Although the precise mechanisms and pathways of schizophrenia remain something of a mystery, there is little dispute that cognitive deficits present as some of the clearest and most debilitating symptoms of the disease. This book describes the characteristics of cognitive deficits in schizophrenia, functional implications, the course of impairments and the genetic and biological contributions, and reviews management options, including neuropsychological, psychological, and pharmacological techniques.

Chapters are written by leading experts in the field, in an accessible and highly informative style, ensuring the content is clinically relevant. State-of-the-art information about new developments in the treatment of related features of the illness, such as disability, is provided. The wide-ranging focus of this volume will appeal to clinicians and academic researchers working with patients impaired by severe mental illness.
Overview

Schizophrenia is a complex neuropsychiatric syndrome presenting with a constellation of symptoms, including positive symptoms (delusions and hallucinations), negative symptoms, affective symptoms, and cognitive deficits. While delusions and hallucinations are considered the hallmark symptoms of the illness, cognitive deficits and affective dysfunction in patients with schizophrenia are increasingly receiving research focus—primarily due to growing consensus that these deficits are a substantial source of disability and loss of functional capacity for patients. The present chapter will focus on recent evidence for cognitive deficits in schizophrenia. First, we will review the behavioral and cognitive neuroscience evidence for dysfunction across different cardinal domains of cognition. In this component of the chapter we will emphasize evidence for abnormalities in working memory (WM), episodic memory (EM), and cognitive control (CC). Second, given the emerging wealth of knowledge from animal studies and computational models, we focus on WM as an example to understand cognitive deficits in schizophrenia from a translational perspective. Such a translational framework has the capacity to confer a mechanistic framework for understanding cognitive dysfunction in schizophrenia. To that end, we will discuss evidence across levels of analysis spanning from cells to circuits to systems, which offer clues for better understanding of cognitive dysfunction and developing putative treatment targets in schizophrenia. Building on pharmacological findings in humans, we will outline how such deficits may arise due to abnormalities in N-methyl-D-aspartate (NMDA) glutamate receptor dysfunction, as one hypothesis about the source of at least some cognitive deficits in schizophrenia. In this component of the chapter we will also discuss the critical utility of computational modeling in allowing us to test mechanistically derived translational hypotheses regarding WM abnormalities in schizophrenia derived at the level of cells.

General overview of cognitive dysfunction in schizophrenia

Schizophrenia is a complex and highly heterogeneous syndrome (Walker et al., 2004). Patients exhibit diverse symptoms encompassing distorted beliefs (delusions), aberrant internal visual/auditory percepts (hallucinations), as well as loss of affective expression and

motivational drive (negative symptoms). One additional area of pervasive dysfunction for patients suffering from schizophrenia involves cognitive deficits. Cognitive abnormalities are consistently implicated in functional outcome (Green, 2006; Kee et al., 2003), exhibit onset prior to the emergence of the full syndrome (Cornblatt et al., 1999; Niendam et al., 2003), are relatively stable across the lifespan of the individual (Heaton et al., 2001; Irani et al., 2011), and—perhaps most importantly—are not ameliorated by current pharmacotherapy for psychosis (Buchanan et al., 2007). In fact, since the earliest theories of schizophrenia, cognitive deficits have played a central theme in the clinical characterization of this illness (Kraepelin, 1950). Therefore, understanding the underlying neuropathology, which may give rise to disturbances in cognition, is a crucial challenge for the field of schizophrenia research.

There is clearly evidence for a generalized cognitive deficit in patients with schizophrenia (Dickinson et al., 2008; Gur et al., 2001), as patients suffering from schizophrenia are impaired across virtually all cognitive measures relative to healthy controls. However, a critical question concerns what aspects of cognition reflect a specific deficit embedded in the context of such a generalized deficit, and which may be impaired in schizophrenia even when one accounts for a range of confounding factors that may be associated with psychosis, such as medication status and other disease-related phenomena. A growing body of work implicates WM, EM, and CC as such core deficits in cognition (Elvevåg & Goldberg, 2000), which exhibit a specific pattern of impairment that is present even in unmedicated individuals with schizophrenia (Barch et al., 2001) and individuals thought to be at risk for the development of schizophrenia (e.g., first-degree relatives) (Delawalla et al., 2006). In the following sections we focus more specifically on these regions of cognitive dysfunction in schizophrenia.

However, prior to discussing these broad areas of the literature, it is important to briefly set the stage for the conceptual framework of cognitive neuroscience, which we will use as a platform for understanding cognitive dysfunction in schizophrenia. The past two decades have witnessed an explosive growth of knowledge regarding the neural correlates of various cognitive processes in healthy individuals. This burgeoning field of cognitive neuroscience has generated an increasingly robust platform for interpreting clinical neuropsychiatric phenomena (Barch, 2005a). This is primarily accomplished by garnering an increased understanding of neural systems known to be involved in various cognitive operations in healthy individuals. This understanding in turn constrains our search for what aspects of brain circuitry may be abnormal in clinical populations exhibiting deficits in these same cognitive operations. Therefore, we contend that using a cognitive neuroscience framework offers a promising tool for elucidating and ultimately treating cognitive impairment in schizophrenia by delineating abnormalities in neural circuits, the function of which is increasingly understood in healthy populations. We will review evidence within this cognitive neuroscience framework across cognitive domains—WM, CC, and EM—all of which may be linked by abnormalities in shared neural circuits in schizophrenia. Furthermore, in subsequent sections we will argue that it is precisely this cognitive neuroscience framework that provides great potential for establishing links with translational findings from basic preclinical, pharmacological, and computational neuroscience work. In this context, we will focus on WM specifically, as one domain of cognition that has particular promise for translation.
Working memory in schizophrenia

Cognitive neuroscience models of working memory

Before we proceed with a discussion of WM in the context of schizophrenia, it is important to discuss some of the leading cognitive models of WM to provide conceptual bearings on findings in schizophrenia. Working memory traditionally refers to temporary storage and manipulating information “online,” typically in the service of some goal (Baddeley, 2000; Baddeley & Hitch, 1974). According to one prominent cognitive model, WM is thought to be composed of a central executive resource system, and two slave subsidiary systems: the phonological loop and the visuospatial sketchpad (Baddeley & Hitch, 1974); that is, WM is conceptualized as a multi-store process relying on distinct components. This cognitive model was later updated to include a fourth component: the episodic buffer (Baddeley, 2000). Such a conceptual delineation of WM processes has provided one platform from which we can begin to examine deficits in schizophrenia. Besides dividing the WM process into cognitive modules, one can consider WM as comprising distinct stages in time. In that sense, the WM process can be roughly subdivided into three distinct temporal components (Jonides et al., 2008): encoding of novel information and forming an internal representation; active maintenance of this information (i.e., refreshing the memory trace, which is synonymous with the function of two slave subsystems) over some period; as well as manipulation of maintained information in the service of some goal (which is synonymous with the central executive). In other words, the central executive is thought to be a system responsible for orchestrating the interplay between the various short-term buffers, long-term memory, and control processes that modify and integrate information in WM (Jonides et al., 2008).

It is important to note that there are additional models of WM function, which differ in some aspects from the one outlined here (Cowan, 2001, 2008) (for a detailed treatment of this topic, please refer to prior reviews (Jonides et al., 2008). The present review is not intended to arbitrate between cognitive models of WM, but rather to focus on critical shared aspects across models; namely, representation of information over time in the absence of a stimulus, and manipulation of internal representations in the service of some goal. Importantly, these different aspects of WM are supported by a distributed network-level neural architecture spanning both cortical and subcortical regions (Jonides et al., 2008; Owen et al., 2005). In fact, recent advances in functional neuroimaging support the notion that a distributed network of brain regions, which includes dorsal frontoparietal cortical regions, is involved in WM (Curtis et al., 2004; D’Esposito, 2007; D’Esposito et al., 1998; Miller & D’Esposito, 2005). It is this growing understanding of the distributed neural circuits involved in WM that has allowed clinical researchers to anchor their findings. For instance, our growing knowledge of the critical role of the prefrontal cortex in WM has offered some constraints on what specific circuits may exhibit dysfunction in schizophrenia. Furthermore, cognitive neuroscience paradigms have created a framework within which WM dysfunction can now be probed in neuropsychiatric illness.
Behavioral findings in schizophrenia

To date, the evidence suggests that patients with schizophrenia display deficits in WM, marked by less accurate and slower performance on a variety of tasks irrespective of WM modality (Barch, 2005a; Barch & Smith, 2008; Barch et al., 2001, 2003; Park & Holzman, 1992; Reichenberg & Harvey 2007). Additionally, studies have documented WM deficits when examining medicated and unmedicated patients, first-degree relatives, as well as individuals with schizotypal personality, suggesting that WM is a critical abnormality manifesting along the schizophrenia spectrum (Horan et al., 2008; MacDonald et al., 2003; Snitz et al., 2006). In recent years, a number of meta-analyses have quantified these findings and reported strong evidence for WM impairments in schizophrenia patients as compared to healthy controls. The meta-analytic findings reported effect sizes from 0.61 to 1.18 evident in both verbal and nonverbal WM tasks (Aleman et al., 1999; Dickinson et al., 2007; Heinrichs & Zakzanis, 1998; Lee & Park, 2005; Zakzanis & Heinrichs, 1999).

