The Cognitive Neuroscience of Working Memory: Relevance to CNTRICS and Schizophrenia

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Working memory is one of the central constructs in cognitive science and has received enormous attention in the theoretical and empirical literature. Similarly, working memory deficits have long been thought to be among the core cognitive deficits in schizophrenia, making it a ripe area for translation. This article provides a brief overview of the current theories and data on the psychological and neural mechanisms involved in working memory, which is a summary of the presentation and discussion on working memory that occurred at the first Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) meeting (Washington, D.C.). At this meeting, the consensus was that the constructs of *goal maintenance* and *interference control* were the most ready to be pursued as part of a translational cognitive neuroscience effort at future CNTRICS meetings. The constructs of *long-term memory reactivation, capacity,* and *strategic encoding* were felt to be of great clinical interest but requiring more basic research. In addition, the group felt that the constructs of *maintenance over time* and *updating* in working memory had growing construct validity at the psychological and neural levels but required more research in schizophrenia before these should be considered as targets for a clinical trials setting.

Working memory is perhaps one of the most frequently studied domains in both cognitive science and cognitive neuroscience, with a wealth of accumulated theoretical and empirical work at both the psychological and neural level (1). Further, a large body of work has demonstrated that individuals with schizophrenia have deficits on a varied set of working memory tasks (2,3) that are associated with impairments in a range of neural mechanisms (4). There are some data to suggest that the degree of impairment in certain aspects of working memory predicts later onset of schizophrenia (5,6). In addition, the level of working memory impairment predicts the degree of social and occupational impairment in individuals with schizophrenia (7,8). Further, individuals who share unexpressed genetic components of vulnerability to schizophrenia also experience impairments in working memory function (9,10).

The centrality of working memory deficits in schizophrenia has led this to be one of the most vigorously studied cognitive domains in our attempts to understand the pathophysiology of this disorder. As such, working memory was selected as one of the domains relevant to the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative. This article has two goals. The first is to provide an overview of the summary of the cognitive and neural mechanisms involved in working memory presented at the first CNTRICS meeting in Washington, D.C., in February of 2007. The overview talk on working memory was presented by Ed Smith, and the breakout discussion included a range of participants from industry and academia, both from the basic science side (e.g., Randy Engle, Nelson Cowan, John Jonides, Todd Braver, Michael Frank, Trevor Robbins, Patricio O'Donnell) and the clinical science side (e.g., Diane Gooding, Deanna Barch, Jim Gold, Larry Seidman, Angus MacDonald, Dan Ragland). The

second goal is to describe which mechanisms involved in working memory were selected as being ripe for translation and the ways in which these mechanisms met the criteria outlined as part of the CNTRICS initiative. These criteria are described in detail in the overview article by Carter and Barch at the start of this special section. We do not wish to put forth the results of the discussion about working memory at the first CNTRICs meeting as being completely authoritative. There were clearly experts in the field of working memory who were not present at this meeting and individuals who might disagree with the consensus opinions reached at this meeting—perhaps rightly so. However, there are too many constructs involved in working memory to allow us to pursue measurement of them all simultaneously as part of the CNTRICS initiative. Thus we felt that we had to begin to focus on the most promising constructs through some consensus-based approach.

Cognitive Neuroscience Theories of Working Memory

Working memory is typically defined as the ability to maintain and manipulate information over short periods of time. There are a number of influential models of the processes involved in working memory. One such early model is Baddeley's (11), which distinguishes among four major components: 1) a short-term storage buffer for visual information that is often referred to as the visuospatial scratch pad, 2) a short-term storage buffer for verbal information referred to as the phonological loop (which includes both articulatory rehearsal and phonological processing, 3) a central executive component that guides the manipulation and transformation of information held within the storage buffers, and 4) the episodic buffer (12). Each of these major component processes of working memory can also be further subdivided into subprocesses. A number of studies suggest that articulatory rehearsal is particularly dependent on regions of left ventrolateral prefrontal cortex (VLPFC), including Brodmann's areas 44 and 45. Functional imaging studies examining rehearsal show activation of this region (13,14), and lesions to this region impair articulatory rehearsal (15). In contrast, the processing or storage of phonological representations is thought to be dependent on regions of left posterior parietal cortex (13).

