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Review article

Working memory and long-term memory deficits in schizophrenia: Is there a common substrate?

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ABSTRACT

Patients with schizophrenia exhibit substantial deficits in both working memory (WM) and long-term memory (LTM) tasks. While these two forms of memory are generally viewed as distinct, recent evidence from healthy subjects has challenged the robustness of the double-dissociation between these two types of memory. In light of an emerging view of WM and LTM as being subserved by a largely overlapping network of brain regions, it is possible that WM and LTM deficits in patients with schizophrenia share a common neurobiological substrate. This review revisits the functional neuroimaging literature on both WM and LTM in patients with schizophrenia with these considerations in mind, and reveals a number of commonalities in research findings in both literatures. While there is a paucity of direct evidence bearing on whether patient deficits in these tasks arise from a common functional abnormality, the available literature is consistent with the hypothesis that these deficits have the same origin.

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1. Introduction

A substantial literature has demonstrated impairments of long-term memory (LTM) and working memory (WM) in schizophrenia (SCZ), and WM has been identified as a major target for attempts to improve cognition in SCZ (Barch and Smith, 2008). Meta-analyses indicate that the performance of patients, compared with controls, on LTM recall is somewhat greater than a standard deviation worse (on the order of 1.1–1.5 standard deviations; Heinrichs and Zakzanis, 1998; Aleman et al., 1999), performance on LTM recognition is closer to 0.6 standard deviations worse (Aleman et al., 1999), and performance on WM tasks is about one standard deviation worse (Lee and Park, 2005) and is impaired regardless of stimulus modality (Gooding and Tallent, 2004). There has been considerable interest in these deficits, because both WM and LTM have been shown to be more strongly related to functional outcome in SCZ than disease symptoms and a number of other neuropsychological measures (Green, 1996, 1998), and there is abundant evidence of both prefrontal (e.g. Akbarian et al., 1993; Selemon et al., 1995; Akbarian et al., 1996) and medial temporal lobe pathology (e.g. Arnold et al., 1991; Conrad et al., 1991; Weinberger and Lipska, 1995) in the disorder.

With rare exceptions (e.g. Barch et al., 2002), work investigating LTM dysfunction in SCZ has proceeded independently from work on WM. However, an emerging view from cognitive neuroscience challenges the notion that WM and LTM are truly dissociable constructs (e.g., Ranganath and Blumenfeld, 2005; Jonides et al., 2008), arguing instead that WM and LTM use the same representations (a view also

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presented by Cowan, 1999, 2000), and that the encoding mechanism is the same for both. In light of this view, and the fact that patients with SCZ show substantial deficits in both WM and LTM tasks, it may be useful to consider the available data on the neural correlates of WM and LTM task performance in patients with SCZ to determine whether a single functional abnormality may give rise to deficits in both types of task. While direct evidence suggesting that WM and LTM deficits in SCZ arise from a common neurophysiological substrate is scarce, this may simply reflect the fact that very few studies have addressed this issue directly. Indeed, if there is a substantive overlap in the neural circuitry supporting both WM and LTM, in the absence of evidence demonstrating distinct WM and LTM deficits in patients with SCZ, then the parsimonious view is one that posits a common substrate for both.

With this goal in mind, following a discussion of current views on WM and LTM in cognitive neuroscience and on cognitive impairment in SCZ, a brief review of functional neuroimaging work on LTM and WM in SCZ will be presented, concluding with a discussion of evidence suggesting that, indeed, LTM and WM deficits in patients with SCZ share a common origin.

2. Working memory and long-term memory

In general, the terms “working memory” (WM) and “long-term memory” (LTM) are used in this review to refer to tasks employed in functional imaging studies of patients with SCZ, rather than to specific theoretical constructs per se-although, of course, tasks are designated as WM or LTM tasks based on psychological theory about what these two forms of memory entail. The two most obvious distinctions between WM and LTM tasks are a) the delay between target and probe items, with delays being on the order of seconds for WM tasks and on the order of minutes or hours for LTM tasks, and b) the need for deployment of cognitive control or executive processes (e.g. updating and monitoring) in many WM tasks. However, a substantial subset of tasks described as WM tasks in the literature, for example, Sternberg-like item recognition tasks and delayed match-to-sample tasks, do not require active manipulation of the contents of memory. WM, as used here, includes such tasks, although it is acknowledged that many WM tasks require cognitive processing beyond that needed to simply maintain information over a short delay.