Even though the presence of WM deficits in schizophrenia is clear, it is critical to understand at which stage of the WM process the breakdown may be occurring. As noted previously, given that WM is not a unitary concept (and is not instantiated in a single neural structure), it is important to pinpoint which aspects of WM functioning are compromised. As noted earlier, in addition to focusing on domain-specific functions (i.e., verbal vs. visuospatial), WM can be further subdivided into distinct temporal components that are required for successful operation: (1) selection of stimuli for entry into WM and encoding of these representations; (2) maintenance of the representation in conjunction with protecting the information by inhibiting irrelevant stimuli; and (3) successful retrieval of memoranda when needed (Baddeley, 2000; Baddeley et al., 1974; Jonides et al., 2008; Lee & Park, 2005). Breakdown in any of these components may compromise the overall WM process and produce abnormalities in patients. However, breakdowns in different components may have drastically different implications for understanding the neurobiological underpinning of WM malfunction, as they may be supported by different neurobiological mechanisms. At the risk of oversimplification, consider for instance that WM deficits in schizophrenia are purely a product of encoding abnormalities, which could be a manifestation of lower-level, early visual cortical malfunction (i.e., the incoming information is simply not accurately represented at the lower level of the visual hierarchy). This would imply that information being represented in WM might be degraded even in the absence of maintenance deficits. In contrast, consider that encoding is intact, but that deficits manifest at the maintenance stage of the WM process, which may implicate a completely different neural mechanism; namely, the frontoparietal cortical system (Leung et al., 2002; Wager & Smith, 2003) responsible for keeping real-time mnemonic representations once the physical stimuli are no longer available. Therefore, to best understand WM abnormalities in schizophrenia, it is critical to determine at which stage (or stages) the breakdown in the WM process may be occurring.

Working memory: encoding deficits or maintenance deficits in schizophrenia?

An influential meta-analysis suggested that patients with schizophrenia exhibit deficits in all phases of WM and that the degree of impairment is fairly constant even when extending the
maintenance period (Lee & Park, 2005). Specifically, Lee and Park found that the effect size of the observed impairment across studies did not change as a function of the delay period used. This may imply that breakdowns in WM may be occurring as early as the encoding stage; that is, when internal representations are still forming. Consistent with this framing, studies examining encoding deficits have demonstrated that patients with schizophrenia exhibit short-term memory deficits even in the absence of a delay (Hartman et al., 2003; Tek et al., 2002). However, other work has qualified these findings. Specifically, two studies have shown that encoding impairments can be minimized if patients are allotted more time to complete the encoding process, which suggests a speed-of-processing deficit rather than a pure encoding process deficit per se (Badcock et al., 2008; Hartman et al., 2003). Nevertheless, speed-of-processing reductions at encoding may still be interpreted as an encoding deficit in that the speed with which the information can be encoded robustly will degrade the quality of internal representations. Badcock and colleagues conducted a study that highlights this issue. They employed a spatial WM task during which they presented small circles located on a hidden radial grid. Subjects were required to identify the location of the circle using a touch screen following a zero-second and a four-second delay. This allowed the authors to examine encoding and maintenance components of WM as well as two components of encoding accuracy: (1) general direction on the radial grid (i.e., global features); and (2) precise distance from the target location (fine-grained detail). First, they focused on the zero-second delay, which allows a more pure assessment of encoding deficits. They demonstrated that using fixed- and short-target durations (<500 ms) resulted in only a small fraction of the patient sample (<50%) performing at a high level of accuracy (~80%). In other words, when patients were not given very much time to encode the stimuli, most of the sample performed poorly. In contrast, when given the same brief encoding duration, a much larger fraction of the control sample (73%) performed well (~80% accuracy). However, when equating for processing speed at encoding using an adaptive staircase procedure, there were no significant differences between patient and control subjects in general direction and overall precision accuracy, even though the patient group still demonstrated numerically lower performance. In other words, when patients were allowed more time to represent the stimuli in WM, their performance following a zero-second delay performance was not significantly different than that of control subjects. Nevertheless, it should be noted that other studies demonstrated that encoding deficits exist even after controlling for perceptual processing differences (Tek et al., 2002) (although not the time necessary to encode the stimulus). A complementary study in the verbal WM domain by Javitt and colleagues (Javitt et al., 1997) demonstrated that patients with schizophrenia show similar tone discrimination at short delays when the difficulty of the task was taken into account. Therefore, while encoding deficits may be reduced in the presence of more time to encode, these findings still argue that speed of processing can impact precision of WM representations. Taken together, these studies suggest that inefficiencies in the encoding process could certainly be a contributing factor to the overall profile of WM deficits in schizophrenia.

At the same time, Badcock and colleagues as well as other researchers have shown that patients demonstrate WM deficits when a delay period is introduced (i.e., maintenance component is added), which persist even when controlling for encoding differences (Badcock et al., 2008; Lee & Park, 2005; Tek et al., 2002). For instance, Badcock et al. showed that even after equating for the time needed to encode the stimuli, there were significant differences between the groups following a four-second delay, suggesting
a persistent maintenance deficit (although delays longer than 4 s also raise the issue of active vs. passive maintenance). An elegant study by Lencz et al. (2003) demonstrated the presence of both encoding and maintenance deficits in a visual delayed match-to-sample task. Specifically, they showed that when performance at encoding (i.e., no delay) was titrated at the single-subject level, maintenance deficits persisted (i.e., 4-s 8-s delay). Additional work in the visuospatial domain further suggests the presence of WM deficits in schizophrenia during the delay phase. For instance, Fleming and colleagues examined WM and basic perceptual processing (no memory component required) in schizophrenia (Fleming et al., 1997). Specifically, they used a delayed response task with a seven-second and zero-second (no) delay in addition to the Judgment of Line Orientation Test (a simple visual perception task) (Treccani et al., 2005). Their findings suggested relatively spared visuospatial processing in patients (i.e., when no memory demands were required), but deficits on tasks with a mnemonic component. Of note, there are other findings suggesting basic perceptual deficits in patients with schizophrenia (Blanchard & Neale, 1994; Buchanan et al., 1994; Hardoy et al., 2004). However, these studies did not include a spatial WM task in the same sample, thus making it difficult to examine if the patient samples in these studies would have demonstrated more severe differential deficits when performing a WM task. Another investigation by Dreher and colleagues further characterized WM deficits using tasks tapping into either spatial recall (item) or temporal recall (order) in schizophrenia (Dreher et al., 2001). Specifically, they employed a computerized version of the Corsi Block Task typically employed in neuropsychological testing (Lezak, 1995), where they manipulated set size and the delay period thus allowing examination of different difficulty levels, as well as deficits related to encoding and maintenance components of WM. In summary, patients demonstrated overall worse performance across all four tasks and both delay periods. However, patients performed significantly worse as the delay period increased, in contrast to controls whose performance did not differ significantly as a function of delay. In addition, unlike controls, patients with schizophrenia performed worse at longer delays as a function of increasing WM set size. Other studies have replicated these core findings, confirming the presence of spatial WM deficits in schizophrenia (Pukrop et al., 2003; Saperstein et al., 2006).

Taken together, the reviewed evidence suggests that there are abnormalities evident across both encoding and maintenance phases of WM in schizophrenia. Results indicate that encoding deficits may manifest in part due to the time necessary to form an accurate internal representation rapidly (Badcock et al., 2008; Hartman et al., 2003), and/or to reflect a deficit in the ability to represent the sensory properties of the stimulus, irrespective of time (Tek et al., 2002). While the precise nature of encoding abnormalities has yet to be ascertained, some authors have argued that these deficits do not represent pure sensory abnormalities in patients, but may also encompass an attentional component (Lencz et al., 2003). Therefore, it is likely that abnormalities in early formation of internal representations interact with subsequent deficits in ongoing maintenance of this information once the physical stimulus is absent. However, maintenance abnormalities could be taking place due to separate or joint malfunctions in two very different mechanisms: (1) deficiencies in cognitive and neural systems responsible for maintaining information, resulting in more rapid information decay regardless of external influences; and/or (2) deficiencies in neural systems responsible for protection of internal WM stores from external/internal sources of interference. Importantly, the abnormalities in these separate aspects of WM function may implicate distinct neurobiological mechanisms contributing to maintenance deficits in
schizophrenia; namely, dorsal and ventrolateral prefrontal executive regions shielding information from distraction (Thompson-Schill et al., 2002) or superior frontoparietal regions that seem to be involved in representing information over extended periods of time (Curtis et al., 2004). We briefly review behavioral evidence for these possibilities.

