonstrate that individuals with schizophrenia who are currently off medications or who have never taken medications show the same general patterns of cognitive deficits as those of medicated individuals with schizophrenia (e.g., Barch et al. 2003, Saykin et al. 1994). Thus, cognitive deficits in schizophrenia clearly are not simply a side effect of medication treatment. Unfortunately, researchers have performed fewer studies of cognitive task-related functional brain activation in unmedicated individuals with schizophrenia, let alone in medication-naïve individuals with schizophrenia. The study of medicated individuals with schizophrenia presents an even larger confound in functional imaging than in behavioral studies, as we know little about the influences of antipsychotic medications on global blood flow or the brain mechanisms that govern the coupling between neural responses and blood flow, the process that forms the basis of commonly used techniques such as functional magnetic resonance imaging (fMRI). The existing studies of unmedicated individuals with schizophrenia have found disturbances in cognitive task-related functional brain activation (Andreasen et al. 1992, Barch et al. 2001, Berman et al. 1986). Studies of individuals at risk for the development of schizophrenia (but whom have never taken medications) also suggested changes in functional brain activation (Callicott et al. 2003a, Keshavan et al. 2002, Thermenos et al. 2004). However, much more information is needed on the ways in which various drugs may influence either the integrity of functional brain activation in particular brain regions or potentially alter mechanisms that form the basis of imaging techniques.

Potential Confounds Related to Poor Performance

Not surprisingly, the vast majority of studies designed to examine the cognitive neuroscience of schizophrenia find that patients tend to perform worse than controls on a range of cognitive tasks. Such behavioral impairments are to be expected if one hypothesizes that individuals with schizophrenia have disturbances in neural systems that support particular cognitive functions. At the same time, one commonly raised concern is that changes in functional brain activation associated with poor performance may simply reflect a failure to engage in the task rather than some inherent disturbances in that brain region or system. In response to this criticism, researchers have taken one of three approaches: (a) Use tasks that do not elicit performance differences between patients and controls, though it is hard

to find valid measures of WM and EM that do not elicit performance deficits in patients. (b) Examine subsets of individuals matched on behavioral performance and compare results to the full sample of participants. Such an examination can determine whether findings of altered brain activation hold in individuals with schizophrenia who perform relatively well, but raises issues regarding selection bias and sample representativeness. (c) Use event-related experimental designs that allow one to examine activation associated with errors versus correct responses separately. Findings of altered brain activation in correct trials among individuals with schizophrenia may be consistent with theories positing impairments in the brain systems that typically support performance on the task of interest and would avoid some of the effort or motivation confounds that plague studies of cognitive processing in schizophrenia. However, such findings do raise interesting questions regarding how individuals with schizophrenia were able to get the trial correct. It is possible that individuals with schizophrenia sometimes employ alternative strategies (which may be less efficient or effective than more commonly used strategies) to accomplish the task, which in turn may engage a different brain region or set of brain regions than those typically activated by controls.

WORKING MEMORY

Cognitive Neuroscience Theories of Working Memory

The work on the basic cognitive neuroscience of schizophrenia has helped to frame and guide the research on WM in schizophrenia. WM is typically defined as the ability to maintain and manipulate information over short periods of time. Although many individuals use the term WM as if it were a unitary construct, it is widely agreed that WM involves several different component processes. Baddeley's (1986) influential theory of WM distinguishes among four major subcomponents: (a) a short-term storage buffer for visual information that is often referred to as the visuospatial scratch pad; (b) a short-term storage buffer for verbal information, referred to as the phonological loop; (c) a central executive component that guides the manipulation and transformation of information held within the storage buffers; and (d) the more recently described episodic buffer (Baddeley 2000). Each of these major component processes of WM can be subdivided further into processes, some of which have been associated with the function of specific brain systems. For example, the phonological loop is thought to involve articulatory rehearsal of phonologically based representations. A number of studies suggest that articulatory rehearsal is particularly dependent on regions of left ventrolateral prefrontal cortex (VLPFC), including Brodmann's area (BA) 44 and BA45. Figure 1 (see color insert) shows the location of these regions. Functional imaging studies examining rehearsal show activation of this region (e.g., Chein & Fiez 2001), and lesions to this region impair rehearsal but not the ability to use phonological representation (Vallar et al. 1997). In contrast, the processing or storage of phonological representation is thought to be dependent on regions of left posterior parietal cortex (see Figure 1),

again based on data from both lesion and imaging studies in healthy humans (e.g., Ravizza et al. 2004, Vallar et al. 1997).

The specific component processes of the visual-spatial scratch pad are less clear. One hypothesis regarding how we maintain spatial information is that we use covert shifts of attention to the spatial locations to be remembered, a process that has been referred to as attention-based rehearsal (e.g., Awh & Jonides 2001). These covert shifts of attention are thought to depend, at least in part, on the same neural systems that support spatial attention processing, such as right posterior parietal cortex (Postle et al. 2004). Consistent with this hypothesis, imaging studies of spatial WM consistently demonstrate activation of right posterior parietal regions (RPPC) (Postle et al. 2004), and lesions to RPPC lead to selective deficits in spatial WM (Pisella et al. 2004). In addition to RPPC, studies of spatial WM also consistently activate regions such as the frontal eye fields (FEFs) and the supplementary eye fields (SEFs). Curtis et al. (2004) recently argued that information about the spatial location of cue information is represented in posterior parietal regions (PPC), whereas information about the director of visual saccades is processed and/or maintained in FEF/SEF regions.

A host of different processes may fall into the central executive function, including those involved in the manipulation of information being stored in the buffers, protection from interference created by competing information or decay across time, temporal coding or sequence, and updating of the contents of WM. At the most simplistic level, many of the processes associated with the central executive function have been assumed to be supported by the dorsolateral region of prefrontal cortex (DLPFC), typically BA46 and BA9 bilaterally. A large body of empirical data, both from lesion and functional imaging studies in healthy humans, support the idea that DLPFC is indeed critical for many processes ascribed to the central executive function (Smith & Jonides 1999). However, it is also clear that regions other than DLPFC are also important, and we should not assume isomorphism between DLPFC and executive function.

A related way in which the component processes of WM have been divided is in the distinction between maintenance and manipulation (e.g., Owen 1997). In many ways, this distinction maps onto the division between buffer systems (maintenance) and the central executive function (manipulation). A number of functional neuroimaging studies have suggested that DLPFC and VLPFC are differentially involved in maintenance versus manipulation components of WM. These studies suggest that VLPFC regions are engaged by both maintenance and manipulation processes (with the explanation that manipulation tasks almost invariably require maintenance of some type), whereas DLPFC regions are engaged primarily by manipulation processes (e.g., Curtis et al. 2000).

The discussion of the neural basis of WM above is focused on specific brain regions. However, a great deal of work in the cognitive neuroscience of WM has also focused on understanding the contributions of specific neurotransmitter systems to the processes engaged in WM tasks. It is beyond the scope of this chapter to exhaustively review this large body of literature. However, it is fair to

say that the dopamine system has received the most attention in this domain, driven in large part by the seminal work of Patricia Goldman-Rakic and her colleagues (Goldman-Rakic et al. 2000), who have demonstrated a pivotal role for dopamine function in nonhuman primate models of WM. A growing body of research also suggests that dopamine agents can modulate WM function in humans, although the results in this domain vary as a function of factors such as the nature of the task and the ability level of the participant (for a review, see Barch 2004). A number of researchers have postulated specific computational roles for dopamine in WM. For example, Cohen and colleagues (Cohen et al. 1991) have suggested that dopamine serves to modulate the signal-to-noise ratio. More recently, Braver and colleagues (Braver et al. 1999, 2002) have suggested that dopamine may serve as a cue for updating information in WM.

