

## WHAT CAN RESEARCH ON SCHIZOPHRENIA TELL US ABOUT THE COGNITIVE NEUROSCIENCE OF WORKING MEMORY?

D. M. BARCH

*Psychology, Washington University, Box 1125, One Brookings Drive, St. Louis, MO 63130, USA*

**Abstract**—Work with individuals with lesions to specific brain regions has long been used to test or even generate theories regarding the neural systems that support specific cognitive processes. Work with individuals who have neuropsychiatric disorders that also involve neurobiological disturbances may be able to play a similar role in theory testing and building. For example, schizophrenia is a psychiatric disorder thought to involve a range of neurobiological disturbances. Further, individuals with schizophrenia are known to suffer from deficits in working memory, meaning that examining the work on the neurobiology of working memory deficits in schizophrenia may help to further our understanding of the cognitive neuroscience of working memory. This article discusses the pros and cons of extrapolating from work in schizophrenia to models of healthy working memory function, and reviews the literature on working memory function in schizophrenia in relationship to existing human and non-human primate models of the cognitive neuroscience of working memory. © 2005 IBRO. Published by Elsevier Ltd. All rights reserved.

**Key words:** working memory, schizophrenia, prefrontal cortex, parietal cortex.

There is a long history of using work with patients who have lesions to specific brain regions to test, validate, or even generate theories regarding the cognitive processes supported by particular neural systems. A famous example is the case of H.M., an individual who had a bilateral resection of the hippocampus and surrounding medial temporal areas (Scoville and Milner, 1957). Following this operation, H.M. demonstrated profound deficits in the ability to learn and/or retrieve new episodic and semantic memories, despite relatively intact cognitive functioning in other domains (Corkin, 1984; Scoville and Milner, 1957; Squire, 1987), helping to inspire decades of work on the role of the medial temporal cortex in episodic memory function. However, one challenge of working with such lesion patients is that they are relatively rare, and it is difficult to generate large samples of such individuals. Individuals with neuropsychiatric disorders are, unfortunately, much more common than individuals with focal brain lesions. Many theories of neuropsychiatric disorders

Tel: +1-314-935-8729; fax: +1-314-935-8790.

E-mail address: dbarch@artsci.wustl.edu.

**Abbreviations:** DIPPC, dorsal inferior PPC; DLPFC, dorsolateral regions of prefrontal cortex; FEF, frontal eye field; R PPC, right posterior parietal region; SEF, supplementary eye field; TMS, transcranial magnetic stimulation; VIPPC, ventral inferior posterior parietal cortex; VLPFC, ventral lateral prefrontal cortex.

0306-4522/05/\$30.00+0.00 © 2005 IBRO. Published by Elsevier Ltd. All rights reserved.

doi:10.1016/j.neuroscience.2005.09.013

such as schizophrenia suggest that these diseases are caused at least in part by disturbances in specific neural systems. As such, one can also use work with neuropsychiatric populations to potentially test and/or generate theories about brain–behavioral relationships. For example, a large body of work has demonstrated that individuals with schizophrenia have deficits in working memory (Goldman-Rakic, 1991; Park and Holzman, 1992), suggesting that studies of individuals with schizophrenia may shed light on the neural systems that support working memory. The goal of the current article is to discuss the pros and cons of doing so, and to provide examples of how research on schizophrenia can help to inform our understanding of the cognitive neuroscience of schizophrenia.

### Pros and cons

Before reviewing the research on schizophrenia that is relevant to understanding the cognitive neuroscience of working memory, it is important to discuss some of the pros and cons of attempting to use work on neuropsychiatric populations to inform theories of normative human brain function. In healthy humans, the most commonly used techniques for studying the neural bases of cognition are functional imaging methods such as evoked response potentials (ERPs), positron emission tomography (PET), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI). While these techniques have contributed enormously to work on human cognitive neuroscience, they are at heart correlational techniques that can tell us whether a brain region is activated by a particular cognitive probe, but cannot tell us whether the brain region is necessary for that process. Recent work using transcranial magnetic stimulation (TMS), a technique that involves temporarily disrupting activity in a brain region, can potentially provide greater information about what neural systems are necessary for specific cognitive processes. However, work with TMS is still relatively rare, and is most useful for regions close to the surface, as it is difficult to apply to deeper brain structures. As such, research with individuals who have impairments in specific brain regions or systems can provide stronger evidence for the necessity of certain brain regions for specific cognitive processes. Thus, a clear “pro” of studying individuals with schizophrenia, a disorder thought to involve deficits in brain regions such as prefrontal cortex and medial temporal cortex function, is that this work be able to provide information about the degree to which intact function in these brain regions is necessary for successfully working memory performance.

It is also important, however, to acknowledge the very serious limitations involved in using work with schizophre-

nia or other neuropsychiatry disorders to inform theories of normal brain function. First, individuals with neuropsychiatric disorders often do not have clear and identifiable lesions in a specific brain system. For example, individuals with schizophrenia do not have clear lesions in the prefrontal cortex that one can clearly and easily identify on a magnetic resonance scan. Instead, the nature of the neurobiological disturbances in schizophrenia are much more subtle, involving relatively small changes to brain volume or shape (Csernansky et al., 1983), neuronal cytoarchitecture (Selemon et al., 2003), or even neurochemical function (Grace, 1991). Second, to make matters even more complicated, individuals with schizophrenia or other neuropsychiatric disorders rarely have a single type of neurobiological impairment. For example, work on schizophrenia suggests impairments in a range of brain regions, including prefrontal cortex, medial temporal cortex, the thalamus, and the basal ganglia. Third, individuals with neuropsychiatric disorders often have a host of complicating factors that may contribute to neurobiological deficits that are not a core part of the disorder. For example, many individuals with disorders such as schizophrenia have co-morbid substance abuse or dependence problems that may themselves alter brain function. Fourth, many individuals with neuropsychiatric disorders are taking medication that may themselves alter cognition and/or brain function. For example, individuals with schizophrenia are usually taking antipsychotic medications that involve the dopamine system, as well as other neurotransmitter systems. The dopamine system clearly plays a critical role in working memory (Goldman-Rakic, 1995), and it possible that antipsychotic mediations may have a complicating influence on working memory function in schizophrenia.

There are, of course, approaches to dealing with some of the limitations inherent in studying neuropsychiatric disorders. For example, one can study populations of individuals who are currently (or preferably never) medicated. Such an approach would allow one to avoid complications associated with the potential influences of medications on cognition. Unfortunately, it is very difficult to conduct such work with unmedicated populations, both for ethical and practical reasons. In addition, if one finds very clear differential deficits or double dissociations in cognition or brain function among individuals with disorders such as schizophrenia, then this work may be able to more clearly inform our understanding of the cognitive neuroscience of cognition, despite the multifactorial nature of the neural basis of schizophrenia. In summary, the strength or clarity of interpretations that one can make regarding brain-behavior relationships in neuropsychiatric disorders needs to be modulated by the caveats associated with the limitations described above.

### Cognitive neuroscience theories of working memory

Before discussing the evidence regarding the nature of WM deficits in schizophrenia, it is useful to briefly outline the major cognitive and neurobiological theories of WM. WM is typically defined as the ability to maintain and manipulate information over short periods of time. It is

widely agreed that WM involves several different component processes. As described in detail in another contribution to this series, Baddeley's (1986) influential theory of WM distinguishes among four major components; 1) a short-term storage buffer for visual information that is often referred to as the visuo-spatial scratchpad; 2) a short-term storage buffer for verbal information referred to as the phonological loop; 3) a central executive component that guides the manipulation and transformation of information held within the storage buffers; and 4) the more recently described episodic buffer (Baddeley, 2000). Each of these major component processes of WM can also be further subdivided 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 areas 44 and 45. Functional imaging studies examining rehearsal show activation of this region (Chein and Fiez, 2001; Fiez et al., 1996), 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, again based on data both from lesions studies and imaging studies in healthy humans (Fiez, 1997; Fiez et al., 1996; Jonides et al., 1998a; Ravizza et al., 2004; Vallar et al., 1997).

The specific component processes of the visual-spatial scratchpad are not as clear as those involved in the phonological loop. One hypothesis regarding how humans 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 (Awh and Jonides, 2001; Awh et al., 1998). 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 (R PPC) (Postle et al., 2004), and lesions to R PPC 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 (FEF) and the supplementary eye fields (SEF). Curtis et al. (2004) have recently argued that information about the spatial location of cue information is represented in PPC, but that information about the director of visual saccades is processed and/or maintained in FEF/SEF regions.