**Working memory maintenance: interference control or decay deficits in schizophrenia?**

To elucidate the source of WM maintenance deficits in schizophrenia, several researchers sought to establish which mechanisms may be contributing to maintenance abnormalities. In their classic studies, Oltmanns and Neale demonstrated that patients with schizophrenia perform more poorly on digit span tests containing distraction when compared to healthy controls (Oltmanns & Neale, 1975). More specifically, they used four different tasks of varying digit span lengths, two of which contained distraction. This yielded two sets of tasks (distractor and no distractor) that were equated on difficulty. Oltmanns and Neale demonstrated that patients show a more precipitous drop in performance as a function of distraction when using the longer digit length task. Critically, Oltmanns and Neale carefully equated the digit span tasks for psychometric properties (i.e., task difficulty, distribution parameters, and reliability), which allowed detection of differential and not generalized deficits (Chapman & Chapman, 1978). Oltmanns and Neale’s overall findings suggest that patients with schizophrenia may exhibit interference control deficits. A series of studies replicated this general pattern of results (Addington et al., 1997; Finkelstein et al., 1997; Harvey & Pedley, 1989; Oltmanns et al., 1978). Furthermore, a recent elegant behavioral study by Hahn and colleagues demonstrated WM filtering deficits, although when focusing on the encoding period. They manipulated spatial WM encoding by rendering specific encoding items more salient (by surrounding them with a flicker). Their results demonstrated that patients and controls benefit from bottom-up effects on attention during WM encoding. However, when the bottom-up manipulation was distracting (by flickering around items not required to be encoded), patients were unable to override prepotent bottom-up visual distraction during WM encoding and bias their attention away from such distraction. In fact, individuals with schizophrenia encoded items that co-occurred with salient distractors more robustly, whereas such distraction was successfully filtered by control participants (Hahn et al., 2010).

Other recent behavioral experiments conducted by Cellard and colleagues demonstrated that effects of interference in schizophrenia extend to the maintenance phase in the visuospatial domain (Cellard et al., 2007). They employed a spatial WM task that required subjects to reconstruct a sequence of dots presented at random locations. Interference trials contained a centrally presented dot that subjects were instructed to ignore. The results indicated that patients performed worse than controls on both the interference-free and distractor versions of the tasks; however, the effect of distraction on patients’ performance was significantly greater than that for healthy controls. In addition, Leiderman and colleagues employed a WM task that included a single (object or spatial WM alone) or dual task component (object and spatial combined, which the authors suggested taps into the central executive component of the WM process) (Leiderman & Strejilevich, 2004). They also used two delay periods (5 sec and 30 sec) and introduced a distractor task (counting) during all conditions. Leiderman and colleagues demonstrated that patients performed worse in the dual task condition (spatial-object task) when compared to single
task conditions (object or spatial). In contrast, control subjects did not show the additional performance drop as a function of dual task demands as did schizophrenia patients. This suggests that the added task demands introduced during the maintenance period (as a function of the dual task) impacted schizophrenia patients’ performance more than that of healthy controls. Patients’ performance degraded even further on the dual task once a longer temporal delay was introduced (30 sec). Javitt and colleagues (Javitt et al., 1997) reported similar results in the context of echoic WM. We briefly reviewed earlier that their findings suggested similar group results across extended delays when matched for performance. However, their experiment also contained a condition with distraction, which was presented across all difficulty levels. These findings are in concert with those in the visuospatial domain—patients’ performance across increasing delays degraded more extensively when faced with distraction even in the easier condition (patients’ performance was virtually at floor during the more difficult condition; thus making it difficult to test distractor effects).

Taken together, these results argue that deficits exist not only in the maintenance mechanisms but also in the ability to resist external sources of interference, and that these abnormalities are present in both visuospatial and verbal domains. That is, there are certainly problems evident with the decay of WM information across increasing temporal delays (although such deficits may not have been assessed under optimal psychophysical conditions; e.g., complete darkness and silence). However, there is also clear evidence for a major problem in interference control in schizophrenia. Most recently, we have extended this work to show that patients exhibit increased distractibility during object WM even when matched for performance in the absence of distraction on a single-subject level (Anticevic et al., 2011b). This work also points to specific neural abnormalities present in schizophrenia that are associated with distractor filtering, which we discuss more extensively in the next sections.

Neuroimaging findings during working memory in schizophrenia

In addition to the behavioral evidence of WM deficits, there is growing functional neuroimaging literature demonstrating the presence of brain abnormalities associated with WM dysfunction in schizophrenia. The majority of findings suggest that regions comprising the dorsal frontoparietal network are affected in patients and may be contributing to WM abnormalities (Manoach, 2003). Specifically, reductions in the dorsolateral prefrontal cortex (DLPFC) (Brodmann’s area 9/46) activations have been documented while patients perform WM tasks, suggesting that patients exhibit task-related “hypo-frontality” (Barch et al., 2001; Callicott et al., 1998). These findings have also been confirmed through quantitative meta-analytic studies (Glahn et al., 2005; van Snellenberg et al., 2006), both of which point to the DLPFC as playing a key role in WM deficits present in schizophrenia.

Prefrontal recruitment during working memory: the inverted-U hypothesis

The emerging evidence has generated a controversy regarding the precise pattern of cortical blood oxygenation level-dependent (BOLD) signal abnormalities associated with WM dysfunction in patients with schizophrenia (Manoach, 2003). Specifically, there are discrepant findings with regard to over- or under-recruitment of dorsal prefrontal regions
during WM (Callicott et al., 2003). A number of findings have suggested that WM capacity in healthy subjects may be dependent on the level of recruitment of the DLPFC, which is thought to operate according to an inverted-“U” model of WM capacity (Driesen et al., 2008; Goldman-Rakic et al., 2000; Johnson et al., 2006; Potkin et al., 2009). In other words, the model suggests that with increasing WM demands, there is a concomitant parametric DLPFC BOLD signal increase (Braver et al., 1997). However, as WM load demands reach and exceed capacity limitations, DLPFC signals begin to drop, presumably due to information load exceeding available computational resources (Braver et al., 1997; Goldman-Rakic et al., 2000). In line with this hypothesis, recent evidence suggests that patients with schizophrenia may exhibit a shifted inverted-U function, such that capacity limitations are reached faster (i.e., with lower WM load levels), which may result in over- or under-recruitment when compared to healthy controls, depending on the level of WM load at which the groups are compared (Johnson et al., 2006). For instance, the hypothesis states that at low difficulty levels patients may find performance more effortful and may have to recruit more prefrontal computational resources to accomplish the task. Evidence for this framework was advanced by studies demonstrating that patients activated the DLPFC more when performing above chance (but slightly worse than controls) (Callicott et al., 2000; Monoach, 2003; Monoach et al., 1999, 2000, 2003). Comparing the two groups at such a difficulty level has resulted in findings of DLPFC “hyper-frontality” in the patient group when compared to controls. Conversely, as the difficulty of the task exceeds capacity limits in the patient group (which happens at lower task difficulty when compared to controls), the observed DLPFC signals may show a drop if patients cannot sustain task engagement (Monoach, 2003; Monoach et al., 1999, 2000, 2003). This may result in findings of DLPFC “hypo-frontality” in patients with schizophrenia at higher WM difficulty levels when compared to controls. In contrast, when WM performance is matched across patients and controls, such that both patients and controls perform the task at similar levels of accuracy, both groups can demonstrate relatively similar levels of prefrontal recruitment (Monoach et al., 2000; Callicott et al., 2000; Honey et al., 2002) (however, see Anticevic et al., 2011a). Taken together, this evidence suggests that some studies investigating DLPFC abnormalities associated with WM function may not have adequately matched the groups on performance, which may in turn result in either findings of hypo- or hyper-frontality, depending on specific task parameters employed (i.e., overall difficulty level). Indeed, in line with this hypothesis, a meta-analysis by Van Snellenberg and colleagues demonstrated that the magnitude of WM performance differences between patients and healthy controls was positively correlated with magnitude of activation differences in dorsolateral prefrontal regions (van Snellenberg et al., 2006). In other words, Van Snellenberg and colleagues showed that studies with the largest difference in WM performance between patients and controls (such that patients performed worse) are the ones documenting the largest evidence for DLPFC hypo-frontality in patients—between-group differences in WM performance significantly moderated between-group DLPFC findings. This finding implies that different studies may be examining different locations of the inverted-U curve, thus showing evidence of hyper- or hypo-frontality in patients with schizophrenia, depending on task parameters. To this end, it is crucial to ensure careful performance matching for valid interpretation of brain activation differences between patients and controls.

In summary, even though the controversy surrounding the precise pattern of lateral prefrontal signals during WM may not be fully resolved (and the proposed inverted-U
model may be an oversimplification of the underlying pathophysiology involved in WM), there is still considerable evidence from functional neuroimaging studies that patients show aberrant patterns of brain activity while performing WM tasks (Glahn et al., 2005; Ragland et al., 2007; Reichenberg & Harvey, 2007). Importantly, recent investigations are adding evidence in support of the shifted inverted-U model of DLPFC functioning in schizophrenia, suggesting that there may be inefficient prefrontal recruitment that is manifested differently depending on WM demands (Callicott et al., 2003; Glahn et al., 2005; Manaoch, 2003; Potkin et al., 2009). Even though most studies examining prefrontal cortex dysfunction in schizophrenia have typically studied patients on psychotropic medication, there is also evidence that medication-naïve patients exhibit abnormalities in prefrontal activation (Barch et al., 2001).