One way in which humans may maintain visual spatial information is to use covert shifts of attention to the spatial locations to be remembered, a process that has been referred to as attention-based rehearsal (16). These covert shifts of attention are thought to depend, at least in part, on the same neural

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systems that support spatial attention processing, including the right posterior parietal cortex (17), part of the dorsal attention system (18). In addition to right posterior parietal cortex, studies of spatial working memory also consistently activate regions such as the frontal eye fields (FEF) and the supplementary eye fields (SEF) (17).

The episodic buffer is a newer addition to Baddeley's model (12). Baddeley has suggested that this episodic buffer is able to create or store representations that integrate different types of information and supports the binding of information into an "episode." This concept makes contact with other conceptions of binding in working memory, which suggests that multidimensional representations can be maintained in working memory as integrated units rather than sets of independent features (19).

A number of processes are often referred to as being part of the central executive, including those involved in the manipulation of information being stored in the domain-specific buffers, protection from interference due to competing information, temporal coding or sequencing, updating of the contents of working memory, and the maintenance of goal representations in working memory. Importantly, most, if not all, of these processes are unlikely to be specific to working memory. At a general level, dorsolateral regions of prefrontal cortex (DLPFC), typically Brodmann's areas 46 and 9 bilaterally, have been associated with many of the processes attributed to central executive (20). However, regions other than DLPFC are also important for the processes ascribed to the central executive, and we should not equate DLPFC and executive function. As one example, Jonides and colleagues have shown that a region of left VLPFC is involved in the resolution of proactive interference, a process that many have ascribed to the central executive (21,22). Further, Wager and Smith (23) performed a meta-analysis of working-memory tasks that presumably recruit the central executive and found that the most frequently activated area across studies was in the posterior parietal cortex.

A different, but increasingly influential, model of working memory put forth by Cowan suggests that there are not qualitative or structural differences in the representations used to support working memory compared with episodic memory, in the sense of there being dedicated storage buffers that only maintain information "contained" in working memory. Instead, Cowan's model suggests that the information contained in working memory is simply the activated portion of working long-term memory that is currently the focus of attention. This model is gaining increasing acceptance and provides an excellent fit to much of the extant behavioral and neurobiological data. Further, this model has an interesting, and somewhat different, set of implications for the neural substrates of working memory, as articulated recently by D'Esposito (1). Specifically, a Cowan type model suggests that the neural systems supporting information that is currently the focus of attention in working memory should use the same systems used to process initially or store information in long-term memory. Work by D'Esposito and colleagues (24) has shown that working memory tasks requiring the maintenance of face information activates the fusiform face area (an area putatively specialized for processing and storing face information), whereas the maintenance of house representations differentially activates the parahippocampal place area (25,26).

In a related vein, Engle and colleagues (27,28) have emphasized the centrality of *goal maintenance and interference control* in working memory. This body of work suggests that a critical aspect of working memory is the ability to maintain goal representations that allow one to select task-relevant information

from task-irrelevant information and to protect this information from distraction or interference (i.e., working memory as "controlled attention"). Engle and colleagues (29,30) have argued that this conceptualization of working memory helps to explain why individual differences in working memory capacity relate to performance on tasks such as the antisaccade and the Stroop, which also require *goal maintenance*.

A great deal of work in the cognitive neuroscience of working memory has also focused on understanding the contributions of specific neurotransmitter systems. The dopamine system has received the most attention. Goldman-Rakic and her colleagues (31) have demonstrated that working memory function is impaired in nonhuman primates following 6-hydroxy-dopamine lesions in prefrontal cortex (32) or administration of dopamine antagonists (33). Dopamine agents can also modulate working memory function in humans, although the results in this domain vary as a function of facts such as the nature of the task, the ability level of the participants, and even their genetic makeup (for a review, see ref. 4). A number of researchers have postulated specific computational roles for dopamine in working memory (34,35). Braver and colleagues (36,37) have suggested that dopamine may serve as a cue for updating information in working memory and that phasic dopamine signals help to gate or regulate what information is loaded into working memory, a process that can help to protect from interference due to distracting information. In a similar vein, Frank and O'Reilly (38) argued that basal ganglia mediated dopamine signals serve to update representations in working memory. Durstewitz and Gabriel (39) elaborated models in which *N*-methyl-D-aspartate activity interacts with dopamine to modulate recurrent activity in neural networks thought to support working memory representations.