In many ways, the central executive component of WM is the least well-specified component in Baddeley's model, a problem clearly acknowledged by Baddeley (1986) and others. There are a number of different processes that are often referred to as being part of the central executive, including those involved in the manipulation of information being stored in the domain specific buffers, protection from interference due to competing information or decay across

time, temporal coding or sequencing, updating of the contents of WM, etc. At the most simplistic level, many of the processes associated with the central executive have been assumed to be supported by the dorsolateral regions of prefrontal cortex (DLPFC), typically Brodmann's areas 46 and 9 bilaterally. A great deal of empirical data, from both lesion studies and functional imaging studies in healthy humans to support the idea that DLPFC is indeed critical for many processes ascribed to the central executive (Smith and Jonides, 1999). However, regions other than DLPFC are also important for the processes ascribed to the central executive and we should not equate DLPFC and executive function. As one example, Jonides and colleagues (D'Esposito et al., 1999c; Jonides et al., 1998b) have shown that a region of left VLPFC is involved in the resolution of proactive interference, a process that many have ascribed to the central executive.

Other researchers have parsed the processes involved in WM by distinguishing between maintenance and manipulation (Owen, 1997; Owen et al., 1999; Petrides, 1995). In many ways, this distinction maps on to the division between buffer systems (maintenance) and the central executive (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), while DLPFC regions are engaged primarily by manipulation processes (Curtis et al., 2000; D'Esposito et al., 1999b; Veltman et al., 2003) or by higher maintenance loads that may require chunking or reorganizing of the material to be maintained in WM.

A great deal of work in the cognitive neuroscience of WM has also focused on understanding the contributions of specific neurotransmitter systems. It is beyond the scope of this paper to review the literature on the role of these systems, as this body of work is now quite large. However, the dopamine system has likely received the most attention in this domain, driven in large part by the breakthrough work of Goldman-Rakic et al. (2000). These researchers demonstrated that WM function is impaired in non-human primates following 6-hydroxy-dopamine lesions in prefrontal cortex (Brozoski et al., 1979), or administration of dopamine antagonists (Sawaguchi and Goldman-Rakic, 1994). Further, low dose dopamine agonists can improve WM in monkeys (Williams and Goldman-Rakic, 1995), especially in those with impaired performance associated with factors such as advanced age (Arnsten et al., 1994; Cai and Arnsten, 1997; Castner et al., 2000). Dopamine agents can also modulate WM function in humans, although the results in this domain vary as a function of facts such as the nature of the task, the ability level of the participants, and even their genetic makeup (for a review, see Barch, 2004). A number of researchers have postulated specific computational roles for dopamine in WM. For example, Cohen and Servan-Schreiber (1992) have suggested that dopamine serves to modulate the

signal to noise ratio and to enhance the fidelity of representations in WM. More recently, Braver and Cohen (2001) have suggested that dopamine may serve as a cue for updating information in WM, and that phasic dopamine signals help to gate or regulate what information is loaded into WM, a process that can help to protect from interference due to distracting information.

### Working memory function in schizophrenia

The overview of current models of WM described above can provide an organizing framework for examining the nature of WM deficits in individuals with schizophrenia. As described above, models of WM distinguish between processes involved primarily in the maintenance of information (e.g. the buffer systems) and those involved in central executive or manipulation processes. If one could demonstrate that individuals with schizophrenia have deficits in one aspect of WM (e.g. central executive or manipulation) and not another aspect (e.g. maintenance), the presence of such a dissociation would provide support for these being critical distinctions in normal WM function.

### Phonological loop in schizophrenia

As described above, one of the key components of the maintenance of information in WM is thought to be the phonological loop. One can ask questions about whether the phonological loop is intact in schizophrenia either by examining performance on tasks thought to depend upon the phonological loop, or by examining the function of brain regions thought to support the phonological loop. Though no cognitive task measures a single process, some WM tasks are more dependent on the phonological loop than others. For example, 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. According to at least some researchers, such tasks require both intact articulatory rehearsal and intact phonological storage/representations to perform successfully, but do not necessarily require central executive processes. A number of studies have shown that individuals with schizophrenia demonstrate relatively intact performance on digit span forward tasks, particularly when the number of items is at or below WM span ( $7 \pm 2$ ) (Clare et al., 1993; Cohen et al., 1999; Fitzgerald et al., 2004; Park and Holzman, 1992; Rushe et al., 1998; Salame et al., 1998) and when there is no verbal interference (Fleming et al., 1995; Oltmanns and Neale, 1975). Other work has shown that individuals with schizophrenia do not show disproportionate impairment for recall of lists with phonologically similar versus dissimilar items, suggesting an intact ability to represent phonological information (Elvevag et al., 2002). Further, studies suggest intact serial position curves among individuals with schizophrenia (Wexler et al., 2002), which is indicative of intact articulatory rehearsal mechanisms. However, work by Wexler and Stevens (Stevens et al., 1998; Wexler et al., 1998) has suggested that at least a subset of patients may have deficits in a verbal serial recall task that specifically probes for position information, more



so than on tone serial recall task. Further, a recent meta-analysis of the performance of individuals with schizophrenia did find significant impairment on digit span forward, though with a relatively small effect size compared with performance in other memory domains (Aleman et al., 1999).

One can also ask whether there is any evidence that individuals with schizophrenia are differentially impaired on verbal as compared with non-verbal WM tasks as another way to address the integrity of the phonological loop in schizophrenia. Many of the studies that have directly compared verbal WM to non-verbal WM in individuals with schizophrenia have found equal deficits across domains (Barch et al., 2002; Franke et al., 1999; Walter et al., 2003) or sometime worse non-verbal than verbal WM (Salame et al., 1998). Further, a recent meta-analysis of WM function in schizophrenia concluded that there was little evidence for any domain specific WM deficit in schizophrenia (Lee and Park, in press).

A third approach to determining whether the phonological loop is intact in schizophrenia is to determine whether individuals with schizophrenia show functional abnormalities in brain regions thought to be critical for phonological loop function. As described above, such regions include left VLPFC (BA 45 and 44) as well as left PPC. Examination of the WM-related functional activation literature suggests that the vast majority of studies report intact activation of VLPFC regions during WM performance in individuals with schizophrenia. For example, a recent review of studies using the N-back test of WM found that only three of 16 studies found any evidence for impaired VLPFC activity in schizophrenia (Barch, 2005). Studies using other types of WM tasks have also reported intact activation of VLPFC regions in individuals with schizophrenia (Barch et al., 2001; MacDonald and 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 which did not find cell density changes in Brodmann's area 44 (Selemon et al., 2003), though such changes are found in Brodmann's area 9, as discussed in more detail below.

Although the majority of functional imaging studies using WM tasks in schizophrenia report intact activation in VLPFC, a number of these same studies report abnormal activation in PPC, either in terms of the degree of activation or connectivity with other brain regions (Barch et al., 2002; Kim et al., 2003; Menon et al., 2001; Meyer-Lindenberg et al., 2001; Quintana et al., 2003; Schlosser et al., 2003a). Further, a number of imaging studies using the N-back WM task in schizophrenia have found abnormal PPC activation (Barch, 2005). Importantly, however, recent work by Fiez and colleagues has demonstrated that there are multiple regions of posterior parietal cortex active during WM tasks (Ravizza et al., 2004). One of these regions is sensitive to the type of information (verbal versus non-verbal) being maintained in WM and potentially corresponds to a left PPC region that supports phonological storage. The other PPC area was bilateral and sensitive to load irrespective of material type, and may play a

role in the maintenance or updating of information in WM across stimulus domains. The region sensitive to material type was more ventral than the region sensitive to load, and Fiez and colleagues have referred to these different PPC regions as ventral inferior PPC (VIPPC) and dorsal inferior PPC (DIPPC) respectively. As such, it is important to determine which of these regions of PPC tends to show altered activation in individuals with schizophrenia, as evidence of impaired VIPPC function in schizophrenia may point to a disturbance in phonological store or processing that could contribute to maintenance disturbances in WM. However, recent work specifically focused on examining the integrity of VIPPC versus DIPPC activation in schizophrenia during WM found intact VIPPC activity in schizophrenia (Barch and Csernanksy, submitted for publication). Thus, the work using functional imaging to study brain function in schizophrenia suggests relatively intact function of the brain regions thought to support the phonological loop, including VLPFC and VIPPC. In sum, the work on schizophrenia suggests that the function of the phonological loop is relatively intact in this disorder. As will be discussed in further detail below, this contrasts with the wealth of data indicating deficits in central executive function. As such, the dissociation between deficits in central executive function, but not phonological loop function (or at least less severe in the phonological loop) provides evidence for the proposal that this represent distinct components of working memory that may have different neural substrates.