Neural evidence for abnormalities across phases of working memory in schizophrenia

Most studies reviewed in the previous sections have employed a variety of continuous performance tasks (e.g., N-back) (Glahn et al., 2005), which blend different WM processes. However, as noted, WM is not composed of a single operation (Jonides et al., 2008) and both cognitive (Baddeley, 2000) and neurobiological (Goldman-Rakic, 1994) models have identified different WM processes: (1) encoding of novel information; (2) maintenance, manipulation, and updating; and (3) retrieval of information. Thus to fully understand WM dysfunction in schizophrenia, it is critical to employ tasks that assay distinct WM processes because dysfunction of each process may contribute unique sources of deficit in this illness (Neufeld, 2007). As described earlier, behavioral studies have reported both encoding and maintenance abnormalities in schizophrenia (Lee & Park, 2005). Therefore, it is critical to parse the temporal aspects of brain activation in schizophrenia more carefully by using WM tasks that temporally dissociate encoding, maintenance, and response periods, which we will refer to as “delayed” WM tasks (Driesen et al., 2008). The use of delayed WM tasks allows examination of different components of WM to determine whether schizophrenia is associated with abnormal WM signal patterns during the encoding, maintenance, or response phase (or any combination of these three possibilities). It should be noted here that the limited temporal resolution of functional magnetic resonance imaging (fMRI) may, to a certain extent, prevent one from drawing clear lines between encoding and “early maintenance.” This can be a very important distinction from a neurobiological perspective as distinct mechanisms have been implicated in encoding versus early maintenance of WM (Durstewitz & Seamans, 2002, 2008; Durstewitz et al., 1999, 2000). Nevertheless, fMRI work has offered some clues regarding phase-specific WM deficits in schizophrenia.

To address such questions, Driesen and colleagues (2008) used a delayed spatial WM task, which was an adaptation of tasks typically employed in neurophysiological studies of nonhuman primates and has been used as a reliable probe of prefrontal maintenance signals in healthy controls (Leung et al., 2002). Importantly, this task included a long delay interval (16 s) that allowed the separate investigation of encoding and maintenance activity. Driesen and co-workers specifically focused on three right-lateralized prefrontal regions of interest (ROI) previously implicated in WM processes (i.e., superior middle frontal gyrus, middle frontal gyrus, and inferior frontal gyrus) (Leung et al., 2002). Overall, Driesen et al. demonstrated that, even in the absence of between-group accuracy differences,
patients showed little decay in prefrontal signal levels at encoding, but demonstrated marked BOLD signal loss in frontal regions during maintenance. In addition, at probe onset, patients did not show the same level of BOLD signal recovery as did controls. These results suggested that patients demonstrated abnormalities in sustained prefrontal signal during the maintenance phase of WM (although in specific isolated prefrontal ROIs), which is consistent with behavioral studies documenting increased WM decay in the absence of interference, as well as possible concomitant deficits in retrieval-related processes.

Another study examining delayed WM in the verbal domain was conducted by Johnston et al. (2006). They examined between-group differences during WM encoding and retrieval (they omitted maintenance from the analysis as they argue that signals during maintenance and encoding are highly collinear, possibly due to the resolution of the fMRI signal). Furthermore, they examined differences as a function of a WM load, such that performance was comparable between groups at different load levels. When focusing on the encoding phase, they identified a distributed network of regions including both frontal and parietal components that patients failed to recruit to the same level as controls, even when comparing conditions that resulted in similar performance levels. Interestingly, they found that patients also failed to recruit certain regions to the same extent as controls did during the retrieval phase—but this was only true when examining performance matched conditions. That is, when comparing patients and controls at the same lower load condition, patients over-recruited a wide network of regions encompassing frontal, parietal, and hippocampus clusters. This complex pattern of group differences across WM phases, modulated by load/difficulty, only highlights the importance of considering all phases of WM when making inferences regarding deficits in schizophrenia.

It should be noted, however, that Johnson and colleagues could not offer additional evidence regarding maintenance deficits in the verbal domain. Nevertheless, somewhat in contrast to results reported by Driesen et al., work in the verbal domain did not find the most prominent group activation differences during WM maintenance (Schlösser et al., 2008); Schlösser and colleagues found more prominent group differences when examining conditions requiring manipulation of verbal information (i.e., alphabetizing the remembered letters). This reflected mainly over-recruitment of executive regions in the patient group relative to healthy subjects. One possibility is that this activation difference reflected task demands; that is, Schlösser and co-workers employed a task that was substantially more challenging for patients and, as noted, performance has been shown to be a critical moderating variable of group activation differences (Van Snellenberg et al., 2006). Another possibility may be that there are critical neural activation differences between maintenance of verbal versus spatial WM representations in schizophrenia—a hypothesis that awaits direct and systematic prospective testing.

Our subsequent work has replicated and extended the aforementioned findings using a comparable nonverbal delayed WM task that employed ambiguous polygon shapes as memoranda. We showed that, when examining a broader network of regions involved in WM, patients indeed exhibited encoding abnormalities, but there was clear evidence for maintenance deficits as well, primarily centered on the prefrontal cortex. Importantly, we ensured careful performance matching to rule out performance-related confounds related to differences in DLPFC signals (Van Snellenberg et al., 2006). Our findings suggest that the profile of WM deficits across phases of WM is in line with behavioral findings; that is, patients exhibit both encoding and maintenance activation abnormalities even when matched for performance.
Interestingly, our results also revealed abnormalities in regional deactivation in areas mainly overlapping with what is termed the default mode network (DMN), a finding consistent with other studies on DMN activity during WM in schizophrenia (Metzak et al., 2011; Whitfield-Gabrieli et al., 2009). Specifically, control participants showed suppression during the encoding phase on WM trials in a superior frontal cortical region as well as around the right angular gyrus cortex, whereas patients failed to exhibit this deactivation. Furthermore, for healthy controls there was a significant inverse linear relationship between prefrontal activation and regional suppression at encoding; however, patients showed a breakdown in this relationship, which was highly consistent with a prior report showing a similar effect (Metzak et al., 2011). Taken together, these findings suggest that there may be a malfunction in reciprocal communication between brain networks involved in active task engagement and passive mental states—a function attributed to the DMN (Andrews-Hanna et al., 2010). That is, DMN activation is typically associated with self-referential and spontaneous cognition, in contrast to regions associated with active engagement in effortful mental tasks such as the frontoparietal networks (Dosenbach et al., 2008). It is now widely accepted, based on evidence from both task-based and connectivity findings, that in healthy adults there exists an inverse/anti-correlated relationship between these distributed neural systems purportedly supporting these broad, but different aspects of cognition (Fox et al., 2005; Shulman et al., 1997). In fact, our previous work in healthy adults has clearly demonstrated that the degree of DMN suppression is directly related to accurate WM performance (Anticevic et al., 2010). Thus, only focusing on deficits in task-based activation, while important, may not provide the complete picture of neural deficits that may compromise WM function in schizophrenia. Related to this point, in the preceding sections on behavioral deficits we have discussed that filtering and interference resolution is a critical component of WM function and that there is clear evidence for breakdowns in WM filtering during the WM maintenance phase. In that sense, one can conceptualize the lack of suppression in patients as possibly contributing additional sources of unwanted signals during WM. In other words, if there is a breakdown of such distributed regional suppression during WM in patients, superfluous activation of regions involved in passive mentation may contribute an additional source of noise during WM and render the ongoing task representations more susceptible to interference.

While this framework argues that lack of task-based suppression may be interpreted in part as contributing additional noise to WM, understanding neural deficits in suppressing external interference during WM is equally critical. Despite strong behavioral evidence, there have been very few attempts to date to understand the neural basis of putative filtering deficits during WM in schizophrenia, either during encoding or maintenance. To that end, in a parallel investigation, we examined the neural correlates of deficits associated with WM interference (Anticevic et al., 2011b). Using the same delayed WM task framework described earlier, we presented various types of distraction during the maintenance period of WM. We found that patients fail to recruit a right lateralized DLPFC region previously implicated in distractor resistance (Postle, 2005), a region that control participants clearly activated in response to distraction (Figure 12.A). Moreover, the degree of DLPFC recruitment in our study predicted correct WM performance for control participants such that higher BOLD signals correlated with better WM performance, specifically during distraction (Figure 12.B). In contrast, patients not only failed to activate this region but also did not show a relationship between regional BOLD signals and performance, suggesting a breakdown in the ability to filter distraction.
Taken together, our recent findings suggest that, while it is critical to examine abnormalities in WM signals across regions showing activation in response to cognitive probes, it is also important to consider deactivation abnormalities present during WM, as well as breakdowns in protection of WM stores (i.e., filtering deficits). In fact, at present it is unclear to what extent neural abnormalities in resisting external interference independently contribute to breakdown in WM functioning in schizophrenia, be it from lack of suppression of task-irrelevant internal signal or excessive external interference. Such deficits may also arise from proactive interference suppression (Sakai et al., 2002) (i.e., failure of preparatory filtering signals in the face of upcoming distraction) or from resolving interference once distraction actually occurred (reactive interference resolution). It will be important for future work to adjudicate to what extent there are neural deficits in these possibly separate mechanisms of distractor resistance in schizophrenia (Fletcher, 2011).