After a formal presentation by Ed Smith on mechanisms involved in working memory, the attendees of the CNTRICS meeting engaged in a discussion on the degree to which various mechanisms involved in working memory met the criteria identified as being important for selecting mechanisms for immediate translation (see Table 1 in the Carter and Barch article). These criteria include the degree of evidence for neural and psychological construct validity, the ability to measure the process in humans (including amenability to use in imaging studies), the evidence for impairment in schizophrenia and links to functional outcome, and the availability of an explicit animal model. This discussion allowed the participants to group mechanisms into three general categories: 1) those recommended for immediate translation, 2) those recommended for more basic and clinical research, and 3) those recommended for more basic research (Table 1).

Constructs Ready for Immediate Translation

Goal Maintenance
Clarity of the Understanding of the Cognitive Mechanism. As described earlier, Engle's theory of working memory emphasizes the centrality of the ability to maintain goals that delineate the type of information that is currently relevant for the contents of working memory (e.g., the focus of attention) as a means of selecting task-relevant information for inclusion in working memory and as a means to protect this information from interference from competing information (27,28). The term *goal* in this context refers to a range of information, including task instructions, representations of target stimuli, and the results of processing prior stimuli. For example, in the type of working

Table 1. Grouping of Working Memory Constructs in Terms of Their Readiness for Translation

Ready for Immediate Translation
  Goal maintenance: the processes involved in activating task-related goals or rules based on endogenous or exogenous cues, actively representing them in a highly accessible form, and maintaining this information over an interval during which that information is needed to bias and constrain attention and response selection
  Interference control: the processes involved in protecting the contents of working memory from interference from either other competing internal representations or external stimuli
In Need of More Clinical Research in Schizophrenia
  Maintenance over time: the ability to maintain information internally over time in the absence of interference
  Updating: the ability to update the contents of working memory
In Need of More Basic Research
  Strategic encoding: the ability to select and implement strategies that facilitate encoding into working memory
  Long-term memory reactivation: the ability to retrieve representations from long-term memory for use in working memory
  Capacity: the amount of information that can be maintained in working memory (the focus of attention)

memory task used by Luck and colleagues (19), the goal representation might include information about the task features (color, orientation, etc.) relevant for memory selection. Further, the specific mechanisms by which goals could be actively maintained and bias ongoing information processing in working memory have been delineated in several computational models that have helped to clarify our understanding of this construct (38,40,41). This construct is easily measured in humans through a variety of tasks, such as various versions of complex span tasks (42), task switching tasks, variations on the continuous performance task, and others.

Clarity of the Link to a Specific Neural Circuit. Not surprisingly, *goal maintenance* in working memory has been linked to the function of DLPFC, with both empirical and theoretical work suggesting that dopaminergic inputs to DLPFC are critical (although recent work has specified an important role for both glutamate [39] and norepinephrine [43] as well). Such mechanisms have been explicitly implemented in biologically plausible computational models designed to formalize the interactions between prefrontal and basal ganglia systems in *goal maintenance* (37,38). Further, a number of functional imaging studies have shown activation of dorsolateral prefrontal cortex when individuals are required to maintain goals in working memory (44,45).

Strong Evidence of Impairment in Schizophrenia. Numerous studies have provided evidence that individuals with schizophrenia have difficulties maintaining goals in working memory. Such deficits that are present in both medicated and unmedicated individuals and at both acute and chronic stages of the illness (46,47–51). In addition, such deficits in *goal maintenance* are found in the first-degree relatives of individuals with schizophrenia (52,53), as well as in individuals with schizotypal personality disorder (54,55). Individuals with schizophrenia also show strong evidence of impairment on other tasks that may tap into *goal maintenance*, such as the Stroop task (56) and the antisaccade task (57), as do their first-degree relatives (54). Individuals with schizophrenia also show consistent evidence of impaired prefrontal activity, particularly in dorsolateral regions, during tasks that require *goal maintenance* (51,58,59). Again, the first-degree relatives of individuals with schizophrenia also show evidence of impaired prefrontal activation during *goal maintenance* (53,60). Lastly, there is evidence that such deficits in *goal maintenance* in schizophrenia are specific and cannot be accounted for by a generalized deficit (47,50–52).