Working Memory in Schizophrenia

PHONOLOGICAL LOOP IN SCHIZOPHRENIA One can ask questions about the integrity of the phonological loop in schizophrenia either by examining performance on tasks thought to depend upon the phonological loop, or by examining the integrity of brain activation in regions thought to support the phonological loop. Serial recall tasks with relatively low numbers of items (such as digit span forward, Sternberg, or Brown-Petersen paradigms) and no interference are considered by some to be prototypical phonological loop tasks. Such tasks require both intact articulatory rehearsal and intact phonological storage/representations to perform successfully, but do not necessarily require other aspects of WM, such as central executive processes. A number of studies have shown that individuals with schizophrenia demonstrate: (a) relatively intact performance on digit span forward tasks, particularly when the number of items is at or below WM span (7 ± 2) (e.g., Cohen et al. 1999) and when there is no verbal interference (Fleming et al. 1995); (b) no disproportionate impairment for recall of lists with phonologically similar versus dissimilar items, suggesting an intact ability to represent phonological information (Elvevag et al. 2002); (c) intact serial position curves among individuals with schizophrenia (Wexler et al. 2002); and (d) equal impairments on verbal and nonverbal working memory tasks (e.g., Barch et al. 2002, Walter et al. 2003). However, work by Wexler, Stevens, and colleagues (Wexler et al. 1998) suggests that deficits in a verbal serial recall task that specifically probes for position information may be greater for at least a subset of patients than are deficits on a tone serial-recall task. Further, a recent meta-analysis of the performance of individuals with schizophrenia on a range of WM and EM did find significant impairment on digit span forward, though of a fairly small effect size compared with performance in other memory domains (Aleman et al. 1999).

Another way to examine the integrity of the phonological loop in schizophrenia is examine whether individuals with schizophrenia show abnormalities in the function of brain regions thought to be critical for phonological loop function (VLPFC and PPC). The vast majority of the WM functional activation studies

report intact activation of VLPFC regions during WM performance in individuals with schizophrenia. Table 1 presents a summary of the studies that have used one type of WM task, an Nback task, to probe WM in schizophrenia (and that have provided direct statistical comparisons of the groups). Of the fourteen studies in Table 1, only three found altered activation in left inferior frontal cortex. In addition, studies using other types of WM tasks have also reported intact activation of VLPFC regions in individuals with schizophrenia (Barch et al. 2001, MacDonald & Carter 2003, Manoach et al. 2000). Interestingly, these findings of intact activation in left VLPFC during WM tasks with verbal materials are consistent with the findings of a recent postmortem study that did not find cell density changes in BA44 (Selemon et al. 2003), though such changes are found in BA9.

Although they primarily report intact VLPFC, a number of these same studies describe abnormal activation in PPC, either in terms of the degree of activation or of connectivity with other brain regions (e.g., Barch et al. 2002, Menon et al. 2001, Meyer-Lindenberg et al. 2001) (see also Table 1). Recent work by Fiez and colleagues (Ravizza et al. 2004) suggests multiple regions of PPC are active during WM tasks, with one region sensitive to the type of information (verbal versus nonverbal), potentially corresponding to a left ventral PPC region that supports phonological storage. The other region was a bilateral, more dorsal region that was sensitive to load irrespective of material type; it may play a role in the maintenance or updating of information in WM across stimulus domains. Figure 1 shows the location of regions of abnormal PPC activation found in Nback studies in schizophrenia in relation to the ventral and dorsal PPC regions. It is not clear whether the PPC regions showing abnormal activation in schizophrenia should be characterized as ventral or dorsal. This suggests that more work is needed to clarify the location of the PPC regions showing abnormal WM activation in schizophrenia. If PPC regions showing altered WM activity in schizophrenia are sensitive to material type, it might suggest impairments in the processing of phonological representations. If not, it would suggest disturbances in other processes critical to WM tasks that may be supported by more dorsal parietal regions.

Visual-Spatial Scratch Pad in Schizophrenia

It is much more difficult to answer questions about selective disturbances in the visual-spatial scratch pad in individuals with schizophrenia because there is less evidence about the critical behavioral and neural biological markers of scratch pad functions even in healthy humans. Among individuals with schizophrenia, a large body of evidence exists for impairments on visual-spatial WM tasks, starting with the seminal work of Park and colleagues (Park & Holzman 1992). Further, there is consistent evidence for impairments on classic measures of the visual-spatial scratch pad, such as memory guided saccade performance (e.g., Snitz et al. 1999). However, as discussed above, little evidence exists for a selective deficit in spatial WM as compared to nonspatial WM in individuals with schizophrenia (Walter et al. 2003). Surprisingly, relatively few functional neuroimaging studies in

TABLE 1 Functional neuroimaging studies using the Nback task to study working memory in individuals with schizophrenia

Study	Age	Sample size	Task	Medication status	Results	Performance
Barch et al. 2002	CON = 36.5 SCZ = 36.3	CON = 48 SCZ = 38	Word and face 2-back (T/NT)	All medicated (79% atypical)	R-DLPFC: CON > SCZ L-DLPFC: CON > SCZ R-VLPFC: CON = SCZ L-VLPFC: CON = SCZ R-PPC: CON > SCZ L-PPC: CON > SCZ ACC: CON = SCZ	CON > SCZ Subgroups matched on performance still show reduced R-DLPFC activation
Perlstein et al. 2001	CON = 36.5 SCZ = 36.5	CON = 16 SCZ = 17	Letter 0-, 1-, and 2-back (3-back in CON only) (T/NT)	All medicated (100% typical)	R-DLPFC: CON > SCZ at 2-back L-DLPFC: CON = SCZ R-VLPFC: CON = SCZ L-VLPFC: CON = SCZ R-PPC: CON = SCZ L-PPC: CON = SCZ ACC: CON < SCZ (irrespective of load)	CON > SCZ Comparing 3-back in CON to 2-back in SCZ eliminated reduced DLPFC in SCZ
Honey et al. 2002	CON = 39.3 SCZ = 34.6	CON = 20 SCZ = 20	Letter 0- and 2-back (T/NT)	All medicated (100% typical)	R-DLPFC: CON = SCZ L-DLPFC: CON = SCZ R-VLPFC: CON = SCZ L-VLPFC: CON = SCZ R-PPC: CON = SCZ L-PPC: CON = SCZ ACC: CON = SCZ	No group differences in accuracy CON < SCZ for RT
Menon et al. 2001	CON = 42.5 SCZ = 44.6	CON = 13 SCZ = 11	Auditory 2-back (T/NT)	All medicated (73% atypical)	R-DLPFC: CON > SCZ L-DLPFC: CON > SCZ R-VLPFC: CON > SCZ L-VLPFC: CON > SCZ	CON > SCZ

(Continued)

TABLE 1 (Continued)