Several authors have now proposed that there is a great degree of commonality, or even identity, between information held in WM and LTM. While this claim appears to contradict the classic double-dissociation between LTM and WM in patients with medial temporal lobe (MTL) damage and lesions of perisylvian cortex (respectively), Ranganath and Blumenfeld (2005) summarize evidence demonstrating that patients with medial temporal lobe lesions do show deficits on WM tasks if the tasks utilize novel materials, and patients with left perisylvian lesions show deficits in LTM if the LTM tasks involve semantically meaningless verbal materials. In this view, the MTL is thought to be critically involved in learning novel relations between, or binding, features or items (Jonides et al., 2008). Thus, the clear role of the MTL in episodic memory arises not from the longer time-scale over which events are remembered (as compared to the time-scale in WM tasks), but rather because episodic memory necessarily requires the learning of relationships between items and events and the context in which they occurred. In this light it is interesting to note that patients with SCZ have been shown to have a specific deficit in binding the relations between features (object and location) in a WM task (Burglen et al., 2004). On the other hand, the deficit in WM tasks observed in patients with lesions of perisylvian cortex arises not because perisylvian cortex is a short-term memory buffer distinct from LTM representations (e.g., the phonological loop in Baddeley's WM model; Baddeley, 2002), but rather because it is necessary for representing the non-semantic phonological information (e.g., non-words) typically employed in the WM tasks used to assess these patients; as mentioned above, these patients *do* show deficits in LTM tasks when the same materials are used (Ranganath and Blumenfeld, 2005).

In addition, considerable evidence indicates that the MTL is necessary for the short-term maintenance of novel material (see Ranganath and Blumenfeld, 2005; Ranganath and D'Esposito, 2005; Jonides et al., 2008; Nee et al., 2008 for relevant reviews). These authors propose that when novel information that has no available representation in LTM is presented and must be remembered over a delay, the relations between individual elements are maintained by the MTL; critically, this is thought to be the same mechanism by which LTM encoding occurs (Jonides et al., 2008). On the other hand, when information is presented in a WM task that *does* have a representation in LTM (i.e., the information is not novel), dorsolateral prefrontal cortex (DLPFC) directs attention to internal representations of the information in posterior cortices (Curtis and D'Esposito, 2003)—the same regions of cortex that subserve LTM representations. Thus, the view of LTM and WM representations outlined here can be contrasted with Baddeley's model of WM, which posits separate modality-specific stores for information held in WM. On the other hand, the view outlined above is in close agreement with Cowan's model of WM (Cowan, 1999, 2000), which maintains that the information held in WM is an attended subset of the information available in LTM, and the nature of the representation is the same in both cases.

Finally, there is evidence to suggest that a region of mid-left inferior frontal gyrus (roughly Brodmann's area 45) is involved in post-retrieval selection in both WM and LTM (Badre and Wagner, 2007). Badre and Wagner argue that during LTM recall some of the information retrieved from LTM is not task-relevant, and so the appropriate information to guide responding must be selected from the information that was retrieved. In WM, this region has been shown to be critically involved in resolving proactive interference from recent trials (Badre and Wagner, 2005; Jonides and Nee, 2006); that is, when a negative probe that was part of the target set on a preceding trial is presented (i.e., a probe in a WM task to which the correct answer on the current trial would be “no,” but to which the correct answer on the preceding trial would have been “yes”), episodic information relevant to the preceding trial is automatically retrieved, and the participant must select between multiple active representations (of the current and preceding trial) in order to respond appropriately. Thus, post-retrieval selection can be seen to be a cognitive process deployed during the performance of both WM and LTM tasks.

In summary, the view taken here is that a large subset of the cognitive processes engaged by WM and LTM tasks are the same. First, the information ‘store’ is presumed to be posterior cortices that represent the information being remembered (words, visual forms, spatial locations, etc.), irrespective of task type. Second, sustained activation or ‘refreshing’ of these posterior representations (that is, maintenance in WM) is mediated by DLPFC (Miller et al., 1996; Raye et al., 2002; Curtis and D'Esposito, 2003; Johnson et al., 2005; Ranganath, 2006) for both task types, based on the assumption that conscious recall from LTM necessarily involves bringing that information into WM; additional regions may also become involved depending on the type of material in memory, such as Broca's area for verbal stimuli and the frontal eye fields for spatial stimuli. Third, stimulus encoding is mediated by the MTL in so far as it binds disparate elements of the stimulus together, and binds the stimulus to the present context (i.e. that a given word was seen by a participant in the present experimental context or, in the case of WM tasks, during the present trial), at least when novel materials (Ranganath and D'Esposito, 2001) or spatial locations (Piekema et al., 2006) are used in WM tasks. Finally, both WM and LTM require some degree of post-retrieval selection in order to guide appropriate responding.