### Visual-spatial scratchpad in schizophrenia

The critical behavioral and neural biological markers of scratchpad functions in healthy humans are much less clear than the markers of phonological loop function. Thus, it is more challenging to determine whether there may be selective disturbances in visual-spatial scratchpad function in schizophrenia. Among individuals with schizophrenia, there is certainly a large body of evidence for impairments on visual-spatial WM tasks, starting with the seminal work of Park and Holzman (1992). Further, there is consistent evidence for impairments on classic measure of the visual-spatial scratchpad, such as memory-guided saccade performance (McDowell et al., 2001; McDowell and Clementz, 1996; Muller et al., 1999; Snitz et al., 1999). However, as discussed above, there is little evidence for a selective deficit in spatial WM as compared with non-spatial WM in individuals with schizophrenia (Lee and Park, in press; Walter et al., 2003). Surprisingly, there are relatively few functional neuroimaging studies in schizophrenia that have used visual-spatial WM tasks that could not be accomplished by verbal recoding (small numbers of spatial locations are typically verbally labeled by participants, turning the task into a verbal WM task). Thus, more studies specifically designed to selectively assess visual-spatial scratchpad functions are needed to help understand the integrity of these processes and the brain regions that support them in schizophrenia.

In summary, much of the work on verbal and/or visual-spatial buffer systems in schizophrenia does not present

clear evidence for impairments in the maintenance of information in WM. Though there is some evidence for deficits on digit span forward type tasks, the effect size for these impairments is relatively small compared with impairments in other memory domains. Further, many other markers of the function of the phonological loop appear to be intact in schizophrenia, such as evidence for phonological similarity effects in WM. The work on functional brain imaging also suggests relatively little evidence for clear impairments in brain regions thought to be critical for phonological loop function, such as VLPFC or VIPPC. Again, the relatively intact function of the buffer systems in schizophrenia, combined with the work indicating deficits in central executive function reviewed below, provides validation for the distinctions made between buffer systems and central executive functions.

### 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. As noted above, many studies suggest that individuals with schizophrenia have deficits on WM tasks with all different material types, with relatively little evidence for selective deficits with one material type over another (Barch et al., 2002; Coleman et al., 2002; Gooding and Tallent, 2004; Kim et al., 2004; Tek et al., 2002). Such a pattern is consistent with a deficit in central executive function (important for all material types) rather than a domain specific buffer system. In addition, 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 (Fleming et al., 1995; Goldberg et al., 1998), and information updating and temporal indexing (Ganzvles and Haenen, 1995; Goldberg et al., 2003; Perlstein et al., 2003). Of note however, 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 that compared maintenance only measures of WM to maintenance plus manipulation measures in individuals with schizophrenia and found a differential deficit on the manipulation measures (Kim et al., 2004; Kimberg et al., 1997; Kimberg and Farah, unpublished observations). Such results mirror early work by Oltmanns and Neale (1975) demonstrating a differential deficit on a digit span task that required protection from interference (a putative central executive function) as compared with a version that did not include such distraction. These authors demonstrated that the maintenance only measures have similar discriminating power to the maintenance plus manipulation measures, providing evidence against a generalized deficit interpretation of the results.

As described above, the basic cognitive neuroscience literature has linked many of the central executive compo-

nents of WM to the function of DLPFC. Consistent with this hypothesis, a large number of functional neuroimaging 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 (Berman et al., 1986, 1988; Weinberger et al., 1986, 1988), mental arithmetic (Hugdahl et al., 2004), self-ordered pointing, and various versions of the N-back task (Callicott et al., 2000; Carter et al., 1998). In most of the earlier studies using the Wisconsin Card Sorting task (Davidson and Neale, 1974), as well as in a number of the more recent studies using tasks such as the N-back and mental arithmetic, the modal finding has been of decreased activation in DLPFC in schizophrenia (Barch et al., 2002; Callicott et al., 1996, 2003; Carter et al., 1998; Fletcher et al., 1998; Honey et al., 2003; Hugdahl et al., 2004; Jansma et al., 2004; Mendrek et al., 2004, 2005; Menon, 1993; Meyer-Lindenberg et al., 2002, 2005; Perlstein et al., 2001; Quintana et al., 2003; Wykes et al., 2002). However, in several recent studies using the N-back 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, 2003; 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 hypothesis put forth to explain these apparently contradictory findings regarding the direction of activation changes in DLPFC among individuals with schizophrenia is the idea that the memory load-DLPFC response curve may be different for individuals with schizophrenia as compared with healthy controls. A typical finding in healthy individuals is that DLPFC activity increases as memory load increases, until WM capacity is exceeded, at which point DLPFC activity decreases (Braver et al., 1997; Callicott et al., 1999; Cohen et al., 1997). Callicott and colleagues (2000, 2003) have suggested that the relationship between memory load and DLPFC activity may be different in individuals with schizophrenia, in one of two ways: 1) same load-activity curve, but a lower WM capacity, leading to a drop-off in DLPFC activity at lower memory loads as compared with controls; or 2) different load-response curve, such that patients show greater DLPFC activity than controls as lower memory loads (referred to as inefficient DLPFC activity), but less DLPFC activity than controls as higher memory loads. A recent review (Barch, 2005) and a recent meta analysis (Glahn et al., 2005) of N-back studies of WM in schizophrenia both suggested that the majority of the research results supports the first hypothesis, with few studies reporting evidence for hyper-DLPFC activation, even when groups are matched on behavioral performance, or high performing patients are compared with controls. Further, the review suggested that the regions of DLPFC showing hyperactivation in some WM studies may be distinct from the DLPFC regions that show hypoactivation, tending to be either more anterior

(particularly on the right) or more inferior (particularly on the left) (Barch, 2005). Such findings raise the possibility that activity of some of these regions may reflect compensatory strategies that are engaged when impairments in the DLPFC regions most commonly activated by central executive components of WM (i.e. BA 46/9) are not able to function properly. Further research that directly compares different WM paradigms that may elicit the use of different types of strategies, or research using paradigms specifically designed to manipulate or constrain the type of processes that can be used to accomplish the task, may help to parameterize the conditions under which individuals with schizophrenia show hyper- or hypo-DLPFC activation.

Although DLPFC is the region most commonly associated with central executive functions in humans, there is a large body of evidence to suggest that regions of parietal cortex are also important for central executive processing (Corbetta et al., 2002; Marshuetz et al., 2000; Peers et al., 2005; Ravizza et al., 2004; Sohn et al., 2000). As described above, there are several different regions of PPC activated in WM tasks, and Fiez and colleagues have suggested that the DIPPC regions are those most likely to play a role in central executive processing (Ravizza et al., 2004). In a recent study designed to examine the integrity of VIPPC versus DIPPC in schizophrenia, we found clear evidence for impaired DIPPC function during both verbal and nonverbal WM performance, in the same individuals who demonstrated intact VIPPC function. Findings of alterations in both DLPFC and DIPPC function in schizophrenia during WM are consistent with the research, reviewed in more detail in another contribution to this series, suggesting a disconnection between frontal and parietal regions among individuals with schizophrenia (Kim et al., 2003; Meyer et al., 2001; Schlosser et al., 2003a,b). Importantly, the regions of PPC showing altered functional connectivity with frontal cortex among individuals with schizophrenia were in the DIPC area thought to be important for central executive function. Such findings of course raise the question of how DIPPC contributes to central executive function. A number of suggestions have been put forward for the role of DIPPC in executive processing. One intriguing hypothesis is that the DIPC makes a specific contribution to the temporal coding of items within working memory using magnitude codes (Marshuetz et al., 2000) in coordination with the dorsolateral prefrontal cortex (D'Esposito et al., 1999b). In schizophrenia, this coordinated activity of the DIPC and DLPFC may be disturbed during WM, leading to difficulties coding the temporal order of items within a working memory task (Brahmbatt et al., 2004).

### **Relationship to normative models of working memory function**

In summary, the literature on WM in schizophrenia provides clear evidence for behavioral impairments on tasks measuring central executive and manipulation functions, but less clear evidence for impairments on tasks measuring maintenance functions of WM, such as the phonological loop or the visual-spatial scratchpad. Further, the

literature on WM-related brain activation in schizophrenia provides consistent evidence for altered activity in DLPFC and DIPPC (or connectivity between the two), but much less evidence for impaired activity in regions thought to support domain specific buffer systems (VLPFC and VIPPC). Thus, the literature on WM function in schizophrenia could be taken as providing evidence for a dissociation between deficits in manipulation versus maintenance components of WM, providing evidence for the validity of making this distinction in normal WM function.