Study	Age	Sample size	Task	Medication status	Results	Performance
Carter et al. 1998	Matched	CON = 8 SCZ = 8	Letter 0- and 2-back (T/NT)	All medicated	R-PPC: CON > SCZ L-PPC: CON > SCZ ACC: CON = SCZ R-DLPFC: CON > SCZ L-DLPFC: CON = SCZ R-VLPFC: CON = SCZ L-VLPFC: CON = SCZ R-PPC: CON > SCZ L-PPC: CON = SCZ ACC: CON = SCZ	CON > SCZ
Callicott et al. 1996	CON = 33.3 SCZ = 34.1	CON = 10 SCZ = 10	Number 0- and 2-back (P)	70% medicated (72% atypical)	R-DLPFC: CON > SCZ L-DLPFC: CON > SCZ R-VLPFC: CON = SCZ L-VLPFC: CON = SCZ R-PPC: CON = SCZ L-PPC: CON = SCZ ACC: CON = SCZ	CON > SCZ. SCZ with best performance did not activate DLPFC
Callicott et al. 2000	CON = 29.6 SCZ = 33.9	CON = 18 SCZ = 13	Number 0-, 1-, and 2-back (P)	Majority medicated	R-DLPFC: CON < SCZ L-DLPFC: CON = SCZ R-VLPFC: CON = SCZ L-VLPFC: CON = SCZ R-PPC: CON = SCZ L-PPC: CON = SCZ ACC: CON = SCZ	CON > SCZ DLPFC still increased in SCZ when compared CON 3back to SCZ 2-back
Walter et al. 2003	CON = 29.8 CON = 28.7	CON = 15 SCZ = 15	Letter and spatial 0- and 2-back (T/NT)	14/15 medicated (13/15 atypical)	R-DLPFC: CON = SCZ L-DLPFC: CON = SCZ R-VLPFC: CON = SCZ L-VLPFC: CON = SCZ ACC: CON < SCZ & CON > SCZ	CON > SCZ

Callicott 2003b	CON = 32.5 SCZ = 31.5	CON = 14 SCZ = 14	Number 0- and 2-back (P)	All medicated	R-PPC: CON = SCZ	CON > SCZ
					L-PPC: CON = SCZ	
Meyer- Lindenberg et al. 2002	CON = 30.4 SCZ = 32.5	CON = 13 SCZ = 13	Number 0- and 2-back (P)	None medicated	ACC: CON < SCZ for verbal; CON = SCZ for spatial.	CON > SCZ
					Altered lateralization as a function of material type.	
Wykes et al. 2002	CON = 36 SCZ = 35	CON = 6 SCZ = 6	Letter 2-back (T/NT)	All medicated	R-DLPFC: CON > SCZ	CON > SCZ
					L-DLPFC: CON > SCZ	
Sabri et al. 2003	CON = 30.7 SCZ = 30.6	CON = 10 SCZ = 11	Number 0- and 2-back (T/NT)	All medicated	R-DLPFC: CON < SCZ	0-back: CON = SCZ 2-back: CON = SCZ (trend for CON > SCZ)
					L-DLPFC: CON = SCZ	
					R-VLPFC: CON = SCZ	

(Continued)

TABLE 1 (Continued)

Study	Age	Sample size	Task	Medication status	Results	Performance
Jansma et al. 2004	CON = 27.8 SCZ = 27.2	CON = 10 SCZ = 10	Location 0-, 1-, 2-, and 3-back (four locations) (P)	All medicated (100% atypical)	L-VLPFC: CON = SCZ R-PPC: CON = SCZ L-PPC: CON = SCZ ACC: CON = SCZ R-DLPFC: CON > SCZ (3-back) L-DLPFC: CON < SCZ (except at 3-back) R-VLPFC: CON = SCZ L-VLPFC: CON = SCZ R-PPC: CON = SCZ L-PPC: CON = SCZ ACC: CON = SCZ	CON > SCZ
Mendrek et al. 2004	CON = 28 SCZ = 30	CON = 8 SCZ = 7	Letter 0- and 2-back (T/NT)	All medicated (100% atypical) first episode, tested within one week of being medicated, 6-8 weeks later	2-back versus 0-back: R-DLPFC: CON > SCZ L-DLPFC: CON > SCZ R-VLPFC: CON = SCZ L-VLPFC: CON = SCZ R-PPC: CON = SCZ L-PPC: CON = SCZ ACC: CON = SCZ 0-back versus rest: L-DLPFC: CON < SCZ R-VLPFC: CON < SCZ Right BA 46: increased in SCZ from first to second session	CON < SCZ

Abbreviations: R-DLPFC = right dorsolateral prefrontal cortex; L-DLPFC, left dorsolateral prefrontal cortex; R-VLPFC, right ventrolateral prefrontal cortex; L-VLPFC, left ventrolateral prefrontal cortex; R-PPC = right posterior parietal cortex; L-PPC, left posterior parietal cortex; ACC, anterior cingulate cortex.

schizophrenia have used visual-spatial WM tasks that could not be accomplished by verbal recoding (in most studies, small numbers of spatial locations are verbally labeled by participants, turning the task into a verbal WM task). Thus, more studies specifically designed to selectively assess visual-spatial scratch pad functions are needed to explain the integrity of these processes and the brain regions that support them in schizophrenia.

Central Executive Function in Schizophrenia

In contrast to the mixed evidence for deficits in the verbal or visual-spatial buffer systems in schizophrenia, there is very consistent evidence that individuals with schizophrenia have difficulty with processes attributed to the central executive component of WM. One strong argument used to support the presence of central executive deficits in schizophrenia is the fact that patients with schizophrenia have deficits on WM tasks with all material types, with relatively little evidence for selective deficits with one material type over another (e.g., Gooding & Tallent 2004, Kim et al. 2004). A second argument is that individuals with schizophrenia consistently show deficits on tasks designed to measure a range of functions ascribed to the central executive, including manipulation (Gold et al. 1997, Kim et al. 2004), interference control and/or dual-task coordination (e.g., Fleming et al. 1995), and information updating and temporal indexing (e.g., Goldberg et al. 2003, Perlstein et al. 2003). Of note, however, is that the majority of these studies have not dealt with the issue of differential deficits and have used measures of central executive function that likely have higher discriminating power than the “control” measures. A recent exception to this is work with individuals with schizophrenia that compared maintenance-only measures of WM to maintenance-plus-manipulation measures that had similar discriminating power, and found a differential deficit on the manipulation measures (Kim et al. 2004).

As described above, the basic cognitive neuroscience literature has linked many of the central executive components of WM to the function of DLPFC. Consistent with this hypothesis, a large number of functional neuroimaging studies using tasks that engage central executive components of WM have found disturbed DLPFC activation among individuals with schizophrenia. These studies have included tasks such as the Wisconsin Card Sorting Task (e.g., Berman et al. 1986), mental arithmetic (Hugdahl et al. 2004), self-ordered pointing, and various versions of the Nback task (Callicott et al. 2000, Carter et al. 1998). In most of the earlier studies using the Wisconsin Card Sorting Task (Davidson & Neale 1974), as well as in a number of the more recent studies using the Nback and other WM tasks, the modal finding has been of decreased activation in DLPFC in schizophrenia (Barch et al. 2002; Callicott et al. 1998b, 2003b; Carter et al. 1998; Fletcher et al. 1998; Honey et al. 2003; Hugdahl et al. 2004; Jansma et al. 2004; Mendrek et al. 2004; Menon et al. 2001; Meyer-Lindenberg et al. 2002; Perlstein et al. 2001; Quintana et al. 2003; Wykes et al. 2002). However, in several recent studies using the Nback and other WM tasks, researchers have reported either no changes in DLPFC (Honey

et al. 2002, Kindermann et al. 2004, Manoach et al. 1999, Stevens et al. 1998, Walter et al. 2003) or increased activation in DLPFC among individuals with schizophrenia (Callicott et al. 2000, 2003b; Jansma et al. 2004; Manoach et al. 2000; Quintana et al. 2003; Sabri et al. 2003) that sometimes co-occurred with decreased DLPFC activation in different regions.