**Summary of working memory findings in schizophrenia**

In summary, both behavioral and functional neuroimaging evidence points to WM abnormalities in schizophrenia, which extend across both encoding and the maintenance phases.
These deficits are also associated with abnormalities in brain signals, which may involve distributed cortical frontoparietal, striatal, and thalamic interactions. Such deficits may involve not only abnormalities in sustaining activation across a delay, but also breakdowns in interference resolution from incoming distraction. While the reviewed cognitive neuroscience literature has undoubtedly advanced our understanding of WM pathology in schizophrenia and constrained our search for neural markers of such deficits, we have yet to form a mechanistic understanding of WM dysfunction. Only such an understanding, grounded in cellular mechanisms, offers the possibility for targeted treatment of cognitive abnormalities in schizophrenia. In the following sections, we discuss a translational cognitive neuroscience framework within the context of WM, which offers the promise of linking our levels of understanding from cells to circuits to symptoms. Prior to proceeding to our discussion of translational cognitive neuroscience of WM, it is critical to revisit our initial arguments concerning broader aspects of cognitive deficits in schizophrenia. In that sense, WM is one cognitive probe showing deficits in schizophrenia, which offers promising translational potential, but breakdowns in circuits that may confer WM deficits may also result in abnormal functioning in other cognitive domains; namely, CC and EM. Therefore, we offer a brief treatment of these additional domains of dysfunction.

**Episodic memory in schizophrenia**

Cognitive neuroscience models of episodic memory

As with trying to understand the nature of WM deficits in schizophrenia, it is useful to review briefly the cognitive neuroscience literature on the processing and brain regions involved in EM as a means of organizing the research pertaining to EM deficits in schizophrenia. A key place to start is work on the specific role that the hippocampal formation plays in EM. For many years we have known that the hippocampus plays a critical role in the formation of long-term memories, based in part on studies with amnesic patients such as H.M., who have had lesions to the hippocampus and/or surrounding medial temporal areas (Scoville & Milner, 1957). Following such lesions, these patients exhibit profound deficits in the ability to learn and/or retrieve new episodic memories, despite relatively intact cognitive functioning in other domains (Corkin, 1984; Scoville & Milner, 1957; Squire, 1987). Nonhuman primate models also demonstrate that lesions within the hippocampus and adjacent medial temporal cortex lead to impairments in the ability to retrieve newly learned information successfully (Murray, 1996). Furthermore, these animal studies have highlighted the importance between the function of the hippocampus proper and surrounding medial temporal cortex, as the severity and nature of EM deficits in nonhuman primates varies as a function of the amount of medial temporal cortex involvement.

A common theme running through theories regarding the role of the hippocampal formation in EM is the idea that it is critical for the rapid binding of novel configurations of information (Cohen & Eichenbaum, 2001; Konkel & Cohen, 2009; McClelland et al., 1995; Shimamura, 2010; Squire & Knowlton, 1995). Consistent with this hypothesis, a number of human neuroimaging studies have shown activation of the hippocampus during the encoding or retrieval of novel relational information (Davachi, 2006; Giovanello et al., 2004; Heckers et al., 2004; Sperling et al., 2001; Wendelken & Bunge, 2010), and work in amnestic patients emphasizes the importance of hippocampal structures in
relational processing (Bowles et al., 2010; Ryan & Cohen, 2004). Moreover, a number of functional neuroimaging studies in healthy humans have demonstrated that enhanced hippocampal/parahippocampal activity at the time of encoding predicts subsequent successful retrieval of that information (Brewer et al., 1998a,b; Kirchoff et al., 2000; Otten et al., 2001; Wagner et al., 1998). In addition, work with depth electrodes implanted in humans undergoing epilepsy surgery has also demonstrated that hippocampal activity at the time of encoding predicted subsequent memory for verbal stimuli (Cameron et al., 2001). Although more recent models of EM suggest differential roles for hippocampal versus perirhinal regions of the medial temporal lobes in encoding of item versus relational memory (Davachi, 2006), there is still a strong consensus on the importance of the hippocampus for relational encoding of a range of information types.

At the same time that we are gaining a better understanding of the specific EM functions subserved by the hippocampus, we have garnered information about the fact that prefrontal structures also make important contributions to EM. Damage to the prefrontal cortex can lead to EM deficits, although EM is not the only cognitive function impaired in these individuals (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 (Janowsky et al., 1989). For example, studies have shown activation of ventral prefrontal regions, such as Brodmann’s areas 45 and 47, when participants are asked to process verbal information using semantic elaboration strategies (Wagner et al., 1998) that promote subsequent memory. In addition, a compelling finding supporting a critical role for such prefrontal structures in EM is results showing that the increased activation during encoding in frontal regions such as BA 45 and 47 is highly predictive of subsequent memory performance (Alkire et al., 1998; Baker et al., 2001; Brewer et al., 1998a,b; Kirchoff et al., 2000; Otten et al., 2001; Wagner et al., 1998). For a recent meta-analysis, see Spaniol et al. (2009). Furthermore, there is recent work suggesting that the DLPFC may contribute specifically to successful relational memory formation and retrieval (Blumenfeld et al., 2011; Murray & Ranganath, 2007).

**Episodic memory impairments in schizophrenia**

As described in the previous section, most theories of hippocampal function posit that it plays a key role in binding together novel configurations of information. One way to examine whether individuals with schizophrenia have binding deficits is to determine if they are more impaired on memory for associative information (e.g., the association of previously unrelated words or items) as compared to memory for individual items. To address this question, Achim and Lepage conducted a meta-analysis comparing performance on associative and item memory tests in individuals with schizophrenia, and concluded that there was evidence for a 20% greater impairment in associative as compared to item memory in individuals with schizophrenia (Achim & Lepage, 2003). However, 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, and the human neuropsychological and imaging literature suggests that prefrontal function may make important contributions to source memory (Mitchell & Johnson, 2009). In addition, few of the studies that have compared item and associative memory have dealt with the ubiquitous problems of discriminating power. Associative memory tests are often more difficult than
item memory tests. Greater task difficulty by itself does not necessarily indicate higher discriminating power, but it does raise the question regarding whether a pattern of greater impairment on associative versus item memory is truly indicative of a selective deficit in binding of novel information. More recently, clinical researchers have begun to use tasks derived from the animal literature on hippocampal function, such as the Transitive Inference Test, which measures the ability to learn the relationships among hierarchically arranged stimulus pairs, as well as the Transitive Patterning Test in which individuals have to learn about the relationship between items for correct selection. Individuals with schizophrenia are impaired on critical conditions of this task requiring relational processing, but not on conditions that require simpler associative reinforcement mappings (Coleman et al., 2010; Titone et al., 2004) or other control conditions (Hanlon et al., 2005, 2011). Other work has used eye-movement measures of relational memory, shown to be impaired in patients with hippocampal lesions (Hannula & Ranganath, 2008, 2009), to identify relational memory impairments in schizophrenia (Hannula et al., 2010; Williams et al., 2010). There is also work indicating impairments in both item and relational retrieval for information that was relationally encoded in schizophrenia (Ragland et al., 2012). Still other work has provided evidence for greater deficits in recollection than familiarity in schizophrenia, which have also been interpreted as reflecting relational memory impairments (Danion et al., 2005; van Erp et al., 2008).

Many researchers have taken this body of work to suggest that EM impairments in schizophrenia reflect medial temporal lobe deficits, with a specific focus on the hippocampus (Heckers & Konradi, 2010). However, the findings in healthy individuals about the role of the prefrontal cortex in EM raise the possibility that at least some EM impairments among individuals with schizophrenia also reflect deficits in prefrontally mediated cognitive functions that contribute to successful memory encoding and retrieval, including strategic mechanisms that may facilitate memory formation. Consistent with this hypothesis, a number of studies suggest that individuals with schizophrenia are impaired in their ability to generate effective mnemonic strategies (for review, see Barch, 2005a). 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 (Bonner-Jackson & Barch, 2011; Bonner-Jackson et al., 2008; Heckers et al., 1998; Koh & Peterson, 1978; Ragland et al., 2003, 2005; Weiss et al., 2003), and can even show intact item recognition when provided with support for effective encoding (Mathews & Barch, 2004). Furthermore, a meta-analysis of brain activity alterations during EM performance in schizophrenia showed consistent evidence for reduced activation in both the ventrolateral prefrontal cortex and the DLPFC, but did not find consistent evidence for altered hippocampal activity (Ragland et al., 2009). Recent work on relational memory encoding and retrieval has shown evidence for impaired DLPFC function associated with impaired relational memory function in schizophrenia (Ragland et al., 2011), although other recent work has also implicated hippocampal function (Hanlon et al., 2005, 2011; Luck et al., 2010; Ongur et al., 2006). These findings do suggest a need to take into account a role for prefrontally mediated cognitive functions as well as hippocampal-mediated functions in understanding the source and nature of EM deficits in schizophrenia. Furthermore, the findings on strategic changes in schizophrenia and the role of the DLPFC in EM suggest that examining the role of executive control deficits and effective encoding manipulations may be a fruitful avenue for future research on enhancing EM in schizophrenia.
Executive control in schizophrenia

