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

Deanna M. Barch and
Washington University

Ed Smith
Columbia University

Abstract

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 one of the core cognitive deficits in schizophrenia, making it a ripe area for translation. The current 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 CNTRICS meeting in Washington, D.C. At this meeting, the consensus was that the constructs of <u>goal maintenance</u> and <u>interference control</u> were the most ready to be pursued as part of a translational cognitive neuroscience effort in the remaining CNTRICS meetings. The group felt that the constructs of <u>long-term memory reactivation</u>, <u>capacity,</u> and *strategic encoding* were of great clinical interest, but required more basic research. In addition, the group felt that the constructs of <u>maintenance over time</u> and <u>updating</u> in working memory had growing construct validity at the psychological and neural levels, but required more research in schizophrenia before knowing whether they should be 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 [e.g., 2,3] that are associated with impairments in a range of neural mechanisms [4]. There is 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 [e.g., 7,8]. Further, individuals who share unexpressed genetic components of vulnerability to schizophrenia also experience impairments in working memory function [e.g., 9,10].

Corresponding Author: Deanna M. Barch, Ph.D., Washington University, Department of Psychology, Box 1125, One Brookings Drive, St. Louis, MO. 63130, Phone: 314-935-8729, Fax: 314-935-8790, Email: dbarch@artsci.wustl.edu.

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 manuscript 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 should note that we do not wish to put forth the results of the discussion about working memory at the first CNTRICs meeting as somehow completely authoritative. There were clearly experts in the field of working memory that 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 all of them 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 different 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 visuo-spatial 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 [e.g., 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 systems that support spatial attention processing, including the right posterior parietal cortex [17], part of the dorsal attention system [e.g., 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].

There are a number of different processes that are often referred to as being part of the central executive, including those involved in the manipulation of information being stored in the domain specific buffers, protection from interference due to competing information, 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 (2003) 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 as compared to 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 in 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 in the focus of attention in working memory should use the same systems used to initially process or store information in long term memory. Work by D'Esposito and colleagues 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), while the maintenance of house representations differentially activated the parahippocampal place area [23] [see also 24,25].

In a related vein, Engle and colleagues have emphasized the centrality of *goal maintenance* and *interference control* in working memory [e.g., 28,29]. 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 have argued that this conceptualization of working memory helps to explain why individual differences in working memory capacity explain performance on tasks such as the antisaccade and the Stroop, which also require *goal maintenance* [30,31].

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 [32] have demonstrated that working memory function is impaired in non-human primates following 6-hydroxy-dopamine lesions in prefrontal cortex [33], or administration of dopamine antagonists [34]. 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, se [4]). A number of researchers have postulated specific computational roles for dopamine in working memory [e.g., 37,38]. Braver and colleagues 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 [39,40]. In a similar vein, Frank and O'Reilly have argued that basal ganglia mediated dopamine signals serve to update representations in working memory [41]. Durstewitz has elaborated models in which NMDA activity interacts with dopamine to modulate recurrent activity in neural networks thought to support working memory representations [42].

After a formal presentation on mechanisms involved in working memory given by Ed Smith, the attendees of the CNTRICS meeting engaged in a discussion as to 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 above, 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 of protecting this information from interference from competing information [e.g., 28,29]. 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 memory task used by Luck and colleagues, the goal representation might include information about the task features (color, orientation, etc.) relevant for memory selection [19]. Further, the specific mechanisms by which goals could be actively maintained and bias ongoing information processing in working memory have been delineated in several different computational models that have helped to clarify our understanding of this construct [e.g., 41,44,45]. This construct is **easily measured in humans** through a variety of tasks, such as various versions of complex span tasks [46], task switching tasks, variations on the continuous performance task, etc.

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 (though recent work has specified an important role for both glutamate [42] and norepinephrine [47] 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* [e.g., 40,41]. Further, a number of **functional imaging studies** have shown activation of dorsolateral prefrontal cortex when individuals are required to maintain goals in working memory [e.g., 48,49].