One obvious potential reason for differences in the pattern of activation across studies is variation in the type of task used. Thus, in trying to understand how and why DLPFC deficits may vary across studies, it is useful to examine studies that have used variants on the same task (see Table 1). The most frequently used task in recent functional neuroimaging studies of WM in schizophrenia is the Nback task. In this test, participants are presented with a series of items and told to press the target button whenever the current stimulus is the same as the one that was present *N* trials back (*N* ranges from 0 and 3), or to respond on the current trial using the stimulus presented *N* trials back. Eight of the fourteen studies in Table 1 demonstrated reduced DLPFC activation in individuals with schizophrenia. The two studies that examined a subset of patients and controls matched on behavioral performance still found reduced DLPFC activity in patients (Barch et al. 2002, Callicott et al. 1996), whereas the study comparing a higher memory load (3-back) in controls to a lower memory load in patients (2-back) reported that the DLPFC differences were no longer significant (Perlstein et al. 2001). Two other studies reported no differences between patients and controls in DLPFC activity, despite patients either being slower or less accurate than controls. The remaining four studies report some evidence of enhanced DLPFC activity in patients with schizophrenia as compared with controls.

One interesting hypothesis put forth to explain these apparently contradictory findings is the idea that the memory load–DLPFC response curve for individuals with schizophrenia may be different from that of healthy controls. A typical finding in individuals with schizophrenia is that DLPFC activity increases as memory load increases, until WM capacity is exceeded, at which point DLPFC activity decreases (Callicott et al. 1999). However, as shown in Figure 2, Callicott and colleagues (Callicott et al. 2000, 2003b) have suggested that the relationship between memory load and DLPFC activity may be different in individuals with schizophrenia in one of two ways: (a) the load-activity curve may be the same, but WM capacity may be lower, leading to a drop-off in DLPFC activity at memory loads lower than those of controls; or (b) the load-response curve may be different, such that patients show greater DLPFC activity than do controls at lower memory loads (referred to as inefficient DLPFC activity), but show less DLPFC activity than do controls at higher memory loads.

The data provided in Table 1 suggest that most research results support the first hypothesis, with few studies reporting evidence for hyperactivation of DLPFC, even when groups are matched on behavioral performance or when high-performing patients are compared with controls. Another important consideration is the possibility that the regions of DLPFC that show hyperactivation are distinct from the DLPFC regions that show hypoactivation. Figure 3 (see color insert) plots the

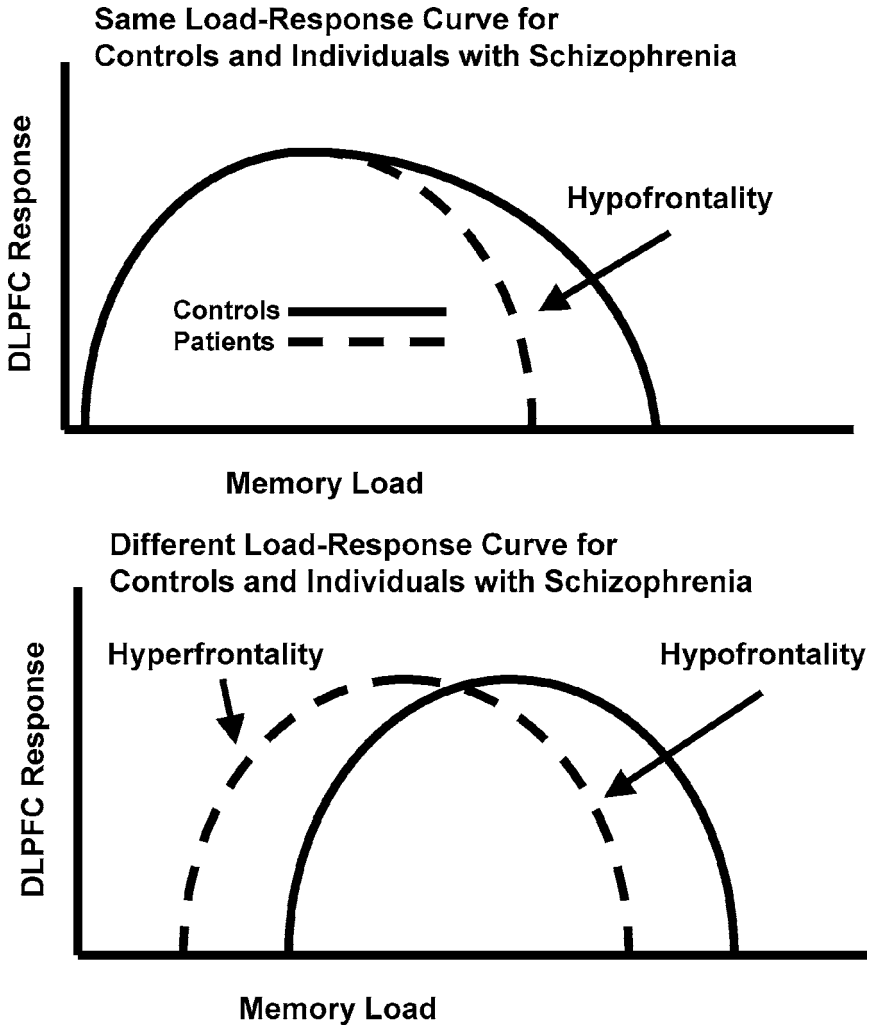


Figure 2 Illustrative graph modeled after Callicott et al. 2003b. The Y-axis plots hypothetical activation responses in DLPFC; the X-axis plots increased load in working memory. The top panel illustrates the condition in which DLPFC activity drops off at a smaller working memory load for individuals with schizophrenia than for controls, described by Callicott et al. as the same load-response curve for individuals with schizophrenia and controls. The bottom panel illustrates the condition in which DLPFC activity at lower working memory loads is increased in individuals with schizophrenia as compared with controls, but at higher working memory loads is decreased in individuals with schizophrenia as compared with controls. Callicott et al. (2003b) refer to this condition as a different load-response curve for individuals with schizophrenia and controls.

location of the DLPFC regions showing such hyperactivation versus hypoactivation in WM studies in schizophrenia. The regions of hyperactivation generally do not overlap with regions showing hypoactivation, and tend to be either more anterior (particularly on the right) or more inferior (particularly on the left). Such findings raise the possibility that activity of some of these regions reflects compensatory strategies that are engaged when the DLPFC regions most commonly activated by central executive components of WM (i.e., BA46/9) are not able to function properly. Further research using paradigms specifically designed to constrain the type of processes that can be used to accomplish the task, as well as the direct comparison of multiple tasks in the same individuals, may help to clarify the conditions under which individuals with schizophrenia show hyperactivation or hypoactivation of DLPFC.

FOCAL VERSUS CIRCUIT-LEVEL ABNORMALITIES A second issue is whether DLPFC disturbances during WM in schizophrenia represent focal disturbances in specific regions or are the result of disturbances in the connections between sets of regions that collectively support a range of WM functions (though these are not necessarily mutually exclusive possibilities). A growing number of studies suggest that even in the absence of altered levels of activity in regions such as DLPFC, individuals with schizophrenia demonstrate altered patterns of connectivity between DLPFC and other WM-related regions such as PPC (e.g., Kim et al. 2003, Schlosser et al. 2003) and temporal cortex (e.g., Fletcher et al. 1995, Meyer-Lindenberg et al. 2001). As increasingly sophisticated methods become available to address questions regarding functional and/or effective connectivity among brain regions involved in cognitive task performance, the issue of focal versus circuit-level abnormalities in schizophrenia will likely receive increased attention.

OTHER EVIDENCE FOR DLPFC IMPAIRMENTS IN SCHIZOPHRENIA In addition to functional imaging studies, a number of other sources provide evidence for impairments in DLPFC in schizophrenia. For example, in studies of DLPFC in individuals with schizophrenia, studies have reported (a) reduced gray matter volume (e.g., Shenton et al. 2001), (b) a variety of cellular and molecular abnormalities (e.g., Selemon et al. 2003), (c) reduced N-acetylaspartate concentrations (e.g., Bertolino et al. 1996), particularly in dorsal as compared with ventral regions (Bertolino et al. 1996), and (d) a relationship between poor WM performance (as measured by the Nback task) and increased D1 receptor availability in DLPFC, which was interpreted as reflecting compensatory upregulation of D1 receptors in response to sustained reductions in DA input to PFC (Abi-Dargham et al. 2002). Although there have been negative findings as well in each of these areas, the weight of the evidence suggests structural, cellular, and molecular abnormalities as well as functional abnormalities in the DLPFC of individuals with schizophrenia.