The previously discussed reviews of WM and EM function in schizophrenia posit a potentially central role for impairments in prefrontal cortex function, although it is clear that prefrontal deficits cannot account for all WM and EM impairments in schizophrenia. In addition, numerous other studies suggest impairments on a range of tasks designed to measure various aspects of executive function in schizophrenia, a cognitive domain also thought to rely heavily on prefrontal functions. However, despite this wealth of empirical evidence on the existence of executive function deficits in schizophrenia, there is relatively little agreement on the precise nature or causes of executive control impairments in schizophrenia. Again, the basic cognitive neuroscience literature provides several theories or hypotheses as to what the nature of executive control dysfunction in schizophrenia might be. We will briefly review several of these theories, including the hypotheses regarding the role of the DLPFC and dopamine-mediated context processing disturbances and/or proactive control as well as the hypotheses regarding 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 put forth the hypothesis that the intact function of dopamine in the DLPFC was responsible for the processing of context, and that a disturbance in this mechanism was responsible for a range of cognitive deficits in schizophrenia (Barch et al., 2001; Braver et al., 1999; Braver & Cohen, 1999; Cohen & Servan-Schreiber, 1992; Cohen et al., 1999). Context refers to prior task-relevant information that is represented in such a form that it can bias selection of the appropriate behavioral response. Because context representations are maintained online, 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 govern 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, this theory argues 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 & Cohen, 1999; Cohen & Servan-Schreiber, 1992; Cohen et al., 1999). When a task involves competing, task-irrelevant processes (as in the Stroop task), 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, the mechanism employed to represent context information can be used to maintain task-relevant information against the interfering and cumulative effects of noise over time. Additionally, 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 executive control tasks that may not involve a high WM load (e.g., Stroop) (Barch et al., 1999). Furthermore, 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). Numerous
prior studies have provided support for these hypotheses concerning context-processing
deficits in schizophrenia (for a review, see Barch & Braver, 2007), as well as evidence for
impairments in individuals at risk for schizophrenia (MacDonald et al., 2005, 2006; Snitz
et al., 2006), suggesting that such deficits may be associated with liability to schizophrenia
as well as manifest illness.

Proactive and reactive control in schizophrenia

In more recent years, the key role of context processing in cognition and in schizophrenia
has been re-conceptualized somewhat more broadly as the function of proactive CC
(Barch & Braver, 2007; Braver et al., 2009; Edwards et al., 2010; Haddon & Killcross,
2007). This conceptualization builds upon earlier ideas of context processing to argue for
flexible mechanisms of CC that allow humans to deal with the diversity of challenges that
we face in everyday life. In this theory, termed dual mechanisms of control (Braver et al.,
2007, 2009; Edwards et al., 2010), a distinction is made between proactive and reactive
modes of CC. The proactive control model can be thought of as a form of “early selection,”
in which goal-relevant information is actively maintained in a sustained or anticipatory
manner, before the occurrence of cognitively demanding events. This allows for optimal
biasing of attention, perception, and action systems in a goal-driven manner. In this
case, goals refer to the information one needs to accomplish in a particular task situation
or the intended outcome of a series of actions or mental operations. In real life, such goal
information may include the main points one wishes to communicate in a conversation, or
the need to organize a shopping trip so that one can make sure to get everything that is
needed. In contrast, in the reactive mode, attentional control is recruited as a “late correc-
tion” mechanism that is mobilized only when needed, such as after a high-interference
event is detected (e.g., an unexpected distracting stimulus is encountered and there is a need
to retrieve the topic of conversation). Thus, proactive control relies on the anticipation and
prevention of interference before it occurs, whereas reactive control relies on the detection
and resolution of interference after its onset.

This theory postulates that proactive control depends on actively representing infor-
mation in the lateral prefrontal cortex, and that the updating and maintenance of such
information depends on precise inputs from neurotransmitter systems such as dopamine
into the prefrontal cortex. However, as discussed in more detail later, it is clear that
other neurotransmitter mechanisms are critical for active maintenance of information in
the prefrontal cortex, and that deficits in NMDA receptor function may underlie
impaired delay-related activity during WM in schizophrenia. As outlined in detail in
Braver (in press), proactive and reactive control functions are not mutually exclusive,
and some balance between the two modes is necessary to meet most ongoing cognitive
demands successfully. However, Braver (in press) has argued that the two control modes
can be distinguished based on their temporal characteristics (e.g., when they are engaged
in the course of cognitive processing) and the requirement to actively maintain control
representations over time for proactive control. In addition, Braver has suggested that
there may be biases to favor one processing mode over the other, which may be
dependent on task demands (e.g., high conflict situations may push toward a proactive
control mode) and individual differences like WM capacity, fluid intelligence, and even
personality traits such as reward sensitivity. Proactive control may also be particularly
vulnerable to disruption, given that it is resource demanding and dependent upon
temporally precise active maintenance mechanisms. Thus, populations characterized by disordered prefrontal function (such as schizophrenia) may rely more heavily on reactive control, as it may be more robust in the face of such dysfunction (Edwards et al., 2010). Consistent with this hypothesis, there is ample evidence for an association between impairments in DLPFC activity and deficits of proactive control in schizophrenia (Barbalat et al., 2009; Minzenberg et al., 2009), for both medicated (Holmes et al., 2005) and unmedicated patients (Barch et al., 2001; MacDonald et al., 2005) as well as those at risk for the development of schizophrenia (Fusar-Poli et al., 2007; MacDonald et al., 2009). For example, a recent comprehensive meta-analysis of imaging studies of executive control and proactive control conducted by Minzenberg and colleagues (Minzenberg et al., 2009) provided clear evidence for reduced activity in the DLPFC in schizophrenia.

Conflict detection/error monitoring

The reviews of WM and EM discussed earlier, and the description of context processing and proactive control in schizophrenia, placed a heavy emphasis on the function of the prefrontal cortex, especially the dorsolateral regions. However, it is very clear that regions other than the DLPFC play a role in executive control, and that mechanisms other than just active maintenance or proactive control influence executive function. Thus, an alternative (or perhaps complementary) hypothesis about the specific nature of executive control deficits in schizophrenia suggests that disturbances in the ability to detect conflict or errors in ongoing processing emerge at least in part due to dysfunction of the anterior cingulate cortex (ACC). Such ACC abnormalities may lead to deficits in the ability to regulate and control a range of other components of executive control in schizophrenia. This hypothesis builds on models of ACC function that postulate a critical role for this brain region in either detecting conflict or errors and signaling the prefrontal regions to enhance CC (Botvinik et al., 2001), predicting conditions likely to elicit errors (Alexander & Brown, 2011; Brown & Braver, 2005), or detecting mismatches between “correct” or intended output (Holroyd & Coles, 2002).

At the behavioral level, there is very mixed evidence in schizophrenia regarding impairments on indices thought to reflect the ability to detect or respond to conflict or errors. For example, some studies have found that individuals with schizophrenia detect and/or correct errors as frequently as do healthy controls (Kopp & Rist, 1994), while other studies have found reduced rates of error correction among individuals with schizophrenia (Turken et al., 2003). In addition, some studies have found that individuals with schizophrenia show an intact “Rabbit” effect, which is the slowing of responses on trials following errors (Laurens et al., 2003; Mathalon et al., 2002; Morris et al., 2006; Polli et al., 2006, 2008), while other studies have found that this effect is reduced in patients with schizophrenia (Alain et al., 2002; Becerril et al., 2011; Carter et al., 2001; Enticott et al., 2011; Kerns et al., 2005; Kopp & Rist, 1999). In contrast, evoked response potential (ERP), fMRI, and positron emission tomography (PET) studies have provided more consistent evidence for altered conflict/error processing. For example, a number of studies have shown reduced error-related negativity (ERN) amplitudes or ACC activity in patients with schizophrenia on error trials (Alain et al., 2002; Bates et al., 2002, 2004; Becerril et al., 2011; Carter et al., 2001; Kerns et al., 2005; Kopp & Rist, 1994, 1999; Laurens et al., 2003; Mathalon et al., 2002, 2009; Perez et al., 2011; Polli et al., 2008), even when these same
individuals show intact behavioral indices or error detection (Kopp & Rist, 1994, 1999; Laurens et al., 2003). Furthermore, there is also some evidence of reduced ACC responses to error likelihood prediction in schizophrenia (Krawitz et al., 2011). Interestingly however, there is some evidence that individuals with schizophrenia may show intact feedback-related negativity (FRN) responses to explicit external feedback, even in the context of impaired ERN responses (Horan et al., 2011). This may reflect a difference between externally provided information about accuracy (indexed by the FRN) versus internal representations of accuracy that must be generated by the individuals (and potentially better indexed by the ERN).

At the same time that there is consistent evidence for reduced ACC activity in responses to errors in schizophrenia, it is interesting to note that many imaging studies of WM and executive control in schizophrenia have shown robust activation of the ACC among individuals with schizophrenia (Barch, 2005b), with even some evidence for increased ACC activity (Minzenberg et al., 2009). Any of the theories of ACC function described would predict that ACC activity should be increased in individuals with schizophrenia if they were actually experiencing greater conflict or errors, which is the typical behavioral result for WM and executive control studies in schizophrenia. Such findings raise interesting questions about the relationship between deficits in ACC and DLPFC function in schizophrenia, in that theories about primary deficits in either area would also predict deficits in the function of the other region as a consequence. If ACC activity is important for the recruitment of control processes supported by the 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 (if they experience more conflict and errors that would elicit ACC activity), but 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 potentially reflect the common importance of dopaminergic inputs to both the 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 help provide a better understanding of the dynamic processes that give rise to WM and executive control deficits in schizophrenia.