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 [e.g., 50,51–55]. In addition, such deficits in _goal maintenance_ are found in the first-degree relatives of individuals with schizophrenia [56,57], as well as in individuals with schizotypal personality disorder [58,59]. Individuals with schizophrenia also show strong evidence of impairment on other tasks that may tap into _goal maintenance_, such as the Stroop task [e.g., 60] and the antisaccade task [e.g., 61], as do their first degree relatives [58] Individuals with schizophrenia also show consistent evidence of impaired prefrontal activity, particularly in dorsolateral regions, during tasks that require _goal maintenance_ [e.g., 55,62,63]. Again, the first-degree relatives of individuals with schizophrenia also show evidence of impaired prefrontal activation during _goal maintenance_ [57,64]. Lastly, there is evidence that such deficits in _goal maintenance_ in schizophrenia are specific, and cannot be accounted for by a generalized deficit [e.g., 50,53–55].

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 interference with the processing of subsequent stimuli [65]. 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 [28,66]. The mechanisms involved in proactive interference and _interference control_ at the psychological level have been well studied [e.g., 67] and formalized in computational models [68]. 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 [67], making this a construct **easily measured in humans.**

Clarity of the link to a specific neural circuit: There is a nice body of research, recently summarized by both Badre and Wagner [65] and Jonides and Nee [67], 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 ventral lateral prefrontal cortex on task trials in which individuals have to inhibit the interfering effects of previously presented information on correct responding [e.g., 22,69]. Further, individuals who are better at preventing proactive interference show greater activity in left ventrolateral prefrontal cortex [70]. In addition, lesions to left ventrolateral prefrontal cortex make individuals more susceptible to proactive interference in working memory [71], as does TMS over left ventrolateral prefrontal cortex [72].

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 as compared to no distraction [73]. This finding has been replicated by a number of researchers [e.g., 74,75]. In more recent work, Brahmbhatt and colleagues 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 [e.g., 76]. 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 [e.g., 77], though some studies have found increased proactive interference in episodic memory in schizophrenia [78]. 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 above, 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/concerns about these constructs. For example, there is little evidence about the relationship of these constructs to functional impairment in schizophrenia, though 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_ can 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 which they felt 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 above, the phonological loop is thought to support rehearsal and maintenance of verbally coded information, while 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 via self-sustained recurrent synaptic activity [e.g., 79,80]. Alternatively (or in addition), active maintenance may occur via synchronous oscillations between neuronal populations within regions or across regions [79].

The issue in regards 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 [e.g., 2]. Thus, these studies cannot be taken as evidence for impaired maintenance in the absence of distraction, as distraction may engage _interference control_ mechanisms. For example, Kim found no impairments in individuals with schizophrenia on maintenance only (without distraction) for either verbal or visual spatial information [81]. However, a study by Tek did equate for initial encoding, and found some evidence for impaired maintenance of spatial information over an unfilled delay of 3 seconds [82]. Similar results were found in a recent study of visual-spatial memory using a 4 second unfilled delay [83].

There is also mixed evidence as to whether the phonological loop is intact in schizophrenia. Though no cognitive task measures a single process, some working memory tasks are more dependent on the phonological loop than others. For example, serial recall tasks with relatively low numbers of items (such as digit span forward, Sternberg or Brown-Petersen paradigms) and no interference are considered by some to be prototypical phonological loop tasks. According to at least some researchers, such tasks require both intact articulatory rehearsal and intact phonological storage/representations to perform successfully. 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) [e.g., 2,54,84] and when there is no verbal interference [e.g., 73]. 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 [85]. Further, studies suggest intact serial position curves among individuals with schizophrenia [86], 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, though with a relatively small effect size compared to performance in other memory domains [88]. Thus, more work is needed to establish whether or not 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 [e.g., 89]. 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 [40,90]. Recently work by Galletly using ERPs was interpreted as reflecting deficits in *updating* [91]. However, the consensus was that there was relatively little evidence as to whether or not 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 [92]. 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[27], 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 plus or minus 2 [93]. However, more recent work suggests that our capacity really has something more like a mean of 4 for both verbal and non-verbal materials [e.g., 19]. Using a variety of paradigms, there is very good evidence to suggest that individuals with schizophrenia have reduced capacity in working memory [e.g., 94]. 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 modeling that may eventually clarify this question [e.g., 95][96]. 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 spontaneously detect and apply 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 [e.g., 97,98]. However, we really 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 for this process.