Interference Control
Clarity of the Understanding of the Cognitive Mechanism. The idea that there are mechanisms involved in the protection of

information in working memory (as well as long-term memory) from interference has a long history and tradition in cognitive science. One of the ways in which this has been more commonly studied is in the domain of proactive interference, in which exposure to or processing of a set of previous stimuli interferes with the processing of subsequent stimuli (61). Proactive interference can lead to slowed responding and impaired performance in a range of domains and thus is clearly a critical aspect of human information processing (27,62). The mechanisms involved in proactive interference and *interference control* at the psychological level have been well studied (63) and formalized in computational models (64). The majority of the models of the mechanisms involved in interference control suggest that this is accomplished by the maintenance of representations of the relevant task parameters, with the addition of selection mechanisms that may compare incoming information to templates or stored representations. There are numerous paradigms available to study proactive interference in working memory (63), making this a construct easily measured in humans.

Clarity of the Link to a Specific Neural Circuit. There is a good body of research, recently summarized by both Badre and Wagner (61) and Jonides and Nee (63), implicating left ventral lateral prefrontal cortex in *interference control* in working memory. For example, a number of *functional neuroimaging studies* have shown activation of left VLPFC on task trials in which individuals have to inhibit the interfering effects of previously presented information on correct responding (22,65). Further, individuals who are better at preventing proactive interference show greater activity in left VLPFC (66). In addition, lesions to left VLPFC make individuals more susceptible to proactive interference in working memory (67), as does transcranial magnetic stimulation over left VLPFC (68).

Evidence of Impairment in Schizophrenia. Evidence has existed for deficits in *interference control* in working memory in schizophrenia as early as the seminal work of Oltmanns and Neale, which demonstrated a differential deficit in working memory span in the face of distraction compared with no distraction (69). This finding has been replicated by a number of researchers (70,71). In more recent work, Brahmbhatt and colleagues (72) have shown heightened sensitivity to proactive interference among individuals with schizophrenia in the context of an n-back working memory task. A number of other researchers have also suggested impaired distractibility in the context of working memory or attention tasks in schizophrenia (73). Interestingly, however, the literature does not suggest strong evidence for enhanced proactive interference among individuals with schizophrenia in the context of long-term or episodic

memory (74), although some studies have found increased proactive interference in episodic memory in schizophrenia (75). This may reflect the fact that in long-term memory, memory deficits for the stimuli that could cause proactive interference in individuals with schizophrenia may actually reduce the effects of proactive interference. In contrast, interference from concurrent or recently presented stimuli may still be problematic for individuals with schizophrenia.

As described earlier, the group felt that the constructs of *goal maintenance* and *interference control* met the criteria outlined as important for selecting constructs in the CNTRICs survey. Nonetheless, the group still felt that there were some open issues and concerns about these constructs. For example, there is little evidence about the relationship of these constructs to functional impairment in schizophrenia, although this absence reflects a lack of research, rather than negative results in existing research. In addition, there was some concern as to the degree to which *goal maintenance* and *interference control* could be considered dissociable constructs, given that successful *interference control* may depend, at least in part, on intact *goal maintenance*.

Constructs in Need of More Clinical Research

There were two constructs—rehearsal (active *maintenance over time*) and *updating*—that the conference participants felt had reasonable construct validity at the neural and psychological levels but needed more research to determine whether these mechanisms were impaired in schizophrenia. *Maintenance over time* has been well studied in the basic science literature. As described earlier, the phonological loop is thought to support rehearsal and maintenance of verbally coded information, whereas covert shifts of attention may help to support the maintenance of spatial information. Further, at the neural level, many models assume that active maintenance occurs through self-sustained recurrent synaptic activity (76,77). Alternatively (or in addition), active maintenance may occur through synchronous oscillations between neuronal populations within regions or across regions (76).

The issue in regard to individuals with schizophrenia is whether they show consistent evidence of impaired *maintenance over time* once initial encoding is equated and when there is no distracting information in the delay interval. Importantly, the seminal studies on spatial working memory in schizophrenia conducted by Park and colleagues used a paradigm in which an interference task occurred during the delay period (2). Thus these studies cannot be taken as evidence for impaired maintenance in the absence of distraction, because distraction may engage *interference control* mechanisms. For example, Kim (78) found no impairments in individuals with schizophrenia on maintenance only (without distraction) for either verbal or visual spatial information. However, a study by Tek (79) did equate for initial encoding and found some evidence for impaired maintenance of spatial information over an unfilled delay of 3 sec. Similar results were found in a recent study of visual-spatial memory using a 4-sec unfilled delay (80).