The preceding sections summarize our evolving understanding of cognitive impairment in schizophrenia from the perspective of cognitive neuroscience. However, in order to ultimately treat cognitive deficits, we need to move toward understanding the mechanisms underlying observed deficits. To achieve this goal, we need a mechanistic framework. In the final section we will discuss a path forward, which involves combining several leading neuroscientific methodologies, which may allow us to understand cellular-level mechanisms of cognitive deficits in this illness.

**Toward translational cognitive neuroscience of working memory**

As reviewed earlier, cognitive neuroscience has established the tools to probe the underlying circuitry that may be affected in schizophrenia in relationship to disrupted cognition, such as WM, EM, and executive control. Such findings have provided guidance as to
the neurobiological and psychological mechanisms that may be contributing to impairments in these cognitive domains. However, these approaches have had less success in addressing the underlying cellular mechanisms—which is where pharmacological therapies are ultimately applied. Therefore, understanding of cognitive dysfunction at this level is critical to move toward targeted and rationally designed treatment. A way to close this existing explanatory gap is to directly align two leading methodologies with our clinical case-control studies: namely pharmacological neuroimaging (ph-fMRI) (Honey & Bullmore, 2004) and computational modeling (Montague et al., 2012). Testing hypotheses regarding neural dysfunction in schizophrenia via pharmacological manipulations in healthy adults allows mechanistic perturbations of the underlying circuitry thought to be compromised in individuals suffering from the illness. In turn, such manipulations may reveal clues regarding specific links between disruptions in neurotransmitter systems, which can in turn be connected to system-level deficits and ultimately behavior. A powerful approach is to design such investigations to directly test predictions from computational models of neural function. Specifically, we propose that biophysically realistic computational modeling holds tremendous promise for accomplishing this goal and for generating predictions regarding development of future therapies. In the subsequent section we will argue for the critical utility of blending cognitive neuroscience with pharmacological manipulations that transiently and safely mimic the cardinal symptoms of the illness. We will focus specifically on WM as one candidate neurocognitive probe, motivated by recent development of biophysically realistic models of WM function (Brunel & Wang, 2001; Compte et al., 2000; Wang, 2001, 2010; Wang et al., 2004) and the arguments that spatial WM may be a powerful endophenotype for understanding cognitive deficits in schizophrenia (Glahn et al., 2003). We will conclude by articulating how this approach offers a potential experimental framework for understanding mechanisms that ultimately may lead to rational treatment development for cognitive deficits in schizophrenia.

Pharmacological models of psychosis: evolving use in human neuroimaging

As noted, schizophrenia is a highly heterogeneous illness and patients often present with diverse symptoms and differing illness trajectories. Furthermore, most patients in case-control studies are under long-term medication regimens. All of these variables obscure our ability to make inferences regarding specific neural mechanisms (Barch et al., 2001). An alternative approach, which circumvents these confounds, involves transiently and safely modeling the full spectrum of symptoms in healthy volunteers using pharmacological manipulations (Krystal et al., 1994). There are currently two leading pharmacological models of psychosis used to invoke cardinal symptoms of schizophrenia in healthy volunteers; namely, ketamine and delta-9-tetrahydrocannabinol (THC) (D’Souza et al., 2004; Krystal et al., 1994). Here we will focus specifically on the translational potential of ketamine as an example, given the evolving understanding of the NMDA glutamate receptor dysfunction in psychosis and their critical importance for WM functions (Krystal et al., 2002, 2003; Wang et al., 2008) (discussed later). Before proceeding to the translational potential of the ketamine model in the context of WM specifically, we briefly discuss: (1) evidence for behavioral effects of ketamine; (2) neurobiological effects of ketamine particularly in relation to the NMDA hypofunction hypothesis in schizophrenia. We specifically argue that linking such pharmacological models of cognitive
dysfunction with neurocognitive probes of WM offers the promise for mechanistically
testing hypotheses of cognitive disturbances in schizophrenia derived from formal
computational models.

Behavioral effects of ketamine
Ketamine is a well-established pharmacological model of psychosis and its psychotomi-
metic effects have been replicated extensively both in human (Krystal et al., 2003) and
animal studies (Moghaddam & Javitt, 2011). The seminal investigation conducted in
healthy human volunteers by Krystal and colleagues (Krystal et al., 1994) provided
evidence that transient administration of ketamine produced transient symptoms with
striking resemblance to schizophrenia, including positive, negative, disorganized symp-
toms and cognitive deficits—effects that have been replicated across a number of studies
(Krystal et al., 1998; Malhotra et al., 1997; Newcomer et al., 1999; Oye et al., 1992;
Vollenweider et al., 1997). Ketamine effects on thought disorder symptoms mimic those
found in patients (Adler et al., 1998) and ketamine exacerbates symptoms in patients
diagnosed with the illness (Lahti et al., 1995b, 2001). Transient ketamine administration
also produces disturbances in cognition, including effects on attention, WM, declarative
memory, abstract reasoning, mental flexibility, insight, planning, and judgment (Krystal
et al., 1994, 1998, 1999; Malhotra et al., 1997; Morgan & Curran, 2006; Newcomer et al.,
1999)—all deficits present in patients diagnosed with schizophrenia (Reichenberg &
Harvey, 2007). We do not extensively review the large literature examining ketamine
effects on WM (for a more comprehensive review, see Morgan & Curran, 2006); however,
it is important to note that ketamine administration induces reductions in WM perform-
ance in humans (Morgan & Curran, 2006) and other species (Neill et al., 2010). Taken
together, this converging evidence suggests that the behavioral effect of ketamine resem-
bles the schizophrenia syndrome and mimics cognitive disturbance in particular, provid-
ing a powerful platform to examine cognitive deficits in psychosis from a mechanistic
perspective (i.e., the NMDA glutamate receptor hypofunction hypothesis, discussed in the
next section).

Neurobiological effects of ketamine: NMDA hypofunction hypothesis
Optimal cortical function depends on the balanced interaction of pyramidal excitatory
(glutamatergic) and inhibitory (GABAergic) neurons (Shadlen & Newsome, 1994). Disrup-
tions of this balance can have drastic behavioral consequences (Marin, 2012; Yizhar et al.,
2011) relevant to serious mental illness. Building on the rich behavioral evidence of keta-
mine’s effects, there is a growing understanding of its underlying mechanisms of action from
preclinical neuroscience studies that point to ketamine disrupting excitatory and inhibitory
cortical balance. Interestingly, an emerging hypothesis of cellular-level disturbances in
schizophrenia suggests a similar mechanism; namely, a deficit in the interaction between
excitatory and inhibitory cortical neurons (Benes et al., 1991; Lewis & Moghaddam, 2006;
Lewis et al., 2004, 2005, 2012; Marin, 2012). Specifically, this hypothesis is based on the
disrupted mechanism of cortical inhibition; that is, a lack of inhibitory drive from GABA
interneurons onto pyramidal neurons resulting in disinhibition of pyramidal cells (Lewis
et al., 2012; Marin, 2012). One line of evidence for abnormalities in this mechanism comes
from postmortem investigations of the DLPFC in patients with schizophrenia. These post-
mortem studies consistently show reduced levels of the mRNA for the 67-kilodalton isoform
of glutamic acid decarboxylase (GAD67, encoded by GAD1), a key factor in optimal GABA
levels, in the DLPFC of patients with schizophrenia (for review, see Lewis et al., 2005). Furthermore, proper functioning of GABA neurons has been linked to optimal WM function, purportedly by virtue of GABA’s role in exerting lateral inhibition and synchronizing persistent firing of pyramidal cells in the DLPFC (Rao et al., 2000). Therefore, it is hypothesized that a disruption of the excitation/inhibitory balance between pyramidal and GABA neurons may be one crucial pathophysiological mechanism operating in schizophrenia, relevant to observed cognitive deficits.

Importantly, as alluded to earlier, the leading hypothesis regarding ketamine’s effects on cortical function proposes precisely such a disinhibition of the cortical microcircuit (Greene, 2001; Homayoun & Moghaddam, 2007; Kotermanski & Johnson, 2009; Krystal et al., 2002, 2003). Specifically, it is hypothesized that ketamine, and possibly other NMDA antagonists, exert their effects via preferential blockade of NMDA receptors on GABAergic interneurons in the cortical microcircuit (Kotermanski & Johnson, 2009) (for a discussion of mechanisms behind this preferential blockade, see Greene, 2001). In turn, this may result in excessive pyramidal cell activity and a hyper-glutamatergic state of cortical disinhibition (Homayoun & Moghaddam, 2007), which may induce excessive activation and hypersynchrony of cortical circuits, as well as possible “hyper-frontality” (Moghaddam & Javitt, 2011). These hypothesized effects are supported by evidence from human neuroimaging literature, as a number of PET and bloodBOLD fMRI imaging studies have suggested excessive cortical activation during acute administration of ketamine to healthy volunteers (Breier et al., 1997; Lahti et al., 1995a, 2002; Vollenweider et al., 1997, 2000). Extensive treatment of the hypothesized mechanisms behind these observations is beyond the scope of the present review and has received attention in prior reviews (Adell et al., 2011).

Importantly, possible disruptions of cortical inhibition—due to disruptions of GABAergic signaling—may underlie acute effects of ketamine. Through this mechanistic link between ketamine’s effects and hypothesized neuropathology in schizophrenia, we can adapt existing computational models of WM to perturb this very mechanism, balance of excitation and inhibition, allowing a bridge between pharmacology, and cognition and computational modeling.