References

1. D'Esposito M. From cognitive to neural models of working memory. Philosophical Transactions of the Royal Society: Biological Sciences 2007;362(1481):761–72. [PubMed: 17400538]

2. Park S, Holzman PS. Schizophrenics show spatial working memory deficits. Archives of General Psychiatry 1992;49(12):975–982. [PubMed: 1449384]

3. Lee J, Park S. Working memory impairments in schizophrenia: a meta-analysis. Journal of Abnormal Psychology 2005;114(4):599–611. [PubMed: 16351383]

4. Barch, DM. The cognitive neuroscience of schizophrenia. In: Cannon, T.; Mineka, S., editors. Annual Review of Clinical Psychology. American Psychological Association; Washington, D.C.: 2005. p. 321-353.

5. Niendam TA, Bearden CE, Rosso IM, Sanchez LE, Hadley T, Nuechterlein KH, Cannon TD. A prospective study of childhood neurocognitive functioning in schizophrenic patients and their siblings. Am J Psychiatry 2003;160(11):2060–2. [PubMed: 14594759]

6. Cornblatt B, Obuchowski M, Roberts S, Pollack S, Erlenmeyer-Kimling L. Cognitive and behavioral precursors of schizophrenia. Developmental Psychopathology 1999;11(3):487–508.

7. Heinrichs RW, Goldberg JO, Miles AA, McDermid Vaz S. Predictors of medication competence in schizophrenia patients. Psychiatry Research 2008;157(1–3):47–52. [PubMed: 17897721]

8. Cervellione KL, Burdick KE, Cottone JG, Rhinewine JP, Kumra S. Neurocognitive deficits in adolescents with schizophrenia: longitudinal stability and predictive utility for short-term functional outcome. Journal of the American Academy of Child and Adolescent Psychiatry 2007;46(7):867–78. [PubMed: 17581451]

9. Thermenos HW, Seidman LJ, Breiter H, Goldstein JM, Goodman JM, Poldrack R, Faraone SV, Tsuang MT. Functional magnetic resonance imaging during auditory verbal working memory in nonpsychotic relatives of persons with schizophrenia: A pilot study. Biological Psychiatry 2004;55:490–500. [PubMed: 15023577]

10. Glahn DC, Therman S, Manninen M, Huttunen M, Kaprio J, Lonnqvist J, Cannon TD. Spatial working memory as an endophenotype for schizophrenia. Biological Psychiatry 2003;53(7):624–6. [PubMed: 12679242]

11. Baddeley, AD. Working memory. New York: Oxford University Press; 1986.

12. Baddeley AD. The episodic buffer: A new component of working memory? Trends in Cognitive Science 2000;4:417–423.

13. Fiez JA, Raife EA, Balota DA, Schwarz JP, Raichle ME, Petersen SE. A positron emission tomography study of the short-term maintenance of verbal information. The Journal of Neuroscience 1996;16(2)(January 15):808–822. [PubMed: 8551361]

14. Chein JM, Fiez JA. Dissociation of verbal working memory system components using a delayed serial recall task. Cereb Cortex 2001;11(11):1003–14. [PubMed: 11590110]

15. Vallar G, Di Betta AM, Silveri MC. The phonological short-term store-rehearsal system: patterns of impairment and neural correlates. Neuropsychologia 1997;35(6):795–812. [PubMed: 9204486]

16. Awh W, Jonides J, Reuter-Lorenz PA. Rehearsal in spatial working memory. Journal of Experimental Psychology 1998;24(3):780–790. [PubMed: 9627416]

17. Curtis CE V, Rao Y, D'Esposito M. Maintenance of spatial and motor codes during oculomotor delayed response tasks. J Neurosci 2004;24(16):3944–52. [PubMed: 15102910]

18. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nature Reviews Neuroscience 2002;3(3):201–15.

19. Luck SJ, Vogel EK. The capacity of visual working memory for features and conjunctions. Nature 1997;390(6657):279–81. [PubMed: 9384378]

20. Smith EE, Jonides J. Storage and executive processes in the frontal lobes. Science 1999;283:1657–1661. [PubMed: 10073923]

21. Jonides J, Smith E, Marshuetz C, Koeppe R, Reuter-Lorenz PA. Inhibition in verbal working memory revealed by brain activation. Proceedings of the National Academy of Sciences USA 1998;95:8410–8413.

22. D'Esposito, M.; Postle, BR.; Jonides, J.; Smith, EE. The neural substrate and temporal dynamics of interference effects in working memory as revealed by event-related functional MRI; Proceedings of the National Academy of Sciences USA; 1999. p. 7514-7519.