Despite the fact that the data in schizophrenia can be seen as consistent with models of WM such as those put forth by Baddeley, the pattern of results in individuals with schizophrenia could be seen as somewhat inconsistent with the models of WM developed in the animal literature. Specifically, the seminal work by Goldman-Rakic (1987) on the neural basis of WM in non-human primates suggested that neurons in DLPFC showed sustained delay-related activity during performance of WM tasks, even when the delays were not filled with any distracting information. The types of tasks used in these animal studies are ones that would tend to be considered "maintenance only" type tasks in the human literature. However, as described early, the human literature does not necessarily suggest a large role for DLPFC in the "simple" maintenance of information in WM, especially not of single items as in many of the non-human primate studies. Further, research on individuals with lesions to DLPFC does not suggest that these individuals are impaired on simple forward span tasks, thought to measure the maintenance of information in WM (D'Esposito and Postle, 1999). The literature on schizophrenia could be viewed as consistent with the DLPFC lesion literature, with relatively little impairment on span forward tasks, but evidence for impairment on central executive and manipulation tasks as well as altered DLPFC function. Thus, there is somewhat of a discrepancy between the non-human primate literature, which suggests a role for DLPFC in the maintenance of information over unfilled delays, and the human literature, which does not necessarily suggest a critical role for DLPFC in WM maintenance.

This discrepancy might be addressed by looking at delayed-match-to sample tasks in humans, as these are tasks that are more analogous to the non-human primate tasks than are the span forward tasks. D'Esposito and Postle (1999) have suggested that delayed-match to sample tasks are more likely to require rehearsal mechanisms than span tasks, given that span tasks allow one to immediately repeat back the items. In contrast, delayed-match to sample tasks often have relatively longer delays which may necessitate some type of rehearsal or refresh mechanisms to keep the information active, particularly if there is distracting information introduced during the delay. In a review of WM performance in individuals with lesions to DLPFC, D'Esposito and Postle (1999) found evidence for impaired delayed-match-to-sample performance among individuals with DLPFC lesions. However, these impairments were most evident for tasks that included filled delays and thus necessitated protection from interference.



This later finding is actually consistently with non-human primate data suggesting that delay-related activity in DLPFC is particularly important for WM performance in monkey when distracting repeating items intervene between the cue and the probe (Miller et al., 1995).

In the schizophrenia literature, there is also clear evidence for impaired behavioral performance on delayed-match-to-sample tasks, though many of these studies have used tasks that involved some type of distraction during the delay (Goldberg et al., 1998; Lencz et al., 2003; Park and Holzman, 1992), potentially turning the paradigm into a dual task or protection from interference task (which some might suggest engages the central executive). There have been a few studies using delayed-match-to-sample tasks without any distraction that have shown impairments among individuals with schizophrenia (Tek et al., 2002), though some of studies have either not included a no-delay condition (to establish it as a maintenance deficits) (Coleman et al., 2002), or have used more than one or two items in the memory set (leading to the possibility for a role for chunking, a potential type of manipulation) (Goldberg, 1984; Kim et al., 2004). Thus, analogous to individuals with DLPFC lesion, there is evidence for impaired delayed-match to sample performance among individuals with schizophrenia, with the greatest evidence for impairment in conditions that include distracting information.

The fact that the DLPFC lesion and schizophrenia literatures point to some evidence for impairments in the maintenance of information in WM, particularly during distraction, is consistent with the suggestion from the non-human primate literature that the DLPFC is important for maintenance as well as manipulation components of WM. However, the healthy human literature does still suggest a much larger role for DLPFC in manipulation as compared with maintenance, and few studies demonstrate strong DLPFC activation when only an item or two has to be maintained in WM. Further, the Baddeley model of WM does suggest a relatively strict segregation between maintenance and central executive components of WM, a view which is not necessarily consistent with a role for the same regions of DLPFC in both maintenance and WM (though engagement of different regions of DLPFC for maintenance versus manipulation would of course be quite consistent with Baddeley's model). As such, it is not clear how to resolve these seemingly contradictory views of the relationship between DLPFC function, and the maintenance versus manipulation components of WM.

### DLPFC and context processing

A way in which my colleagues and I have tried to resolve this seemingly contradictory views of the functional roles of DLPFC in WM is to postulate that one way in which DLPFC contributes to central executive function is to maintain certain types of information—context representations—that helps to guide the processing and manipulation of other information. More specifically, Cohen and colleagues (Barch et al., 2001; Braver et al., 1999; Braver and Cohen, 1999; Cohen et al., 1999; Cohen and Servan-Schreiber, 1992) have used computational modeling techniques to

help 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. Context refers to prior task-relevant information that is represented in such a form that it can bias selection of the appropriate behavioral response. Context representations can include task instructions, a specific prior stimulus, or the result of processing a sequence of prior stimuli (e.g. the interpretation that results from processing a sequence of words in a sentence). Because context representations are maintained in an active state, they are continually accessible and available to influence processing. Consequently, context can be viewed as the subset of representations within WM that governs how other representations are used. One important insight that has emerged from this work is a single deficit in one aspect of executive control can contribute to deficits in cognitive domains often treated as independent. As such, we have argued that deficits in WM, attention and inhibition in schizophrenia can all be understood in terms of a deficit in context-processing (Barch et al., 2001; Braver et al., 1999; Braver and Cohen, 1999; Cohen et al., 1999; Cohen and Servan-Schreiber, 1992). When a task involves competing, task-irrelevant processes (as in the Stroop task), we have argued that context representations serve to inhibit such task-irrelevant processes by providing top-down support for task-relevant processes. When a task involves a delay between a cue and a later contingent response, we have argued that the mechanism used to represent context information is used to maintain task relevant information against the interfering, and cumulative effects of noise over time (as in a delayed-match-to-sample paradigm). Further, in both inhibition and WM conditions, context representations serve an attentional function, by selecting task-relevant information for processing over other potentially competing sources of information.

Thus, the context hypothesis can explain why patients with schizophrenia demonstrate deficits on at least some tasks thought to tap WM, as well as deficits on other cognitive control tasks that may not involve a high WM load (e.g. Stroop) (e.g. Barch et al., 1999). Further, the context-processing hypothesis explains why patients show deficits on tasks in which context information needs to be determined and maintained, even if this context information constitutes a low WM load (Barch et al., 2003; Cohen et al., 1999). The context hypothesis may also help to explain why individuals with schizophrenia (and those with lesions to DLPFC) do particularly poorly on delayed-match-to-sample tasks that include distraction, as context information may play a critical role in tagging the to-be-protected information or in signifying the need for either rehearsal refreshes or the inhibition of the distracting information.

Several studies have provided support for the hypothesis that individuals with schizophrenia have deficits in context-processing. Behavioral studies have found selective patterns of performance deficits among patients with schizophrenia on tasks specifically designed to measure context-processing (Barch et al., 1998, 2001, 2003; Cohen

et al., 1992, 1999; Condray et al., 1999; Javitt et al., 2000; Niznikiewicz et al., 1997; Servan-Schreiber et al., 1996; Stratta et al., 1998, 2000; Titone et al., 2000). In addition, the siblings of individuals with schizophrenia who do not themselves have schizophrenia also demonstrate a selective deficit in context-processing (MacDonald et al., 2003) as do individuals with schizotypal personality disorder (Barch et al., 2004), suggesting that such deficits may indeed be associated with liability to schizophrenia. In terms of DLPFC activity, medication naïve first episode patients with schizophrenia demonstrate impaired DLPFC activation associated with impaired context-processing (Barch et al., 2001), while psychotic individuals with disorders other than schizophrenia do not show the same impairment in DLPFC activity (MacDonald et al., 2005). Chronic-medicated patients with schizophrenia also show impaired DLPFC activity associated with impaired context-processing (MacDonald and Carter, 2003; Perlestein et al., 2003).