It is important to realize, however, that there are additional cognitive processes not necessarily shared between WM and LTM tasks. For example, LTM retrieval is thought to involve a controlled retrieval process mediated by the anterior left inferior frontal gyrus (Wheeler and Buckner, 2003; Badre and Wagner, 2007) that is presumably not engaged in WM tasks. In addition, many WM tasks

(e.g., *n*-back) require manipulation, updating, and monitoring of the contents of WM in a manner that is typically not required in LTM tasks. Thus, depending on the specific demands of the task, varying degrees of overlap in the neural implementation of WM and LTM may be expected. Indeed, rather than specific 'systems' or 'networks' that subserve the performance of specific tasks, it may be that distinct regions of cortex subserve discrete, modular functions in cognition that can be flexibly brought to bear depending on the demands of the current context (Van Snellenberg and Wager, 2009). Thus, far from arguing that WM and LTM are somehow "the same," it is instead proposed that there is a substantial overlap in the brain regions that subserve performance on the tasks typically given these labels in the literature. Consequently, while *some* of the double-dissociation between WM and LTM in patients with bilateral MTL lesions (e.g., patient H.M.) and patients with Parkinson's disease (Sullivan and Sagar, 1991) can be attributed to differences in task materials (non-novel items in the WM task), and some observed differences (i.e. impaired WM performance in Parkinson's patients) probably reflect true differences in the cognitive processes brought to bear in these tasks. Similarly, the observation that the long-term, but not short-term, recency effect is intact in temporal lobe epilepsy patients (Bengner and Malina, 2007) can be explained by the fact that items still active in WM do not *require* an intact MTL in order to be remembered.

3. Models of cognitive impairment in SCZ

The dominant models of cognitive impairment in SCZ and their historical development were recently reviewed by Ragland et al. (2007), and will not be recapitulated here. However, a few points are relevant to the following discussion. First, work on the prefrontal cortex ultimately led to interest in WM and cognitive control in SCZ, to a large degree under the influence of work by Goldman-Rakic (e.g., 1999). A parallel line of work on the temporal lobe and language began to focus on the MTL and hippocampus, and resulted in a body of research on LTM in SCZ. Finally, growing recognition of the interconnectivity of the prefrontal cortex and the MTL, and findings of a reversed pattern of frontal and temporal activation during word-fluency tasks in patients with SCZ (e.g. Frith et al., 1995; Yurgelun-Todd et al., 1996), led to the hypothesis that frontal–temporal integration is disrupted in SCZ. While this hypothesis has led many investigators to examine the interaction between prefrontal and temporal cortices more closely in a variety of experimental paradigms, for example, by using functional or effective connectivity analyses in functional imaging, the implications of this model for the neurophysiological substrate of LTM and WM deficits have not been widely discussed, and research into deficits on these two types of task continues to proceed largely independently.

4. Functional neuroimaging of working memory in SCZ

The nature of abnormal activation of brain regions during the performance of WM tasks in patients with SCZ remains controversial, due to inconsistent findings in the literature. While some studies have found evidence of reduced activity in DLPFC (e.g. Callicott et al., 1998; Barch et al., 2001; Perlstein et al., 2001; Barch et al., 2002; Schlösser et al., 2007), some have found no difference (e.g. Honey et al., 2002; Walter et al., 2003; Walter et al., 2007) and others have found greater DLPFC activation by patients (e.g. Callicott et al., 2000; Manoach et al., 2000). Intriguingly, it has also recently been demonstrated that reduced DLPFC activation by patients is predicted by adjacent white-matter disturbances (as measured by diffusion tensor imaging; Schlösser et al., 2007). While a recent meta-analysis of 12 studies employing *n*-back tasks revealed significantly lower activation of the DLPFC by patients with SCZ (Glahn et al., 2005), a more inclusive meta-analysis of 29 studies using a wider range of WM tasks failed to reveal a significant difference in DLPFC activation between patients and controls (Van Snellenberg et al., 2006). However, this latter meta-analysis demonstrated a relationship across studies between DLPFC activation differences between patient and control groups and patient–control differences in task performance; poorer performance by patients was predictive of lower DLPFC activation. These findings raise the possibility that reduced DLPFC activation is evident during the performance of *n*-back tasks simply because patients demonstrate greater performance deficits on these than other WM tasks.