23. Ranganath C, DeGutis J, D'Esposito M. Category-specific modulation of inferior temporal activity during working memory encoding and maintenance. Brain Research Cognitive Brain Research 2004;20(1):37–45. [PubMed: 15130587]

24. Ranganath C, Cohen MX, Dam C, D'Esposito M. Inferior temporal, prefrontal, and hippocampal contributions to visual working memory maintenance and associative memory retrieval. Journal of Neuroscience 2004;24(16):3917–25. [PubMed: 15102907]

25. Druzgal TJ, D'Esposito M. Dissecting contributions of prefrontal cortex and fusiform face area to face working memory. Journal of Cognitive Neuroscience 2003;15(6):771–84. [PubMed: 14511531]

26. Mechelli A, Price CJ, Friston KJ, Ishai A. Where bottom-up meets top-down: neuronal interactions during perception and imagery. Cerebral Cortex 2004;14(11):1256–65. [PubMed: 15192010]

27. Ranganath C. Working memory for visual objects: complementary roles of inferior temporal, medial temporal, and prefrontal cortex. Neuroscience 2006;139(1):277–89. [PubMed: 16343785]

28. Kane MJ, Engle RW. Working-memory capacity, proactive interference, and divided attention: limits on long-term memory retrieval. J Exp Psychol Learn Mem Cogn 2000;26(2):336–58. [PubMed: 10764100]

29. Engle, RW.; Kane, MJ. Executive attention, working memory capacity and a two-factor theory of cognitive control. In: Ross, B., editor. The psychology of learning and motivation. Elsevier; New York: 2004.

30. Unsworth N, Schrock JC, Engle RW. Working memory capacity and the antisaccade task: individual differences in voluntary saccade control. Journal of Experimental Psychology: Learning, Memory and Cognition 2004;30(6):1302–21.

31. Kane MJ, Engle RW. Working-memory capacity and the control of attention: the contributions of goal neglect, response competition, and task set to Stroop interference. J Exp Psychol Gen 2003;132(1):47–70. [PubMed: 12656297]

32. Goldman-Rakic PS, Muly EC, Williams GV. D1 receptors in prefrontal cells and circuits. Brain Research Reviews 2000;31:295–301. [PubMed: 10719156]

33. Brozoski TJ, Brown RM, Rosvold HE, Goldman PS. Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. Science 1979;205(31):929–931. [PubMed: 112679]

34. Sawaguchi T, Goldman-Rakic PS. The role of D1-dopamine receptor in working memory: Local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. Journal of Neurophysiology 1994;71(2):515–528. [PubMed: 7909839]

35. Williams GV, Goldman-Rakic PS. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. Nature 1995;376(17)(August):572–575. [PubMed: 7637804]

36. Arnsten AF, Cai JX, Murphy BL, Goldman-Rakic PS. Dopamine D1 receptor mechanisms in the cognitive performance of young adult and aged monkeys. Psychopharmacology 1994;116:143–151. [PubMed: 7862943]

37. Durstewitz D, Seamans JK, Sejnowski TJ. Dopamine-mediated stabilization of delay-period activity in a network model of prefrontal cortex. Journal of Neurophysiology 2000;83(3):1733–1750. [PubMed: 10712493]

38. Cohen JD, Servan-Schreiber D. Context, cortex and dopamine: A connectionist approach to behavior and biology in schizophrenia. Psychological Review 1992;99(1):45–77. [PubMed: 1546118]

39. Braver TS, Cohen JD. Working memory, cognitive control, and the prefrontal cortex: Computational and empirical studies. Cognitive Processing 2001;2:25–55.

40. Braver, TS.; Cohen, JD. On the control of control: The role of dopamine in regulating prefrontal function and working memory. In: Monsell, S.; Driver, J., editors. Attention and Performance XVIII. MIT Press; Cambridge, MA: 2000. p. 713-738.

41. Hazy TE, Frank MJ, O'Reilly R C. Towards an executive without a homunculus: computational models of the prefrontal cortex/basal ganglia system. Philosophical Transactions of Royal Society of London B Biological Sciences 2007;362(1485):1601–13.