Working Memory and Risk for Schizophrenia

A review of the behavioral literature on WM function in individuals who may share genetic components of vulnerability to schizophrenia clearly indicates that these individuals experience WM disturbances. For example, a number of studies have shown that the first-degree relatives of individuals with schizophrenia show impaired performance on a range of WM tasks, including the Nback and spatial delayed-response tasks (e.g., Glahn et al. 2003, Goldberg et al. 2003, Thermenos et al. 2004). Further, some evidence suggests that the stronger the genetic risk, the greater the impairment in WM function in first-degree relatives. For example, siblings from families with more than one affected member perform worse on visual WM tasks than do siblings from families with a single affected member (Tuulio-Henriksson et al. 2003). In addition, the performance of unaffected monozygotic twins on a spatial delayed-response task was as poor as that of their affected cotwins, whereas the performance of unaffected dizygotic twins was intermediate between that of their affected cotwins and controls (Glahn et al. 2003).

There is also work to suggest that children who later develop schizophrenia show greater impairment in verbal WM than do their siblings who do not develop schizophrenia (Niendam et al. 2003). In addition, individuals with schizotypal personality disorder, a part of the spectrum of schizophrenia-related disorders (Siever et al. 2002), also show impairments on WM tasks (e.g., Mitropoulou et al. 2002). There are fewer studies of functional brain activation during WM performance in individuals at risk for schizophrenia, with some finding evidence for hypoactivity (Berman et al. 1992, Brahmhatt et al. 2004, Keshavan et al. 2002), as well hyperactivity (Brahmbhatt et al. 2004, Callicott et al. 2003a, Thermenos et al. 2004). Thus, studies of individuals at risk for schizophrenia also clearly indicate the presence of abnormal DLPFC activation, though the precise form of these abnormalities again differs somewhat across studies. Of note, the Callicott et al. (2003a) study did not find behavioral WM impairments in the siblings, whereas Thermenos et al. (2004) did; both found hyperactivity in DLPFC. Taken together, the results of such behavioral and imaging studies clearly suggest that the presence of WM and DLPFC deficits may be one endophenotypic risk marker for schizophrenia.

Executive Control in Schizophrenia

The above review of WM function in schizophrenia suggests that the literature provides the most consistent evidence for a deficit in the central executive component of WM. Despite this wealth of empirical evidence, there is relatively little agreement on the precise nature or causes of impairment in executive control in schizophrenia. Prominent hypotheses focus on the role of DLPFC and dopamine-mediated context-processing disturbances, and the role of anterior cingulate/dopamine-mediated disturbances in conflict/error detection.

CONTEXT PROCESSING IN SCHIZOPHRENIA In previous work based in part upon computational modeling, Cohen and colleagues have put forth the hypothesis that intact function of dopamine in DLPFC is responsible for the processing of context, and that a disturbance in this mechanism is responsible for a range of cognitive deficits in schizophrenia (Barch et al. 2001, Braver et al. 1999, Cohen et al. 1999, Cohen & Servan-Schreiber 1992). Context refers to prior task-relevant information that is represented and maintained in WM in a form that can bias selection of the appropriate behavioral response. One insight that has emerged from this work is that a single deficit in one aspect of executive control can contribute to deficits in cognitive domains often treated as independent. As such, it is argued that deficits in WM, attention, and inhibition in schizophrenia can all be understood in terms of a deficit in context processing (for full discussion, see Braver et al. 1999, Cohen & Servan-Schreiber 1992). A number of prior studies have supported the hypothesis concerning context-processing deficits in schizophrenia (e.g., Barch et al. 2001, 2003; Cohen et al. 1999; Javitt et al. 2000; Stratta et al. 1998), in individuals at risk for schizophrenia (MacDonald et al. 2003), and in individuals with schizotypal personality disorder (Barch et al. 2005), which suggests that such deficits may indeed be associated with liability to schizophrenia. In terms of DLPFC activity, medication-naïve first-episode patients and chronic patients with schizophrenia demonstrate impaired DLPFC activation associated with impaired context processing (Barch et al. 2001, Perlstein et al. 2003).

Computational simulations of context processing that specify the role of dopamine in DLPFC in relationship to WM and executive control deficits in schizophrenia provide an organizing framework for understanding the ways in which modulations of the dopamine system and DLPFC should influence schizophrenia (Braver et al. 2002). For example, a number of studies suggest that various indices of altered DLPFC integrity are associated with evidence for hyperdopaminergic function in subcortical systems (e.g., Abi-Dargham et al. 2002, Meyer-Lindenberg et al. 2002). Such findings are consistent with recent modifications of the context-processing theory of cognitive dysfunction in schizophrenia, which suggests that phasic dopamine bursts generated by subcortical systems normally serve to regulate the gating of information, including context representations, into WM (Braver et al. 2002). Abnormalities in the activity of the subcortical dopamine system dysregulate the ability to appropriately gate information into WM, leading to perseverative behaviors when WM representations cannot be updated and susceptibility to interference due to poor stability of WM representations. Findings that modulation of the dopamine system can improve WM and executive function performance in schizophrenia (e.g., Daniel et al. 1989) are at least indirectly consistent with the tenets of the context-processing theory. In addition, the role of dopamine in the context-processing theory also helps to explain the ways in which variations in genes that influence dopamine function in DLPFC, such as COMT (Egan et al. 2001), may contribute to alterations in WM performance as well as other measures of executive function.

CONFLICT DETECTION/ERROR MONITORING An alternative (or potentially complimentary) theory suggests that disturbances in the ability to detect conflict or errors in ongoing processing, due at least in part to the function of anterior cingulate cortex (ACC), may lead to deficits in the ability to regulate and control a range of other components of executive control in schizophrenia. A recent update to the error-processing hypothesis explicitly incorporates information about the dopaminergic inputs to ACC in articulating a role for ACC in the detection of and response to errors (Holroyd & Coles 2002). The conflict hypothesis suggests ACC plays a crucial role in the monitoring and detection of conflict in ongoing processing (Botvinick et al. 2001). A crucial tenet of the conflict hypothesis is that the output of ACC's response to conflict indicates the need for additional cognitive control functions that may be subserved at least in part by DLPFC regions. These two theories differ in the specific functions that they attribute to ACC. Nonetheless, both theories predict that ACC disturbances that contribute to failures to detect conflict and/or errors would have a detrimental effect on a range of cognitive functions, in that detection of errors/conflict may be a critical means by which control is engaged and regulated.

There is mixed evidence at the behavioral level in schizophrenia regarding impairments on indices thought to reflect the ability to detect or respond to conflict or errors: Some studies have found evidence for impairments (e.g., Laurens et al. 2003), whereas others have not (e.g., Kopp & Rist 1994). In contrast, event-related potential, fMRI, and positron emission tomography studies have provided more consistent evidence for altered conflict/error processing (e.g., Kopp & Rist 1994, Laurens et al. 2003) and abnormal ACC function in schizophrenia (e.g., Carter et al. 1997). In addition, structural and postmortem studies also provide evidence for ACC abnormalities in schizophrenia (e.g., Benes 2000). However, it is interesting to note that a number of other studies have shown robust and intact activation of ACC among individuals, such as the vast majority of studies using WM tasks. Table 1 includes information on ACC activation during N-back tasks in schizophrenia. Out of fourteen studies, only four reported evidence for differential ACC activity between patients and controls. Of these four studies, three reported ACC activity that was greater in individuals with schizophrenia than in controls. Both the conflict and the error theory would predict that ACC activity would be increased in individuals with schizophrenia who experienced greater conflict or errors, which is the typical behavioral result for WM studies in schizophrenia.