Of course, the verbal description of context processing provided above does not necessarily make clear how this helps to explain a role for DLPFC in the maintenance of information over filled or unfilled delays, as in delayed-match-to-sample tasks. However, work using computational simulations that specify the role of dopamine in DLPFC in relationship to WM and executive control deficits in schizophrenia can help to provide a more mechanistic understanding of the role of DLPFC in WM (Braver et al., 2002). For example, a number of studies suggest that various indices of altered DLPFC integrity (task-related functional brain activation, NAA, WM performance) are associated with evidence for hyperdopaminergic function in subcortical systems (Abi-Dargham et al., 2002; Bertolino et al., 1999; 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 and Cohen, 1999, 2000; Braver et al., 2002). Abnormalities in the activity of the subcortical dopamine system then dysregulate the ability to appropriately gate information into WM, leading to both perseverative behaviors when WM representations cannot be updated, and susceptibility to interference due to poor stability of WM representations. Thus, intact dopamine inputs into DLPFC may be critical for guiding what information should be gated into WM buffers and maintained over delays, as well as for helping to gate out potentially distracting information that could interfere during a delay period. Findings that modulation of the DA system can improve WM and or executive function performance in schizophrenia (Barch et al., 1997b; Daniel et al., 1989, 1991) or in individuals with poor WM function (Mattay et al., 2003) are at least indirectly consistent with the tenets of the context processing theory.

The arguments put forth above suggest that the representation and maintenance of context is a function that is different from the maintenance of identity information, and

potentially different from other aspects of manipulation. As noted above, the functional imaging literature provides some evidence for the distinction between the maintenance of identity and the maintenance of context information, in that the maintenance of context reliably engages DLPFC (Barch et al., 1997a, 2001; Braver and Bongiolatti, 2002), while the maintenance of identity information does not always engage DLPFC (D'Esposito et al., 1999b). Further, individuals with schizophrenia often show an intact ability to maintain one or two identity items in working memory, but are impaired on the maintenance of a single "context" representation on the AX-CPT task (Cohen et al., 1999). However, the dissociation of context processing from other types of manipulation has not yet been examined empirically. For example, it would be interesting to compare the regions of DLPFC engaged by context processing versus other forms of manipulation within the same individuals, as well as to examine whether manipulations of the dopamine systems have similar or different influences on context processing versus manipulation within the same individuals (either healthy individuals or those with schizophrenia).

## CONCLUSION

In summary, the literature on WM function in schizophrenia does support the importance of distinguishing between the maintenance and manipulation components of WM. Individuals with schizophrenia show relatively little evidence of impairment on tasks thought to be primarily reliant on the phonological loop, a key component of the verbal maintenance system. Further, individuals with schizophrenia tend to show relatively intact activation in brain regions thought to be important for the mechanisms involved in the phonological loop, such as VLPFC (articulatory rehearsal) and VIPPC (phonological coding or storage). It is less clear whether individuals with schizophrenia show deficits in visual-spatial scratchpad function, primarily because there are not yet clear behavioral markers of the function of this system. Individuals with schizophrenia show clear evidence of deficits on tasks thought to measure various aspects of central executive function and manipulations, as well as robust evidence for impairments in brain regions thought to be associated with executive function, such as DLPFC and DIPPC. However, there is some discrepancy between the models of WM developed in the human and non-human primate literature, particularly in regards to the role that DLPFC plays in the maintenance versus central executive component of WM. The non-human primate literature suggests more of a role for the DLPFC in maintenance components of WM, while the human literature has implicated the DLPFC more in executive processing. The literature on schizophrenia is mostly easily seen as consistent with the view that DLPFC is most involved with various aspects of executive processing, though individuals with schizophrenia do show some evidence of impairment on delayed-match-to-sample maintenance tasks, though most robustly on versions that include distracting information during the delays. To resolve these discrepan-



cies, we have suggested that the DLPFC can be involved in the maintenance of information, but of a specific type (context representation) that helps to guide and coordinate other information held in WM. Further, we have suggested that dopamine deficits in DLPFC among individuals with schizophrenia contribute to deficits in context processing.

*Acknowledgments*—This work was supported by grants NIMH grants MH60887, MH066031 and MH56584, as well as a Conte Center for Neuroscience of Mental Disorders MH071616 grant.

## REFERENCES

- Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, Hwang DK, Keilp J, Kochan L, Van Heertum R, Gorman JM, Laruelle M (2002) Prefrontal dopamine D1 receptors and working memory in schizophrenia. *J Neurosci* 22(9):3708–3719.
- Aleman A, Hijman R, de Haan EHF, Kahn RS (1999) Memory impairment in schizophrenia: A meta-analysis. *Am J Psychiatry* 256(9):1358–1366.
- Arnsten AF, Cai JX, Murphy BL, Goldman-Rakic PS (1994) Dopamine D1 receptor mechanisms in the cognitive performance of young adult and aged monkeys. *Psychopharmacology* 116:143–151.
- Awh E, Jonides J (2001) Overlapping mechanisms of attention and spatial working memory. *Trends Cogn Sci* 5:119–126.
- Awh W, Jonides J, Reuter-Lorenz PA (1998) Rehearsal in spatial working memory. *J Exp Psychol* 24(3):780–790.
- Baddeley AD (1986) Working memory. New York: Oxford University Press.
- Baddeley AD (2000) The episodic buffer: A new component of working memory? *Trends Cogn Sci* 4:417–423.
- Barch DM (2004) Pharmacological manipulation of human working memory. *Psychopharmacology (Berl)* 174(1):126–135.
- Barch DM (2005) The cognitive neuroscience of schizophrenia. In: Annual review of clinical psychology, Vol. 1 (Cannon T, Mineka S, eds), pp 321–353. Washington, D.C.: American Psychological Association.
- Barch DM, Braver TS, Nystrom LE, Forman SD, Noll DC, Cohen JD (1997a) Dissociating working memory from task difficulty in human prefrontal cortex. *Neuropsychologia* 35(10):1373–1380.
- Barch DM, Carter CS, Braver TS, Cohen JD (1997b) The effects of *d*-amphetamine on working memory and language deficits in schizophrenia. *Schizophr Res* 24:129.
- Barch DM, Braver TS, Cohen JD, Servan-Sreiber D (1998) Context processing deficits in schizophrenia. *Arch Gen Psychiatry* 55:187–188.
- Barch DM, Carter C, Perlstein W, Baird J, Cohen J, Schooler N (1999) Increased Stroop facilitation effects in schizophrenia are not due to increased automatic spreading activation. *Schizophr Res* 39(1):51–64.
- Barch DM, Carter CS, Braver TS, McDonald A, Sabb FW, Noll DC, Cohen JD (2001) Selective deficits in prefrontal cortex regions in medication naive schizophrenia patients. *Arch Gen Psychiatry* 50:280–288.
- Barch DM, Carter CS, Cohen JD (2003) Context processing deficit in schizophrenia: Diagnostic specificity, 4-week course, and relationships to clinical symptoms. *J Abnorm Psychol* 112:132–143.
- Barch DM, Csernansky J, Conturo T, Snyder AZ, Ollinger J (2002) Working and long-term memory deficits in schizophrenia. Is there a common underlying prefrontal mechanism? *J Abnorm Psychol* 111:478–494.
- Barch DM, Mitropoulou V, Harvey PD, New AS, Silverman JM, Siever LJ (2004) Context-processing deficits in schizotypal personality disorder. *J Abnorm Psychol* 113(4):556–568.
- Berman KF, Illowsky BP, Weinberger DR (1988) Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. *Arch Gen Psychiatry* 45:616–622.
- Berman KF, Zec RF, Weinberger DR (1986) Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. II: Role of neuroleptic treatment, attention and mental effort. *Arch Gen Psychiatry* 43:126–135.
- Bertolino A, Knable MB, Saunders RC, Callicott JH, Kolachana B, Mattay VS, Bachevalier J, Frank JA, Egan M, Weinberger DR (1999) The relationship between dorsolateral prefrontal N-acetyl-aspartate measures and striatal dopamine activity in schizophrenia. *Biol Psychiatry* 45:660–667.
- Brahmbhatt S, Haut KM, Csernansky JG, Barch DM (2004) Working memory deficits in individuals with schizophrenia and their high risk siblings. Paper presented at the Society for Neuroscience, San Diego.
- Braver TS, Barch DM, Cohen JD (1999) Cognition and control in schizophrenia: A computational model of dopamine and prefrontal function. *Biol Psychiatry* 46:312–328.
- Braver TS, Bongiolatti SR (2002) The role of the frontopolar prefrontal cortex in subgoal processing during working memory. *Neuroimage* 15:523–536.
- Braver TS, Cohen JD (1999) Dopamine, cognitive control, and schizophrenia: The gating model. *Prog Brain Res* 121:327–349.
- Braver TS, Cohen JD (2000) On the control of control: The role of dopamine in regulating prefrontal function and working memory. In: Attention and performance VIII (Monsell S, Driver J, eds), pp 713–738. Cambridge, MA: MIT Press.
- Braver TS, Cohen JD (2001) Working memory, cognitive control, and the prefrontal cortex: Computational and empirical studies. *Cogn Proc* 2:25–55.
- Braver TS, Cohen JD, Barch DM (2002) The role of the prefrontal cortex in normal and disordered cognitive control: A cognitive neuroscience perspective. In: Principles of frontal lobe function (Stuss DT, Knight RT, eds), pp 428–448. Oxford: Oxford University Press.
- Braver TS, Cohen JD, Nystrom LE, Jonides J, Smith EE, Noll DC (1997) A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage* 5(1):49–62.
- Brozoski TJ, Brown RM, Rosvold HE, Goldman PS (1979) Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. *Science* 205(31):929–931.
- Cai JX, Arnsten AFT (1997) Dose-dependent effects of the dopamine D1 receptor agonists A77636 or SKF81297 on spatial working memory in aged monkeys. *J Pharmacol Exp Ther* 283(1):183–189.
- Callicott JH, Bertolino A, Mattay VS, Langheim FJ, Duyn J, Coppola R, Goldberg TE, Weinberger DR (2000) Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. *Cereb Cortex* 10:1078–1092.
- Callicott JH, Mattay VS, Bertolino KF, Coppola R, Frank JA, Goldberg TE, Weinberger DR (1999) Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cereb Cortex* 9(20):20–26.
- Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR (2003) Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. *Am J Psychiatry* 160(12):2209–2215.
- Callicott JH, Ramsey NF, Tallent K, Bertolino A, Knable MB, Coppola R, Goldberg T, van Gelderen P, Mattay VS, Frank JA, Moonen CTW, Weinberger DR (1996) fMRI brain mapping in psychiatry: Methodological issues illustrated in a study of working memory in schizophrenia. Washington, D.C.: NIMH Neuroscience Center at St. Elizabeths.
- Carter C, Perlstein W, Ganguli R, Brar J, Mintun M, Cohen J (1998) Functional hypofrontality and working memory dysfunction in schizophrenia. *Am J Psychiatry* 155(9):1285–1287.
- Castner SA, Williams GV, Goldman-Rakic PS (2000) Reversal of antipsychotic induced working memory deficits by short term dopamine D1 receptor stimulation. *Science* 287:2020–2022.