42. Durstewitz D, Gabriel T. Dynamical basis of irregular spiking in NMDA-driven prefrontal cortex neurons. Cereb Cortex 2007;17(4):894–908. [PubMed: 16740581]

43. Eenshuistra RM, Ridderinkhof KR, Weidema MA, van der Molen MW. Developmental changes in oculomotor control and working-memory efficiency. Acta Psychol (Amst) 2007;124(1):139–58. [PubMed: 17113020]

44. Braver, TS.; Cohen, JD.; Servan-Schreiber, D. A computational model of prefrontal cortex function. In: Touretzky, DS.; Tesauro, G.; Leen, TK., editors. Advances in Neural Information Processing Systems. MIT Press; Cambridge, MA: 1995. p. 141-148.

45. Anderson JR, Reder LM, Lebiere C. Working memory: Activation limiations on retrieval. Cognitive Psychology 1996;30(3):221–256. [PubMed: 8660785]

46. Conway AR, Kane MJ, Bunting MF, Hambrick DZ, Wilhelm O, Engle RW. Working memory span tasks: A methodological review and user's guide. Psychon Bull Rev 2005;12(5):769–86. [PubMed: 16523997]

47. Arnsten AF. Adrenergic targets for the treatment of cognitive deficits in schizophrenia. Psychopharmacology (Berl) 2004;174(1):25–31. [PubMed: 15205875]

48. Passingham D, Sakai K. The prefrontal cortex and working memory: physiology and brain imaging. Curr Opin Neurobiol 2004;14(2):163–8. [PubMed: 15082320]

49. Barch DM, Braver TS, Nystom LE, Forman SD, Noll DC, Cohen JD. Dissociating working memory from task difficulty in human prefrontal cortex. Neuropsychologia 1997;35(10):1373–1380. [PubMed: 9347483]

50. Stratta P, Daneluzzo E, Bustini M, Casacchia M, Rossi A. Schizophrenic deficits in the processing of context. Archives of General Psychiatry 1998;55:186–187. [PubMed: 9477937]

51. Servan-Schreiber D, Cohen JD, Steingard S. Schizophrenic deficits in the processing of context: A test of a theoretical model. Archives of General Psychiatry 1996;53(Dec):1105–1113. [PubMed: 8956676]

52. Lee J, Park S. The role of stimulus salience in CPT-AX performance of schizophrenia patients. Schizophrenia Research 2006;81(2–3):191–7. [PubMed: 16226875]

53. Javitt DC, Shelley A, Silipo G, Lieberman JA. Deficits in auditory and visual context-dependent processing in schizophrenia. Archives of General Psychiatry 2000;57:1131–1137. [PubMed: 11115326]

54. Cohen JD, Barch DM, Carter C, Servan-Schreiber D. Context-processing deficits in schizophrenia: Converging evidence from three theoretically motivated cognitive tasks. Journal of Abnormal Psychology 1999;108:120–133. [PubMed: 10066998]

55. Barch DM, Carter CS, Braver TS, McDonald A, Sabb FW, Noll DC, Cohen JD. Selective deficits in prefrontal cortex regions in medication naive schizophrenia patients. Archives of General Psychiatry 2001;50:280–288. [PubMed: 11231835]

56. MacDonald AW, Pogue-Geile MF, Johnson MK, Carter CS. A specific deficit in context processing in the unaffected siblings of patients with schizophrenia. Archives of General Psychiatry 2003;60:57–65. [PubMed: 12511173]

57. Delawalla Z, Csernansky JG, Barch DM. Prefrontal Cortex Function in Nonpsychotic Siblings of Individuals with Schizophrenia. Biological Psychiatry. 2007

58. Calkins ME, Curtis CE, Iacono WG, Grove WM. Antisaccade performance is impaired in medically and psychiatrically healthy biological relatives of schizophrenia patients. Schizophr Res 2004;71(1):167–78. [PubMed: 15374584]

59. Barch DM, Mitropoulou V, Harvey PD, New AS, Silverman JM, Siever LJ. Context-processing deficits in schizotypal personality disorder. Journal of Abnormal Psychology 2004;113(4):556–68. [PubMed: 15535788]

60. Chen EYH, Wong AWS, Chen RYL, Au JWY. Stroop interference and facilitation effects in first-episode schizophrenia patients. Schizophrenia Research 2001;48:29–44. [PubMed: 11278152]

61. Ettinger U, Picchioni M, Hall MH, Schulze K, Toulopoulou T, Landau S, Crawford TJ, Murray RM. Antisaccade performance in monozygotic twins discordant for schizophrenia: the Maudsley twin study. Am J Psychiatry 2006;163(3):543–5. [PubMed: 16513882]