Such findings raise interesting questions about the relationship between deficits in ACC and DLPFC function in schizophrenia. If ACC activity were important for the recruitment of control processes supported by DLPFC, one would predict abnormal DLPFC activity in individuals with schizophrenia who have such ACC deficits. In contrast, impaired DLPFC function leading to increased conflict and errors would predict increased ACC function in individuals with schizophrenia, according to the conflict-monitoring theory (ACC activity is elicited by more conflict and errors). However, impaired DLPFC function might predict reduced ACC activity according to the error-detection theory, if reduced DLPFC activity reflects

degraded representations of the predictive information needed to drive an error-correcting dopamine signal that in turn elicits ACC activity. Of course, individuals with schizophrenia may experience deficits in both ACC and DLPFC activity that are of equal relevance to understanding cognition, and that potentially reflect the common importance of dopaminergic inputs to both DLPFC and ACC. Clearly, more research is needed that focuses on the relationship between conflict/error detection and the engagement of control processing in individuals with schizophrenia in order to provide a better understanding of the dynamic processes that give rise to WM and executive control deficits in schizophrenia.

EPISODIC MEMORY

Cognitive Neuroscience Models of Episodic Memory

It is useful to briefly review the cognitive neuroscience literature on the processing and brain regions involved in EM as a means to organize the research pertaining to EM deficits in schizophrenia. For many years, we have known that the hippocampus plays a critical role in the formation of long-term memories, a finding based in part on studies with amnesic patients who have had lesions to the hippocampus and/or surrounding medial temporal areas (Scoville & Milner 1957). A common theme in theories regarding the role of the hippocampal formation in EM is that it is critical for the rapid binding of novel configurations of information (Eichenbaum & Cohen 2001, McClelland et al. 1995, Squire & Knowlton 1995). Consistent with this hypothesis, recent human neuroimaging studies have shown activation of the hippocampus during the encoding or retrieval of novel relational information (e.g., Heckers et al. 2004), and recent work in amnesic patients emphasizes the importance of hippocampal structures in relational processing (Ryan & Cohen 2004). It has also become increasingly clear that PFC structures make important contributions to EM. Damage to the PFC can also lead to EM deficits, although EM is typically not the only cognitive function impaired in these individuals (e.g., Janowsky et al. 1989). Such findings have contributed to the hypothesis that prefrontal cortex damage alters EM by impairing strategic contributions to memory formation and retrieval. For example, studies have shown activation of prefrontal regions such as BA45 and BA47 when participants are asked to process verbal information using semantic elaboration strategies (e.g., Wagner et al. 1998) that promote subsequent memory. In addition, the most compelling findings supporting a key role for such prefrontal structures in EM are results showing that increased activation during encoding in frontal regions such as BA 45 and 47 is very strongly predictive of subsequent memory performance (e.g., Wagner et al. 1998).

Another way in which the cognitive neuroscience literature has begun to think about EM is by differentiating between processes that contribute to recollective versus familiarity-based processing in EM (Jacoby 1991). Recollection refers to the ability to retrieve information associated with specific learning episodes and is thought to be influenced by the use of strategies at encoding and retrieval (Jacoby

1991, Tulving 1985). In contrast, familiarity refers to feelings of knowing that may be related to prior exposure to information; familiarity does not depend on the ability to access information about specific learning episodes (Jacoby 1991, Tulving 1985). Although it is dangerous to equate processes with tasks, it has been argued that simple item-recognition EM tasks can be solved through familiarity even when recollection is impaired, whereas recall EM tasks necessitate recollective processes for successful performance. There is currently controversy in the literature regarding whether individuals with damage restricted solely to the hippocampus have deficits primarily in recollection (Aggleton & Shaw 1996) or also in familiarity (Reed & Squire 1997). However, in support of the hypothesis that hippocampal function can play a critical role in recollection, recent human functional neuroimaging research has shown that hippocampal activation at the time of retrieval is associated with responses that indicate a recollective experience (e.g., a “remember” response in contrast to a “know” response, or rich details of encoding experience) (Eldridge et al. 2000). Evidence more consistently shows that individuals with damage to DLPFC are impaired on recall tasks or other tasks that require source information (Janowsky et al. 1989), but are relatively less impaired on tasks that can be solved based primarily on familiarity processes.

Episodic Memory in Schizophrenia

BINDING DEFICITS IN EPISODIC MEMORY IN SCHIZOPHRENIA One way to examine whether individuals with schizophrenia have binding deficits is to determine whether they are more impaired on memory for associative information (e.g., the association of previously unrelated words or items) than on memory for individual items. Achim & Lepage (2003) recently conducted a meta-analysis comparing performance on associative and item memory tests in individuals with schizophrenia. They concluded that there was evidence for a 20% greater impairment in associative memory than in item memory in individuals with schizophrenia. However, it should be noted that a number of the associative memory studies included in this meta-analysis were tests of source memory rather than associations of novel pairs of items. The human neuropsychological literature suggests that prefrontal function may make an important contribution to source memory. In addition, few of the studies that have compared item and associative memory have dealt with the ubiquitous problem of discriminating power. More recently, clinical researchers have begun to use tasks derived from the animal literature on hippocampal function, such as the transitive interference test, which measures the ability to learn the relationships among hierarchically arranged pairs of stimuli (Eichenbaum & Cohen 2001). Titone et al. (2004) have recently shown that individuals with schizophrenia are impaired on the critical conditions of this task that require relational processing but not on the conditions that require the learning of simpler associative reinforcement mappings. Results such as these begin to provide stronger evidence for a disturbance in the type of relational processing or binding of novel pairings thought to be specifically supported by the hippocampal formation.

IMPAIRMENT IN STRATEGIC CONTRIBUTIONS TO EPISODIC ENCODING AND RETRIEVAL Several researchers have hypothesized that individuals with schizophrenia experience deficits in the use of beneficial strategies that may be supported by PFC. Consistent with this hypothesis, a number of studies suggest that individuals with schizophrenia are impaired in their ability to generate effective mnemonic strategies (e.g., Koh 1978), and they encode information less elaborately than do controls (e.g., Brebion et al. 1997). However, when provided with strategies that promote successful episodic encoding, individuals with schizophrenia are typically able to benefit as much as controls from these strategies (e.g., Bonner-Jackson et al. 2005, Heckers et al. 1998).

RECOLLECTION VERSUS FAMILIARITY The evidence reviewed above suggests that individuals with schizophrenia may have EM disturbances in both the binding processes supported by hippocampal function and in the strategic processes supported by prefrontal regions. Deficits in both of these types of processes would predict that individuals with schizophrenia would have deficits in the recollective component of episodic retrieval, but not necessarily with the ability to use familiarity as a basis for recognition. Consistent with this hypothesis, individuals with schizophrenia typically perform worse on recall than on recognition tasks (Aleman et al. 1999). Second, when individuals with schizophrenia are asked to make judgments about the basis of their memory responses, they consistently provide fewer responses indicative of recollective experiences (e.g., Danion et al. 1999). Lastly, patients with schizophrenia also demonstrate deficits in the ability to remember the source or temporal order of encoded information, components of episodic encoding thought to be critical for recollective retrieval of information (e.g., Danion et al. 1999). Taken together, the data on EM processing in schizophrenia suggest clear deficits in recollective components of episodic encoding and retrieval that may stem from deficits in both the ability to bind novel pieces of information and the ability to generate and apply beneficial strategies at either encoding or retrieval.