- Chein JM, Fiez JA (2001) Dissociation of verbal working memory system components using a delayed serial recall task. *Cereb Cortex* 11(11):1003–1014.
- Clare L, McKenna PJ, Mortimer AM, Baddeley AD (1993) Memory in schizophrenia: What is impaired and what is preserved? *Neuropsychologia* 31(11):1225–1241.
- Cohen JD, Barch DM, Carter C, Servan-Schreiber D (1999) Context-processing deficits in schizophrenia: Converging evidence from three theoretically motivated cognitive tasks. *J Abnorm Psychol* 108:120–133.
- Cohen JD, Perstein WM, Braver TS, Nystrom LE, Noll DC, Jonides J, Smith EE (1997) Temporal dynamics of brain activation during a working memory task. *Nature* 386:604–608.
- Cohen JD, Servan-Schreiber D (1992) Context, cortex and dopamine: A connectionist approach to behavior and biology in schizophrenia. *Psychol Rev* 99(1):45–77.
- Cohen JD, Targ E, Servan-Schreiber D, Spiegel D (1992) The fabric of thought disorder: A cognitive neuroscience approach to disturbances in the processing of context in schizophrenia. In: *Cognitive science and clinical disorders* (Stein DJ, Young JE, eds), pp 101–127. New York: Academic Press.
- Coleman MJ, Cook S, Matthyse S, Barnard J, Lo Y, Levy DL, Rubin DB, Holzman PS (2002) Spatial and object working memory impairments in schizophrenia patients: A bayesian item-response theory analysis. *J Abnorm Psychol* 111(3):425–435.
- Condray R, Steinhauer SR, Cohen JD, van Kammen DP, Kasperek A (1999) Modulation of language processing in schizophrenia: Effects of context and haloperidol on the event-related potential. *Biol Psychiatry* 45(10):1336–1355.
- Corbetta M, Kincade JM, Shulman GL (2002) Neural systems for visual orienting and their relationships to spatial working memory. *J Cogn Neurosci* 14(3):508–523.
- Corkin S (1984) Lasting consequences of bilateral medial temporal lobectomy: Clinical course and experimental findings in H. M. *Semin Neurol* 4(2):249–259.
- Csernansky JG, Holman CA, Hollister LE (1983) Variability and the dopamine hypothesis of schizophrenia. *Schizophr Bull* 9(3):325–328.
- Curtis CE, Rao VY, D'Esposito M (2004) Maintenance of spatial and motor codes during oculomotor delayed response tasks. *J Neurosci* 24(16):3944–3952.
- Curtis CE, Zald DH, Pardo JV (2000) Organization of working memory within the human prefrontal cortex: a PET study of self-ordered object working memory. *Neuropsychologia* 38(11):1503–1510.
- D'Esposito M, Postle BR (1999a) The dependence of span and delayed-response performance on prefrontal cortex. *Neuropsychologia* 37(11):1303–1315.
- D'Esposito M, Postle BR, Ballard D, Lease J (1999b) Maintenance versus manipulation of information held in working memory: An event-related fMRI study. *Brain Cogn* 41:66–86.
- D'Esposito M, Postle BR, Jonides J, Smith EE (1999c) The neural substrate and temporal dynamics of interference effects in working memory as revealed by event-related functional MRI. *Proc Natl Acad Sci USA* 96:7514–7519.
- Daniel DG, Berman KF, Weinberger DR (1989) The effect of apomorphine on regional cerebral blood flow in schizophrenia. *J Neuropsychiatry* 1:377–384.
- Daniel DG, Weinberger DR, Jones DW, Zigun JR, Coppola R, Handal S, Bigelow LB, Goldberg TE, Berman KF, Kleinman JE (1991) The effect of amphetamine on regional cerebral blood flow during cognitive activation in schizophrenia. *J Neurosci* 11(7):1907–1917.
- Davidson GS, Neale JM (1974) The effects of signal-noise similarity on visual information processing of schizophrenics. *J Abnorm Psychol* 83(6):683–686.
- Elvevag B, Weinberger DR, Goldberg TE (2002) The phonological similarity effect in short-term memory serial recall in schizophrenia. *Psychiatry Res* 112(1):77–81.
- Fiez JA (1997) Phonology, semantics, and the role of the left inferior prefrontal cortex. *Hum Brain Mapp* 5:79–83.
- Fiez JA, Raife EA, Balota DA, Schwarz JP, Raichle ME, Petersen SE (1996) A positron emission tomography study of the short-term maintenance of verbal information. *J Neurosci* 16(2):808–822.
- Fitzgerald D, Lucas S, Redoblado MA, Winter V, Brennan J, Anderson J, Harris A (2004) Cognitive functioning in young people with first episode psychosis: relationship to diagnosis and clinical characteristics. *Aust N Z J Psychiatry* 38(7):501–510.
- Fleming K, Goldberg TE, Gold JM, Weinberger DR (1995) Verbal working memory dysfunction in schizophrenia: use of a Brown-Peterson paradigm. *Psychiatry Res* 56(2):155–161.
- Fletcher PC, McKenna PJ, Frith CD, Grasby PM, Friston KJ, Dolan RJ (1998) Brain activation in schizophrenia during a graded memory task studied with functional neuroimaging. *Arch Gen Psychiatry* 55:1001–1008.
- Franke P, Gansicke M, Schmitz S, Falkai P, Maier W (1999) Differential memory span: abnormal lateralization pattern in schizophrenic patients and their siblings? *Int J Psychophysiol* 34(3):303–311.
- Ganzevles PG, Haenen MA (1995) A preliminary study of externally and self-ordered task performance in schizophrenia. *Schizophr Res* 16(1):67–71.
- Glahn DC, Ragland JD, Abramoff A, Barrett J, Laird AR, Bearden CE, Velligan DI (2005) Beyond hypofrontality: A quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Hum Brain Mapp* 25(1):60–69.
- Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR (1997) Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. *Arch Gen Psychiatry* 54(2):159–165.
- Goldberg E (1984) Papez circuit revisited: Two system instead of one. In: *Neuropsychology of memory* (Squire LR, Butters N, eds), pp. 183–193. New York: Guilford.
- Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, Goldman D, Weinberger DR (2003) Executive sub-processes in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. *Arch Gen Psychiatry* 60(9):889–896.
- Goldberg TE, Patterson KJ, Taqqu Y, Wilder K (1998) Capacity limitations in short-term memory in schizophrenia: tests of competing hypotheses. *Psychol Med* 28:665–673.
- Goldman-Rakic (1995) Cellular basis of working memory. *Neuron* 14:477–485.
- Goldman-Rakic PS (1987) Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: *Handbook of physiology: the nervous system V, Vol. 5* (Plum F, Mountcastle V, eds), pp 373–417. Bethesda, MD: American Physiological Society.
- Goldman-Rakic PS (1991) Prefrontal cortical dysfunction in schizophrenia: The relevance of working memory. In: *Psychopathology and the brain* (Carroll BJ, Barrett JE, eds), pp 1–23. New York: Raven Press, Ltd.
- Goldman-Rakic PS, Muly EC, Williams GV (2000) D1 receptors in prefrontal cells and circuits. *Brain Res Rev* 31:295–301.
- Gooding DC, Tallent KA (2004) Nonverbal working memory deficits in schizophrenia patients: Evidence of a supramodal executive processing deficit. *Schizophr Res* 68:189–201.
- Grace AA (1991) Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: A hypothesis of the etiology of schizophrenia. *Neuroscience* 41(1):1–24.
- Honey GD, Bullmore ET, Sharma T (2002) De-coupling of cognitive performance and cerebral functional response during working memory in schizophrenia. *Schizophr Res* 53:45–56.
- Honey GD, Sharma T, Suckling J, Giampietro V, Soni W, Williams SC, Bullmore ET (2003) The functional neuroanatomy of schizophrenic subsyndromes. *Psychol Med* 33(6):1007–1018.
- Hugdahl K, Rund BR, Lund A, Asbjørnsen A, Egeland J, Erslund L, Landro NI, Roness A, Stordal KI, Sundet K, Thomsen T (2004)