62. Van Snellenberg JX I, Torres J, Thornton AE. Functional neuroimaging of working memory in schizophrenia: task performance as a moderating variable. Neuropsychology 2006;20(5):497–510. [PubMed: 16938013]

63. Tu PC, Yang TH, Kuo WJ, Hsieh JC, Su TP. Neural correlates of antisaccade deficits in schizophrenia, an fMRI study. J Psychiatr Res 2006;40(7):606–12. [PubMed: 16842821]

64. MacDonald AW 3rd, Becker TM, Carter CSn. Functional magnetic resonance imaging study of cognitive control in the healthy relatives of schizophrenia patients. Biological Psychiatry 2006;60 (11):1241–9. [PubMed: 16945345]

65. Badre D, Wagner AD. Left ventrolateral prefrontal cortex and the cognitive control of memory. Neuropsychologia 2007;45(13):2883–901. [PubMed: 17675110]

66. Anderson, MC.; Neely, JH. Interference and inhibition in memory retrieval. In: Bjork, EL.; Bjork, RA., editors. Memory. Handbook of performance and cognition. Academic Press; San Diego, CA: 1996. p. 237-313.

67. Jonides J, Nee DE. Brain mechanisms of proactive interference in working memory. Neuroscience 2006;139(1):181–93. [PubMed: 16337090]

68. Badre D, Wagner AD. Computational and neurobiological mechanisms underlying cognitive flexibility. Proc Natl Acad Sci U S A 2006;103(18):7186–91. [PubMed: 16632612]

69. Nee DE, Jonides J, Berman MG. Neural mechanisms of proactive interference-resolution. Neuroimage 2007;38(4):740–51. [PubMed: 17904389]

70. Bunge SA, Ochsner KN, Desmond JE, Glover GH, Gabrieli JD. Prefrontal regions involved in keeping information in and out of mind. Brain 2001;124(Pt 10):2074–86. [PubMed: 11571223]

71. Thompson-Schill SL, Jonides J, Marshuetz C, Smith EE, D'Esposito M, Kan IP, Knight RT, Swick D. Effects of frontal lobe damage on interference effects in working memory. Cogn Affect Behav Neurosci 2002;2(2):109–20. [PubMed: 12455679]

72. Feredoes E, Tononi G, Postle BR. Direct evidence for a prefrontal contribution to the control of proactive interference in verbal working memory. Proc Natl Acad Sci U S A 2006;103(51):19530–4. [PubMed: 17151200]

73. Oltmanns TF, Neale JM. Schizophrenia performance when distractors are present: Attentional deficit or differential task difficulty? Journal of Abnormal Psychology 1975;84(3):205–209. [PubMed: 1133249]

74. Harvey PD, Pedley M. Auditory and visual distractibility in schizophrenia: Clinical and medication status correlations. Schizophrenia Research 1989;2:295–300. [PubMed: 2487169]

75. Finkelstein JRJ, Cannon TD, Gur RE, Gur RC. Attentional dysfunction in neuroleptic-naive and neuroleptic-withdrawn schizophrenic patients and their siblings. Journal of Abnormal Psychology 1997;106:203–212. [PubMed: 9131840]

76. Addington J, Addington D, Gasbarre L. Distractibility and symptoms in schizophrenia. J Psychiatry Neurosci 1997;22(3):180–4. [PubMed: 9183116]

77. Hill SK, Beers SR, Kmiec JA, Keshavan MS, Sweeney JA. Impairment of verbal memory and learning in antipsychotic-naive patients with first-episode schizophrenia. Schizophrenia Research 2004;68(2–3):127–36. [PubMed: 15099597]

78. Randolph C, Gold JM, Carpenter CJ, Goldberg TE, Weinberger DR. Release from proactive interference: determinants of performance and neuropsychological correlates. J Clin Exp Neuropsychol 1992;14(5):785–800. [PubMed: 1474146]

79. Wang XJ. Synaptic reverberation underlying mnemonic persistent activity. Trends Neurosci 2001;24 (8):455–63. [PubMed: 11476885]

80. Cohen, JD.; Huston, TA. Progress in the use of interactive models for understanding attention and performance. In: Umilta, C.; Moscovitch, M., editors. Attention and Performance. MIT Press; Cambridge, MA: 1992. p. 453-476.