There is also mixed evidence as to whether the phonological loop is intact in schizophrenia. Although no cognitive task measures a single process, some working memory tasks are more dependent on the phonological loop than others. For example, some consider serial recall tasks with relatively low numbers of items (such as digit span forward, Sternberg, or Brown-Petersen paradigms) and no interference to be prototypical phonological loop tasks. According to at least some researchers, such tasks require both intact articulatory rehearsal and intact phonological storage/representations to perform successfully. A number of studies have shown that individuals with schizophrenia demonstrate relatively intact performance on digit span forward tasks, particularly when the number of items is at or below working memory span (7 ± 2) (2,50,81) and when there is no verbal interference (69). Other work has shown that individuals with schizophrenia do not show disproportionate impairment for recall of lists with phonologically similar versus dissimilar items, suggesting an intact ability to represent phonological information (82). Further, studies suggest intact serial position curves among individuals with schizophrenia (83), which is indicative of intact articulatory rehearsal mechanisms. However, a recent meta-analysis of the performance of individuals with schizophrenia did find significant impairment on digit span forward, although with a relatively small effect size compared with performance in other memory domains (84). Thus more work is needed to establish whether there is robust evidence for maintenance deficits in schizophrenia that are not confounded by encoding accuracy or interference control deficits.

The second construct judged to be in need of more clinical research was *updating* of the contents of working memory. There is a body of cognitive neuroscience research beginning to outline the mechanisms involved in *updating*. This work suggests that interactions between dorsal frontal and parietal regions may be particularly critical for updating the contents of working memory (85). In addition, there are a number of computational models that now suggest that dopaminergic signals from the basal ganglia serve as "gating" signals that indicate when to update the contents of working memory (39,86). Recently work by Gallety using event-related potentials was interpreted as reflecting deficits in *updating* (87). However, the consensus was that there was relatively little evidence as to whether individuals with schizophrenia have specific problems with *updating* the contents of working memory.

Constructs in Need of More Basic Research

There were three constructs that the conference attendees felt were in need of greater basic research to establish psychological and neural construct validity before they were ready for use in a clinical trials context. The first construct was *long-term memory reactivation*, either in terms of the mechanism by which information is moved back into working memory or in terms of the idea that working memory is simply the activated component of long-term memory, as in Cowan's model (88). Although there is indirect evidence consistent with the idea that episodic memory mechanisms interact with or contribute to paradigms that we would describe as tapping working memory (89), the specific mechanisms by which this occurs and how it interacts with the other systems involved in working memory awaits further explication.

The construct of capacity in working memory also came under hot debate. In Miller's original work, human working memory capacities were estimated to be 7 ± 2 (90). However, more recent work suggests that our capacity really has something more like a mean of 4 for both verbal and nonverbal materials (19). Using a variety of paradigms, there is good evidence to suggest that individuals with schizophrenia have reduced capacity in working memory (91). However, we do yet have a clear understanding of the mechanisms that drive capacity limitations at either the psychological or neural level. There is exciting work being conducted in computational and neurophysiological mod-

eling that may eventually clarify this question (92,93). Once we have a clearer sense of the basic mechanisms that drive capacity limitations in human working memory, we should be able to use this information to help us determine and measure why individuals with schizophrenia have added capacity limitations.

The last construct felt to be in need of more basic research was the concept of *strategic encoding* into working memory. By *strategic encoding*, we mean the ability to detect and apply spontaneously effective encoding strategies that would help maintain information in working memory and protect it from interference. The literature on episodic memory gives us good reason to believe that individuals with schizophrenia have difficulty with the spontaneous generation and application of effective encoding strategies (94,95). However, we have very little idea of the mechanisms by which individuals normally spontaneously generate and apply such encoding strategies. Further, we have little idea of the specific neural mechanisms that support the process of generating strategies, other than a general idea that the prefrontal cortex may be important in this process.

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