- Brain activation measured with fMRI during a mental arithmetic task in schizophrenia and major depression. *Am J Psychiatry* 161(2):286–293.
- Jansma JM, Ramsey NF, van der Wee NJ, Kahn RS (2004) Working memory capacity in schizophrenia: a parametric fMRI study. *Schizophr Res* 68(2–3):159–171.
- Javitt DC, Shelley A, Silipo G, Lieberman JA (2000) Deficits in auditory and visual context-dependent processing in schizophrenia. *Arch Gen Psychiatry* 57:1131–1137.
- Jonides J, Schumacher EH, Smith EE, Koeppe RA, Awh E, Reuter-Lorenz PA, Marshuetz C, Willis CR (1998a) The role of parietal cortex in verbal working memory. *J Neurosci* 18(13):5026–5034.
- Jonides J, Smith E, Marshuetz C, Koeppe R, Reuter-Lorenz PA (1998b) Inhibition in verbal working memory revealed by brain activation. *Proc Natl Acad Sci USA* 95:8410–8413.
- Kim J, Glahn DC, Nuechterlein KH, Cannon TD (2004) Maintenance and manipulation of information in schizophrenia: further evidence for impairment in the central executive component of working memory. *Schizophr Res* 68(2–3):173–187.
- Kim J, Kwon JS, Park HJ, Youn T, JKang DH, Kim MS, Lee DS, Lee MC (2003) Functional disconnection between the prefrontal and parietal cortices during working memory processing in schizophrenia. *Am J Psychiatry* 160:919–923.
- Kim JJ, Kwon JS, Park HJ, Youn T, Kang DH, Kim MS, L DS, Lee MC (2003) Functional disconnection between the prefrontal and parietal cortices during working memory processing in schizophrenia: A [<sup>15</sup>O]H<sub>2</sub>O PET study. *Am J Psychiatry* 160:919–923.
- Kimberg DY, D'Esposito M, Farah MJ (1997) Effect of a dopamine agonist on human subjects depends on working memory capacity (No. KO2653). University of Pennsylvania: National Institutes of Health.
- Kindermann SS, Brown GG, Zorrilla LE, Olsen RK, Jeste DV (2004) Spatial working memory among middle-aged and older patients with schizophrenia and volunteers using fMRI. *Schizophr Res* 68:203–216.
- Lee J, Park S. Working memory impairments in schizophrenia: A meta-analysis. *J Abnorm Psychol*; in press.
- Lenz T, Bilder RM, Turkel E, Goldman RS, Robinson D, Kane JM, Lieberman JA (2003) Impairments in perceptual competency and maintenance on a visual delayed match-to-sample test in first-episode schizophrenia. *Arch Gen Psychiatry* 60:238–243.
- MacDonald A, Carter CS, Kerns JG, Ursu S, Barch DM, Holmes AJ, Stenger VA, Cohen JD (2005) Specificity of prefrontal dysfunction and context processing deficits to schizophrenia in a never medicated first-episode psychotic sample. *Am J Psychiatry* 162:475–484.
- MacDonald AW 3rd, Carter CS (2003) Event-related fMRI study of context processing in dorsolateral prefrontal cortex of patients with schizophrenia. *J Abnorm Psychol* 112(4):689–697.
- MacDonald AW, Pogue-Geile MF, Johnson MK, Carter CS (2003) A specific deficit in context processing in the unaffected siblings of patients with schizophrenia. *Arch Gen Psychiatry* 60:57–65.
- Manoach DS, Gollub RL, Benson ES, Searl MM, Goff DC, Halpern E, Saper CB, Rauch SL (2000) Schizophrenic subjects show aberrant fMRI activation of dorsolateral prefrontal cortex and basal ganglia during working memory performance. *Biol Psychiatry* 48:99–109.
- Manoach DS, Press DZ, Thangaraj V, Searl MM, Goff DC, Halpern E, Saper CB, Warach S (1999) Schizophrenia subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI. *Biol Psychiatry* 45(9):1128–1137.
- Marshuetz C, Smith EE, Jonides J, De Gutsis J, Cheney TL (2000) Order information in working memory: fMRI evidence for parietal and prefrontal mechanisms. *J Cogn Neurosci* 12(Suppl 2):130–144.
- Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Kolachana BS, Callicott JH, Weinberger DR (2003) Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proc Natl Acad Sci USA* 100(10):6186–6191.
- McDowell JE, Brenner CA, Myles-Worsley M, Coon H, Byerley W, Clementz BA (2001) Ocular motor delayed-response task performance among patients with schizophrenia and their biological relatives. *Psychophysiology* 38(1):153–156.
- McDowell JE, Clementz BA (1996) Ocular-motor delayed-response task performance among schizophrenia patients. *Neuropsychobiology* 34(2):67–71.
- Mendrek A, Kiehl KA, Smith AM, Irwin D, Forster BB, Liddle PF (2005) Dysfunction of a distributed neural circuitry in schizophrenia patients during a working-memory performance. *Psychol Med* 35(2):187–196.
- Mendrek A, Laurens KR, Kiehl KA, Ngan ET, Stip E, Liddle PF (2004) Changes in distributed neural circuitry function in patients with first-episode schizophrenia. *Br J Psychiatry* 185:205–214.
- Menon RS (1993) A BOLD new horizon for MRI. Paper presented at the 12 annual meeting, New York.
- Menon V, Anagnoson RT, Mathalon DH, Glover GH, Pfefferbaum A (2001) Functional neuroanatomy of auditory working memory in schizophrenia: Relation to positive and negative symptoms. *Neuroimage* 13:433–446.
- Meyer DE, Glass JM, Mueller ST, Seymour TL, Kieras DE (2001) Executive-process interactive control: A unified computational theory for answering 20 questions (and more) about cognitive ageing. *Eur J Cogn Psychol* 13(1/2):123–164.
- Meyer-Lindenberg A, Miletich RS, Kohn PD, Esposito G, Carson RE, Quarantelli M, Weinberger DR, Berman KF (2002) Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. *Nat Neurosci* 5(3):267–271.
- Meyer-Lindenberg A, Poline J, Kohn PD, Holt JL, Egan MF, Weinberger DR, Berman KF (2001) Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. *Am J Psychiatry* 158:1809–1817.
- Meyer-Lindenberg AS, Olsen RK, Kohn PD, Brown T, Egan MF, Weinberger DR, Berman KF (2005) Regionally specific disturbance of dorsolateral prefrontal-hippocampal functional connectivity in schizophrenia. *Arch Gen Psychiatry* 62(4):379–386.
- Miller EK, Erickson CA, Desimone R (1995) Comparison of prefrontal and inferior temporal neurons during performance of a memory task. Paper presented at the Society for Neuroscience Abstracts, San Diego, CA.
- Muller N, Riedel M, Eggert T, Straube A (1999) Internally and externally guided voluntary saccades in unmedicated and medicated schizophrenic patients. Part II. Saccadic latency, gain, and fixation suppression errors. *Eur Arch Psychiatry Clin Neurosci* 249(1):7–14.
- Niznikiewicz MA, O'Donnell BF, Nestor PG, Smith L, Law S, Karapellou M, Shenton ME, McCarley RW (1997) ERP assessment of visual and auditory language processing in schizophrenia. *J Abnorm Psychol* 106(1):85–94.
- Oltmanns TF, Neale JM (1975) Schizophrenia performance when distractors are present: Attentional deficit or differential task difficulty? *J Abnorm Psychol* 84(3):205–209.
- Owen AM (1997) The functional organization of working memory processes within human lateral frontal cortex: The contribution of functional neuroimaging. *Eur J Neurosci* 9:1329–1339.
- Owen AM, Herrod NJ, Menon DK, Clark JC, Downey SP, Adrian MJ, Carpenter T, Minhas PS, Turkheimer FE, Williams EJ, Robbins TW, JSB (1999) Redefining the functional organization of working memory processes within human lateral prefrontal cortex. *Eur J Neurosci* 11:567–574.
- Park S, Holzman PS (1992) Schizophrenics show spatial working memory deficits. *Arch Gen Psychiatry* 49(12):975–982.
- Peers PV, Ludwig CJ, Rorden C, Cusack R, Bonfiglioli C, Bundesen C, Driver J, Antoun N, Duncan J (2005) Attentional functions of parietal and frontal cortex. *Cereb Cortex*.