81. Kim J, Glahn DC, Nuechterlein KH, Cannon TD. Maintenance and manipulation of information in schizophrenia: further evidence for impairment in the central executive component of working memory. Schizophr Res 2004;68(2–3):173–87. [PubMed: 15099601]

82. Tek C, Gold JM, Blaxton T, Wilk C, McMahon RP, Buchanan RW. Visual perceptual and working memory impairments in schizophrenia. Archives of General Psychiatry 2002;2002(59)

83. Badcock JC, Badcock DR, Read C, Jablensky A. Examining encoding imprecision in spatial working memory in schizophrenia. Schizophr Res. 2007

84. Fitzgerald D, Lucas S, Redoblado MA, Winter V, Brennan J, Anderson J, Harris A. Cognitive functioning in young people with first episode psychosis: relationship to diagnosis and clinical characteristics. Aust N Z J Psychiatry 2004;38(7):501–10. [PubMed: 15255822]

85. Elvevag B, Weinberger DR, Goldberg TE. The phonological similarity effect in short-term memory serial recall in schizophrenia. Psychiatry Res 2002;112(1):77–81. [PubMed: 12379453]

86. Wexler BE, Donegan N, Stevens AA, Jacob SA. Deficits in language-mediated mental operations in patients with schizophrenia. Schizophr Res 2002;53(3):171–9. [PubMed: 11738530]

87. Stevens AA, Goldman-Rakic PS, Gore JC, Fulbright RK, Wexler R. Cortical dysfunction in schizophrenia during auditory word and tone working memory demonstrated by functional magnetic resonance imaging. Archvies of General Psychiatry 1998;55:1097–1103.

88. Aleman A, Hij R, de Haan EH, Kahn RS. Memory impairment in schizophrenia: A meta-analysis. American Journal of Psychiatry 1999;156(9):1358–1366. [PubMed: 10484945]

89. Tan HY, Chen Q, Goldberg TE, Mattay VS, Meyer-Lindenberg A, Weinberger DR, Callicott JH. Catechol-O-methyltransferase Val158Met modulation of prefrontal-parietal-striatal brain systems during arithmetic and temporal transformations in working memory. J Neurosci 2007;27(49):13393–401. [PubMed: 18057197]

90. Frank MJ, Loughry B, O'Reilly RC. Interactions between frontal cortex and basal ganglia in working memory: A computational model. Cognitive, Affective, & Behavioral Neuroscience 2001;1(2):137–160.

91. Galletly CA, MacFarlane AS, Clark CR. Impaired updating of working memory in schizophrenia. Int J Psychophysiol 2007;63(3):265–74. [PubMed: 17234290]

92. Cowan N. Evolving conceptions of memory storage, selective attention, and their mutual constraints within the human information-processing system. Psychological Bulletin 1988;104:163–191. [PubMed: 3054993]

93. Miller GA. The magical number seven, plus or minus two: Some limits on our capacity for processing information. Psychological Review 1956;63:81–97. [PubMed: 13310704]

94. Gold JM, Fuller RL, Robinson BM, McMahon RP, Braun EL, Luck SJ. Intact attentional control of working memory encoding in schizophrenia. J Abnorm Psychol 2006;115(4):658–73. [PubMed: 17100524]

95. Koene RA, Hasselmo ME. Consequences of parameter differences in a model of short-term persistent spiking buffers provided by pyramidal cells in entorhinal cortex. Brain Res. 2007

96. Haarmann H, Usher M. Maintenance of semantic information in capacity-limited item short-term memory. Psychon Bull Rev 2001;8(3):568–78. [PubMed: 11700909]

97. Ragland JD, Gur RC, Valdez JN, Loughead J, Elliott M, Kohler C, Kanes S, Siegel SJ, Moelter ST, Gur RE. Levels-of-processing effect on frontotemporal function in schizophrenia during word encoding and recognition. American Journal of Psychiatry 2005;162(10):1840–8. [PubMed: 16199830]

98. Bonner-Jackson A, Haut K, Csernansky JG, Barch DM. The influence of encoding strategy on episodic memory and cortical activity in schizophrenia. Biological Psychiatry 2005;58:47–55. [PubMed: 15992522]

99. Postle BR. Working memory as an emergent property of the mind and brain. Neuroscience 2006;139(1):23–38. [PubMed: 16324795]

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).