Computational models of working memory function: promise for integration with pharmacological neuroimaging

Although a number of neuroimaging studies have demonstrated that acute ketamine administration alters cortical function and cognition in humans (Corlett et al., 2006; Honey et al., 2008), very few studies have extended this to cognitive deficits and specifically WM function (Honey et al., 2004). A number of elegant ph-fMRI investigations have successfully employed the ketamine model to examine the neural correlates of positive schizophrenia symptoms—specifically delusion formation—but this has not been fully extended to the domain of cognitive deficits. We argue that this is critical not only from a clinical standpoint but also because WM offers the ideal opportunity for a translational cognitive neuroscience marker that is compromised in schizophrenia (Glahn et al., 2003). To date, only a single ph-fMRI study has examined the effects of ketamine on WM, but did so using a verbal N-back cognitive task that does not allow for clear translation to animal physiology (Honey et al., 2004). We suggest an approach using spatial WM as a translational neuropsychiatry endophenotype. Due to the shared neural substrates, both human neuroimaging and primate neurophysiology have provided increasingly better characterization of visuospatial WM mechanisms (Driesen et al., 2008; Goldman-Rakic,
1984, 1987, 1995, 1996; Goldman-Rakic et al., 2000, 2004; Leung et al., 2002). A series of seminal electrophysiological studies with nonhuman primates conducted by Patricia Goldman-Rakic and colleagues (Funahashi et al., 1989; Goldman-Rakic, 1988, 1995) have shown that the persistent firing of DLPFC pyramidal cells underlie computations necessary for robust and stable internal representations in the face of competing external stimuli (Rao et al., 2000). Furthermore, it is widely understood that optimal WM function depends on the slow NMDA receptors at the recurrent synapses and the balance between synaptic excitation and inhibition between pyramidal and GABAergic interneurons, respectively (Constantinidis & Wang, 2004; Goldman-Rakic & Friedman, 1991; Rao et al., 2000; Wang, 2001, 2010; Wang et al., 2004, 2008). It follows directly that acute antagonism of the NMDA glutamate receptors via ketamine–targeting GABA cells would disrupt cortical signals critical for spatial WM, a hypothesis supported by behavioral evidence (Morgan & Curran, 2006).

Based on such an understanding of the basic cellular properties of spatial WM function derived from primate physiology experiments, Wang and colleagues have developed a biophysically constrained and realistic spatial WM network model of spiking neurons (Compte et al., 2000; Wang, 2001; Wang et al., 2004). The model is based on a Mexican-hat architecture (Camperi & Wang, 1998), with a critical interplay between excitatory and inhibitory cells in a cortical circuit that underlies the persistence of pyramidal cell activity. The model incorporates local recurrent excitation (E-E) between pyramidal cells with similar spatial preferences and broad synaptic feedback inhibition (E-I) from GABAergic cells. When local excitatory synapses are sufficiently activated, the network exhibits robust firing that follows a bell-shaped pattern (or “bump” attractor state), which stores the memory of a spatial location as an analog quantity. Furthermore, consistent with experimental data, prior simulations have found that in this model, WM function depends on the slow NMDA receptors at the recurrent synapses and the balance between synaptic excitation and inhibition (Constantinidis & Wang, 2004; Wang, 2001, 2006), thought to be disrupted in schizophrenia (Marin, 2012). This computational model of WM–grounded in primate physiology–offers a unique possibility to explore the effects of neuromodulation (Brunel & Wang, 2001) and cell-type specific virtual lesions or impairments, as recently accomplished in vivo in rodents (Yizhar et al., 2011). Because the model contains the same basic cellular architecture present in the human cortex, namely E-E and E-I NMDA conductance, hypothesized aspects of schizophrenia neuropathology can be represented within the model itself, as done with dopamine (Brunel & Wang, 2001). This is a unique advantage of biophysically based WM models: while computational modeling of cognition in psychiatry has guided our predictions conceptually (Montague et al., 2012), this framework is distinguished by its foundation in a computational model rooted in neurophysiological data and building on assumptions based on molecular and systems neuroscience. However, the ultimate potential of this framework is to represent hypothesized aspects of schizophrenia neuropathology, articulated earlier (namely NMDA hypo-function on GABA cells), within the model itself and test model predictions via a feasible pharmacological framework that allows for direct and safe experimental comparison in humans. Ketamine administration offers an exciting opportunity in this regard, as it transiently, reversibly, and safely induces some of the characteristic positive, negative, and cognitive symptoms of schizophrenia in healthy volunteers (Krystal et al., 2003) via a mechanism that can be implemented in the model.
While this combination of approaches can generate powerful behavioral predictions, some might argue that biophysical realism at the level of cells may offer little explanatory power when combined with fMRI (Montague et al., 2012) (as the fMRI signal averages over millions of neurons). While this is a reasonable concern, recent work with L-Dopa has already begun to put these concerns to rest and nicely illustrates the power of computational modeling at the level of synapses when combined with human neuroimaging (Moran et al., 2011). Using magnetoencephalographic (MEG) measurement in the context of a WM task, Moran and colleagues have shown that the DLPFC signal tracks specific predictions from a synaptic-level model of cortical functions following L-Dopa pharmacological manipulation. They found that the degree of NMDA and \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) signaling change in the model indeed predicted both MEG and behavioral effects. This study highlights the potential of uncovering hidden cellular mechanisms, invisible with our state-of-the-art human neuroimaging (Figure 12.2), yet critical for our understanding of emergent system-level neural activity and behavior.

**Figure 12.2.** Framework for translational cognitive neuroscience of schizophrenia. The proposed framework combines pharmacological manipulation and cellular-level computational modeling with behavioral measurement and neural system read-out with state-of-the-art fMRI. This allows direct mechanism examination through manipulation of the underlying circuitry and comparing results with deficits observed in schizophrenia patients. This computational neuropsychiatry approach allows us to traverse levels of scientific explanation by establishing mechanistic links between cells, neural systems, and psychiatric symptoms. (See color plate section for colored image.)
We propose that the same approach can and needs to be harnessed in the service of characterizing cognitive deficits in schizophrenia, in this case through understanding of spatial WM deficits specifically. Through the combination of the aforementioned computational models of WM and NMDA glutamate receptor antagonism via ketamine, there is a path forward for a mechanistic understanding of cognitive deficits in schizophrenia. We contend that this approach provides a testable experimental framework using behavior and ph-fMRI, and allows for the iterative implementation of possible cognitive treatments in the model itself in future work. This in turn will generate predictions regarding behavior and neuronal activity that can be tested experimentally using novel compounds that the model predicts to be effective in improving cognitive deficits in schizophrenia. This is critical because most psychiatric treatment regimens, particularly those that are used to treat schizophrenia, have evolved without a rational framework motivating their design and do not alleviate cognitive deficits. Therefore, the articulated translational cognitive neuroscience approach holds promise for defining mechanisms that may help focus our treatments of cognitive dysfunction in individuals suffering from this illness.

Summary and conclusions

In this chapter, we have reviewed the extensive evidence that individuals with schizophrenia experience deficits in WM function and that these deficits extend across both encoding and the maintenance phases of WM. Further, we have also reviewed evidence that WM deficits in schizophrenia are associated with disturbances in a distributed cortical frontoparietal, striatal, and thalamic circuit, although impairments in DLPFC function may play a particular key role. Such impairments may involve not only abnormalities in sustaining activation across a delay, but also breakdowns in interference resolution from incoming distraction. Further, we have reviewed additional evidence suggesting that individuals with schizophrenia also experience deficits in several domains of executive function, including context processing, proactive control, and conflict detection, that may depend—at least in part—on the same neural circuits that support WM function. We have also discussed evidence suggesting that individuals with schizophrenia have deficits in EM function that involve impairments in relational integration and retrieval. These deficits in relational processing of components of EM appear to reflect impairments in both binding processes supported by the hippocampus and the types of beneficial encoding strategies supported by regions of prefrontal cortex. We have also suggested that in order to understand better and thus develop effective treatments for such impairing cognitive deficits in schizophrenia, we may need to adopt a translational cognitive neuroscience approach that uses biophysically plausible computational models and pharmacological challenge approaches that would allow us to test specific mechanistic hypotheses about the sources of cognitive impairment in schizophrenia. We have articulated the use of such a framework to understand the potential role of NMDA receptor dysfunction and excitatory/inhibitory circuits in WM deficits in schizophrenia. However, this is just one potential example and this approach can be extended to model different cognitive deficits (e.g., proactive control, EM) and different potential pathophysiological mechanisms. Regardless of the specific mechanisms tested, it is our belief that the use of such a framework will help move forward the search for effective treatments for cognitive impairment in schizophrenia, given the central role of such deficits in constraining life function for individuals with this illness.
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References


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response during working memory in schizophrenia. Schizophrenia Research, 53, 45–56.


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Newcomer, J. W., Farber, N. B., Jevtovic-Todorovic, V., et al. (1999). Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. Neuropsychopharmacology, 20, 106–118.


Thompson-Schill, S. L., Jonides, J., Marshuetz, C., et al. (2002). Effects of frontal lobe damage on interference effects in working...
memory. *Cognitive, Affective and Behavioral Neurosciences*, 2, 109–120.