HIPPOCAMPAL ABNORMALITIES IN SCHIZOPHRENIA IN RELATION TO EPISODIC MEMORY A number of functional imaging studies using positron emission tomography or fMRI have examined task-related brain activation among individuals with schizophrenia during performance of episodic encoding and retrieval tasks. Many of the more recent functional imaging studies of EM have provided relatively consistent evidence for abnormal hippocampal activation in schizophrenia, at both encoding (e.g., Barch et al. 2002, Jessen et al. 2003) and retrieval (e.g., Barch et al. 2002, Heckers et al. 1998, Jessen et al. 2003, Weiss et al. 2003). These failures to show task-related hippocampal activity at retrieval have been interpreted as reflecting a failure in explicit recollection among individuals with schizophrenia (Heckers et al. 1998, Weiss et al. 2003). A number of other sources provide evidence that individuals with schizophrenia have deficits in hippocampal volume and shape (e.g., Shenton et al. 2001), particularly for those individuals with schizophrenia who have experienced birth complications (e.g., Van Erp et al.

2002). The evidence for hippocampal abnormalities in schizophrenia extends to the cellular level as well (Knable et al. 2004).

Many of the cellular and molecular hippocampal abnormalities found in individuals with schizophrenia have focused on disturbances in glutamatergic functions, with a particular emphasis on *N*-methyl-D-aspartic acid (NMDA) receptor hypofunction. One prominent theory of the neurodevelopmental course of schizophrenia posits that many of the cognitive and clinical symptoms of schizophrenia reflect hypofunction of NMDA receptors that manifests at or following puberty (Olney et al. 1999). NMDA receptors are extremely dense in the hippocampus, and NMDA receptor antagonists disrupt hippocampal long-term potentiation (one of the mechanisms thought to support memory encoding and/or binding) (Newcomer & Krystal 2001). Further, research has consistently shown that in humans, NMDA receptor antagonists such as ketamine or PCP can impair EM and elicit many clinical phenomena analogous to the symptoms of schizophrenia, including hallucinations, delusions, and disorganized speech (e.g., Newcomer & Krystal 2001). Thus, the attempt to understand the role of NMDA receptor hypofunction in the pathophysiology of schizophrenia, as well as the role of glutamatergic function more generally, is an extremely active area of schizophrenia research that may have important implications for understanding the remediation of cognitive deficits in schizophrenia.

PREFRONTAL ABNORMALITIES IN SCHIZOPHRENIA IN RELATION TO EPISODIC MEMORY DEFICITS Many of the functional imaging studies that have investigated EM-related brain activity in schizophrenia have demonstrated abnormalities in a range of prefrontal regions, including both decreased activity (Andreasen et al. 1996; Barch et al. 2002; Crespo-Facorro et al. 1999; Heckers et al. 1998; Hofer et al. 2003; Ragland et al. 1998, 2001, 2004) and increased activity (Heckers et al. 2000, Hofer et al. 2003, Weiss et al. 2003). Figure 4 (see color insert) shows the location of these PFC regions and suggests several notable points. First, unlike WM studies, a number of studies have shown reduced activation in VLPFC regions, including BA47 and BA45, regions associated with semantic elaboration or encoding of information in EM (e.g., Wagner et al. 1998). As such, it has been suggested that reduced activation in these regions reflects a failure to generate and/or apply effective encoding strategies among individuals with schizophrenia. Of importance, individuals with schizophrenia who have been oriented to use effective “deep” encoding strategies can show appropriate activity in these regions (Bonner-Jackson et al. 2005), though they also engage additional regions of PFC to accomplish such meaning-based encoding (Bonner-Jackson et al. 2005).

Second, on average, studies of PFC function in EM encoding have been more likely to find decreased than increased activation. However, Figure 4 suggests that these regions of hypoactivation for episodic retrieval tend to be somewhat more left lateralized than is the pattern for WM tasks (see Figure 3), though this is by no means a dramatic dissociation; the pattern for hypoactivation during episodic encoding is actually somewhat more right lateralized. One interesting possibility is

that this pattern is related to inherent asymmetries associated with EM, as suggested by the hemispheric encoding retrieval asymmetry (HERA) model (Habib et al. 2003). However, it is not clear whether this model would predict the pattern of PFC abnormalities found in schizophrenia. The HERA models suggest that left PFC is relatively more involved in episodic encoding, whereas right PFC is relatively more involved in episodic retrieval. If so, then the patterns of abnormal PFC activation shown by individuals with schizophrenia suggest greater abnormalities in the hemisphere that is thought to be less important to the processes being tapped (e.g., right PFC for encoding, but left PFC for retrieval). However, the pattern of PFC regions showing hyperactivation suggests that hyperactivation is more likely to occur in right frontal polar PFC, at least during retrieval. If right frontal polar PFC is critical for episodic retrieval, then such a pattern might reflect either inefficient processing in these regions or the added effort that individuals with schizophrenia need to expend to retrieve poorly encoded information (Heckers et al. 1998, Weiss et al. 2003).

Episodic Memory and Risk for Schizophrenia

A large number of studies have shown that the unaffected first-degree relatives of individuals with schizophrenia show deficits on EM tasks (e.g., Toulopoulou 2003) that seem to be worse in relatives from multiplex than in relatives from singleplex families (Faraone et al. 2000). There is also evidence of hippocampal N-acetylaspartate reductions (Callicott 1998a) as well as hippocampal volume reductions (e.g., Seidman et al. 2002) in relatives of individuals at risk for schizophrenia. In addition, individuals with schizotypal personality disorder consistently demonstrate EM deficits (e.g., Mitropoulou et al. 2002), though the evidence for altered hippocampal volume is mixed (Siever et al. 2002). Taken together, the results of studies in high-risk individuals suggest that EM deficits that may be linked to hippocampal abnormalities may be stable or mediating vulnerability factors for schizophrenia. However, a number of studies clearly suggest that factors other than genetics influence the severity of EM and/or hippocampal abnormalities in schizophrenia. For example, studies of discordant twins have shown that memory disturbances and hippocampal volume changes are more severe in affected than in unaffected monozygotic twins (e.g., Suddath et al. 1990). Work by Cannon and others has suggested that hippocampal abnormalities in particular may be more likely in those individuals with schizophrenia who have experienced some type of obstetrical complications, pointing to a genetic-environment interaction in the genesis of hippocampal morphology disturbances, and potential EM deficits in schizophrenia.

SUMMARY, UNANSWERED QUESTIONS, AND FUTURE DIRECTIONS

In this chapter, I have argued that individuals with schizophrenia experience deficits in WM function that are related in large part to disturbances in processes attributed to the central executive function. Further, I have reviewed evidence that suggests

deficits in the central executive component of WM in schizophrenia are frequently associated with disturbances in the function and/or structural integrity of PFC, particularly DLPFC, though disturbances in other brain regions and their relationship to DLPFC are also clearly important. Two potential candidates for the specific central executive processes impaired in schizophrenia are deficits in context processing and conflict detection. In addition, I have reviewed evidence that strongly suggests individuals with schizophrenia also have deficits in EM function that reflect greater deficits in recollection than in familiarity processes. These deficits in recollective components of EM appear to reflect impairments in the binding processes supported by the hippocampus and by the types of beneficial encoding strategies supported by regions of PFC.