- Perlstein WH, Carter CS, Noll DC, Cohen JD (2001) Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. *Am J Psychiatry* 158(7):1105–1113.
- Perlstein WM, Dixit NK, Carter CS, Noll DC, Cohen JD (2003) Prefrontal cortex dysfunction mediates deficits in working memory and prepotent responding in schizophrenia. *Biol Psychiatry* 53:25–38.
- Petrides M (1995) Functional organization of the human frontal cortex for mnemonic processing: Evidence from neuroimaging studies. In: *Structure and functions of the human prefrontal cortex*, Vol. 769 (Grafman J, Holyoak K, Boller F, eds), pp 85–97. New York: New York Academy of Sciences.
- Pisella L, Berberovic N, Mattingley JB (2004) Impaired working memory for location but not for colour or shape in visual neglect: a comparison of parietal and non-parietal lesions. *Cortex* 40(2): 379–390.
- Postle BR, Awh E, Jonides J, Smith EE, D'Esposito M (2004) The where and how of attention-based rehearsal in spatial working memory. *Brain Res Cogn Brain Res* 20(2):194–205.
- Quintana J, Wong T, Ortiz-Portillo E, Kovalik E, Davidson T, Marder SR, Mazziotta JC (2003) Prefrontal-posterior parietal networks in schizophrenia: primary dysfunctions and secondary compensations. *Biol Psychiatry* 53(1):12–24.
- Ravizza SM, Delgado MR, Chein JM, Becker JT, Fiez JA (2004) Functional dissociations within the inferior parietal cortex in verbal working memory. *Neuroimage* 22(2):562–573.
- Rushe TM, Woodruff PWR, Murray RM, Morris RG (1998) Episodic memory and learning in patients with chronic schizophrenia. *Schizophr Res* 35:85–96.
- Sabri O, Owega A, Schreckenberger M, Sturz L, Fimm B, Kunert P, Meyer PT, Sander D, Klingelhofer J (2003) A truly simultaneous combination of functional transcranial Doppler sonography and H(2)(15)O PET adds fundamental new information on differences in cognitive activation between schizophrenics and healthy control subjects. *J Nucl Med* 44(5):671–681.
- Salame P, Danion JM, Peretti S, Cuervo C (1998) The state of functioning of working memory in schizophrenia. *Schizophr Res* 30(1): 11–29.
- Sawaguchi T, Goldman-Rakic PS (1994) The role of D1-dopamine receptor in working memory: Local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. *J Neurophysiol* 71(2):515–528.
- Schlosser R, Gesierich T, Kaufmann B, Vucurevic G, Hunsche S, Gawehn J, Stoeter P (2003a) Altered effective connectivity during working memory performance in schizophrenia: a study with fMRI and structural equation modeling. *NeuroImage* 19(3):751–763.
- Schlosser R, Gesierich T, Kaufmann B, Vucurevic G, Stoeter P (2003b) Altered effective connectivity in drug free schizophrenic patients. *Neuroreport* 14(17):2233–2237.
- Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* 20:11–21.
- Selemon LD, Mrzljak J, Kleinman JE, Herman MM, Goldman-Rakic PS (2003) Regional specificity in the neuropathologic substrates of schizophrenia: a morphometric analysis of Broca's area 44 and area 9. *Arch Gen Psychiatry* 60(1):69–77.
- Servan-Schreiber D, Cohen JD, Steingard S (1996) Schizophrenic deficits in the processing of context: A test of a theoretical model. *Arch Gen Psychiatry* 53:1105–1113.
- Smith EE, Jonides J (1999) Storage and executive processes in the frontal lobes. *Science* 283:1657–1661.
- Snitz BE, Curtis CE, Zald DH, Katsanis J, Iacono WG (1999) Neuropsychological and oculomotor correlates of spatial working memory performance in schizophrenia patients and controls. *Schizophr Res* 38(1):37–50.
- Sohn MH, Ursu S, Anderson JR, Stenger VA, Carter CS (2000) The role of prefrontal cortex and posterior parietal cortex in task switching. *Proc Natl Acad Sci USA* 97(24):13448–13453.
- Squire LR (1987) *Memory and brain*. New York: Oxford University Press.
- Stevens AA, Goldman-Rakic PS, Gore JC, Fulbright RK, Wexler R (1998) Cortical dysfunction in schizophrenia during auditory word and tone working memory demonstrated by functional magnetic resonance imaging. *Arch Gen Psychiatry* 55:1097–1103.
- Stratta P, Daneluzzo E, Bustini M, Casacchia M, Rossi A (1998) Schizophrenic deficits in the processing of context. *Arch Gen Psychiatry* 55:186–187.
- Stratta P, Daneluzzo E, Bustini M, Prosperini P, Rossi A (2000) Processing of context information in schizophrenia: relation to clinical symptoms and WCST performance. *Schizophr Res* 44: 57–67.
- Tek C, Gold JM, Blaxton T, Wilk C, McMahon RP, Buchanan RW (2002) Visual perceptual and working memory impairments in schizophrenia. *Arch Gen Psychiatry* 2002(59).
- Titone D, Levy DL, Holzman PS (2000) Contextual insensitivity in schizophrenic language processing: evidence from lexical ambiguity. *J Abnorm Psychol* 109(4):761–767.
- Vallar G, Di Betta AM, Silveri MC (1997) The phonological short-term store-rehearsal system: patterns of impairment and neural correlates. *Neuropsychologia* 35(6):795–812.
- Veltman DJ, Rombouts SA, Dolan RJ (2003) Maintenance versus manipulation in verbal working memory revisited: an fMRI study. *Neuroimage* 18(2):247–256.
- Walter H, Wunderlich AP, Blankenhorn M, Schafer S, Tomczak R, Spitzer M, Gron G (2003) No hypofrontality, but absence of prefrontal lateralization comparing verbal and spatial working memory in schizophrenia. *Schizophr Res* 61:175–184.
- Weinberger D, Berman K, Illowsky B (1988) Physiological dysfunction of the dorsolateral prefrontal cortex: III. A new cohort and evidence for a monoaminergic mechanism. *Arch Gen Psychiatry* 45:609–615.
- Weinberger DR, Berman KF, Zec RF (1986) Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia: I. Regional cerebral blood flow evidence. *Arch Gen Psychiatry* 43:114–125.
- Wexler BE, Donegan N, Stevens AA, Jacob SA (2002) Deficits in language-mediated mental operations in patients with schizophrenia. *Schizophr Res* 53(3):171–179.
- Wexler BE, Stevens AA, Bowers AA, Sernyak MJ, Goldman-Rakic PS (1998) Word and tone working memory deficits in schizophrenia. *Arch Gen Psychiatry* 55:1093–1096.
- Williams GV, Goldman-Rakic PS (1995) Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature* 376(17): 572–575.
- Wykes T, Brammer M, Mellers J, Bray P, Reeder C, Williams C, Corner J (2002) Effects on the brain of a psychological treatment: cognitive remediation therapy: functional magnetic resonance imaging in schizophrenia. *Br J Psychiatry* 181:144–152.