One question that often arises in the context of understanding cognitive function in individuals with schizophrenia is the degree to which the severity of cognitive deficits varies as a function of specific aspects of symptomatology versus being related more generally to the overall diagnosis of schizophrenia. Quite a few studies suggest that the severity of disturbances in WM, executive control, and/or DLPFC function are particularly associated with the severity of disorganization symptoms (e.g., Barch et al. 2003; MacDonald & Carter 2003; Menon et al. 2001; Perlstein et al. 2001, 2003; Stratta et al. 2000) as well as negative symptoms (e.g., Barch et al. 2003, Pantelis et al. 2004). This raises the question of how and why WM deficits might be related to these symptoms. For example, others and I have argued that deficits in the ability to maintain or manipulate discourse representations within WM may play a contributing role in disorganized speech among individuals with schizophrenia (Docherty et al. 1996, Melinder & Barch 2003). However, further work is needed to examine the precise relationship between WM deficits and the other clinical manifestations of schizophrenia. In regard to EM, a growing number of studies suggest a relationship between the severity of EM deficits and negative symptoms in schizophrenia (e.g., Fitzgerald et al. 2004). However, few theories have been proposed regarding the specific pathways by which EM deficits may contribute to the particular types of negative symptoms, an area in which more work is clearly needed.

A second question that arises is the degree to which deficits in putatively different cognitive domains such as WM and EM reflect independent cognitive deficits with dissociable neural substrates. The above review described the commonalities in the neural systems and cognitive processes that support both WM and EM, and presented evidence for correlations between deficits in WM and EM in schizophrenia, in addition to suggesting some common causal factors. A number of candidates exist for such common factors, including motivation, overall slowing, and the influence of the substance abuse that often occurs in schizophrenia; they are potentially less interesting from the perspective of trying to understand the pathophysiology of this disorder. At the same time, potential common factors provide crucial cues as to the source of WM and EM deficits in schizophrenia. For example, the cognitive neuroscience and human neuropsychological literatures have clearly demonstrated that regions of PFC such as DLPFC play important roles in both WM and EM. The work on schizophrenia is consistent with this

hypothesis in that research has demonstrated deficits in components of WM and EM that are thought to reflect processes supported by DLPFC, such as central executive functions in WM and recollective processing in EM. Further, there is a growing recognition in the cognitive neurosciences literature that hippocampal regions can make important contributions to WM encoding, and at least one case has been reported of impaired hippocampal activity during both WM and EM processing in schizophrenia. As such, it seems likely that deficits of both prefrontal and hippocampal systems contribute to disturbances in a number of different cognitive domains, each making different contributions to the nature and severity of cognitive impairments in schizophrenia. If so, a critical direction for future research is how deficits in different brain regions/neural systems interact to generate the pattern of cognitive disturbances found in individuals with schizophrenia, a more complicated but potentially more fruitful research agenda for ongoing work focused on understanding the cognitive neuroscience of schizophrenia.

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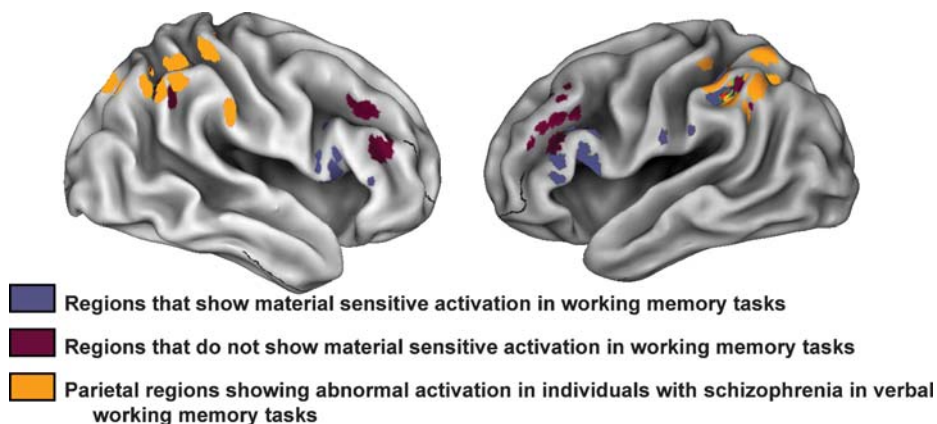


Figure 1 Frontal and parietal regions that do and do not demonstrate material-sensitive activation during working memory tasks in healthy participants, as well as parietal regions showing abnormal activation during verbal working memory tasks in individuals with schizophrenia. Regions are spheres, 6 mm in diameter, drawn around Talairach coordinates provided in primary research articles.

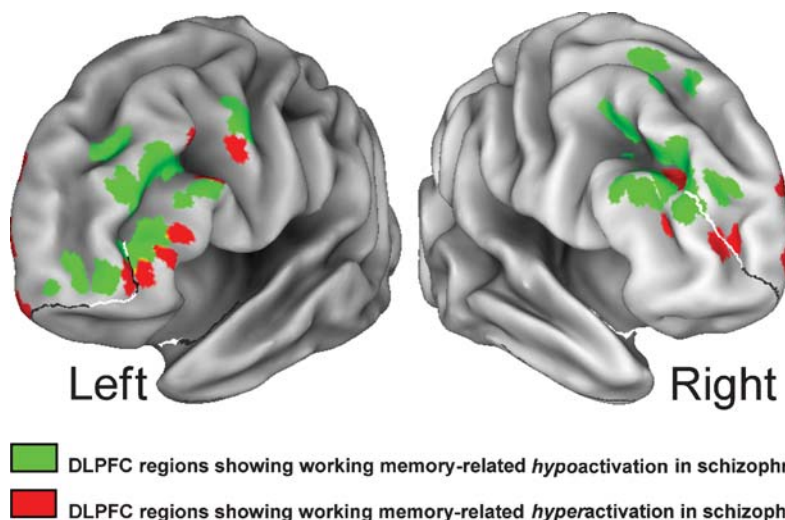


Figure 3 Dorsolateral prefrontal cortex regions showing either increased (hyper) or decreased (hypo) working memory-related activation among individuals with schizophrenia. Regions are spheres, 6 mm in diameter, drawn around Talairach coordinates provided in primary research articles.

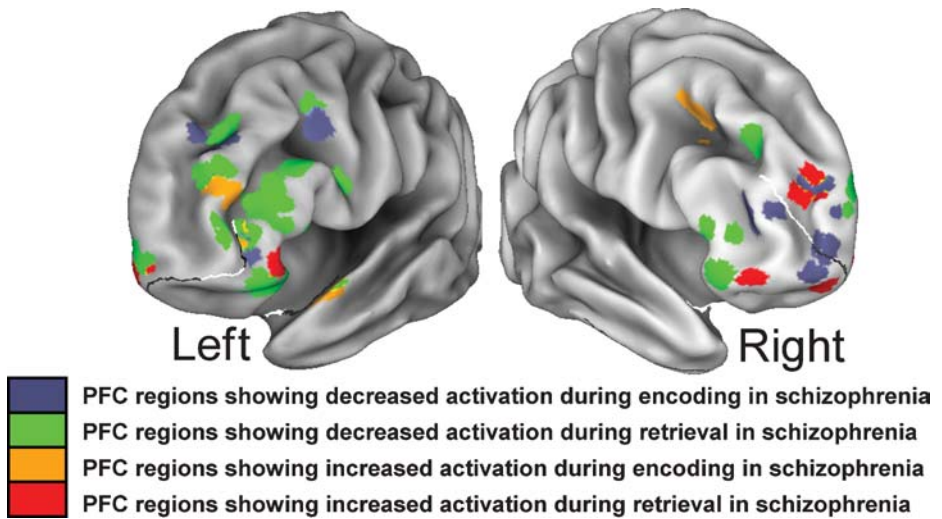


Figure 4 Prefrontal cortex regions exhibiting abnormal activation during either episodic encoding or retrieval tasks among individuals with schizophrenia. Regions are spheres, 6 mm in diameter, drawn around Talairach coordinates provided in primary research articles.

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