In addition to the meta-analytic association between DLPFC activation and WM task performance described above, a similar result has been demonstrated in a matched sample of patients and controls. Callicott et al. (2003) split their patient and control samples into high- and low-performing groups on an *n*-back task, and compared both patient groups to both groups of controls. When low-performing patients were compared to either group of controls, they demonstrated reduced activation of the DLPFC, but when high-performing patients were compared to low-performing controls, they showed increased DLPFC activity. Intriguingly, when high-performing patients were compared to high-performing controls, there were discrete regions of the DLPFC that were more active in patients and other regions that were less active in patients, suggesting that patients employed a different brain network than controls in order to achieve high levels of task performance. In addition, findings of increased activation of the DLPFC by high-performing patients with SCZ have recently been replicated using a different WM task and with performance treated as a continuous, rather than dichotomous, variable (Karlsgodt et al., 2007).

In addition to task performance, several other factors may contribute to inconsistent findings of patient–control differences in the DLPFC during the performance of WM tasks. For example, several studies have shown increases in prefrontal activation in patients during the performance of WM tasks following treatment with atypical antipsychotics (Honey et al., 1999; Meisenzahl et al., 2006; Wolf et al., 2007b), raising the possibility that treatment with different pharmacological agents between studies may account for discrepant findings in the literature. However, in two of these studies (Honey et al., 1999; Meisenzahl et al., 2006), the change in prefrontal activation was not associated with improved WM performance, leaving the functional significance of the change in prefrontal activation somewhat ambiguous. Manoach (2003) also reviewed a number of other potential explanations for inconsistent findings of altered DLPFC activation in patients. Patients exhibit greater spatial heterogeneity in DLPFC activation that can (spuriously) result in lower observed activation due to normalization to a standard template for group averaging (Manoach et al., 2000), a finding that may be due to greater variability in the morphology of prefrontal cortex in patients with SCZ (also see Anticevic et al., 2008). Finally, some discrepancies between studies in terms of task domain (verbal, spatial, etc.) and other task parameters may also occur (Manoach, 2003), although a meta-analysis that looked for task differences between studies predicting differences in DLPFC activation by patients failed to find any such effects (Van Snellenberg et al., 2006).

The finding that poor-performing patients tend to exhibit reductions in DLPFC activation, while high-performing patients tend to activate prefrontal regions not normally activated by controls, suggests that patients have a functional deficit in the network that normally subserves working memory tasks, but that some patients are able to at least partially overcome this deficit by recruiting an alternative network to subserve task performance (Callicott et al., 2003; Van Snellenberg et al., 2006). At present, the precise nature of the functional deficit is unclear, but work by Meyer-Lindenberg et al. (2001, 2005) has demonstrated abnormal functional connectivity between medial temporal lobe regions and DLPFC during working memory tasks. Using a canonical variates technique, it was shown that patients and controls could be perfectly classified independent of task (that is, during baseline or during WM task performance) on the basis of high levels of activation in the inferior temporal lobe, hippocampus, and cerebellum in patients and activation of the DLPFC and the cingulate gyrus in controls (Meyer-Lindenberg et al., 2001). In

addition, during WM task performance a second pattern of activation emerged, but was significantly more variable in patients than in controls, suggesting a difficulty in maintaining activation of a task-appropriate functional network. Findings of altered connectivity between DLPFC and MTL regions during memory tasks are potentially of crucial importance to understanding the nature of WM and LTM deficits in patients with SCZ.

While this study does not clearly demonstrate that altered functional connectivity between medial temporal lobe regions and DLPFC occurs in patients during the performance of WM tasks, Meyer-Lindenberg et al. (2005) have subsequently provided strong evidence for this with a whole-brain search for voxels showing functional connectivity to voxels in the hippocampal formation (HF) in patients and controls during both control and WM tasks. The HF was shown to be negatively functionally coupled to both DLPFC and the inferior parietal lobe in both groups during the control task, while the relationship between HF and DLPFC activation diminished in control participants, but not in patients, during performance of the WM task. Thus, patients exhibit a failure to decouple activation between DLPFC and HF during the performance of a WM task.

Unfortunately these results have not been replicated, as the vast majority of WM studies of patients with SCZ do not employ techniques to investigate functional connectivity. However, some recent activation studies have demonstrated aberrant activation of the medial temporal lobe in patients with SCZ. In one study, increased activation of medial temporal lobe structures was the most robust activation difference between patients and controls observed during the performance of a WM task (Johnson et al., 2006), and another group recently showed that a failure to deactivate a region of temporal cortex during a WM task was the only finding that distinguished patients with SCZ from both normal controls and depressed patients (Walter et al., 2007). While little attention has been paid to abnormal activation of MTL regions by patients with SCZ in WM tasks, a few studies have reported patient–control differences in activation of this region during WM tasks (Callicott et al., 2000; Meyer-Lindenberg et al., 2001; Barch et al., 2002; Johnson et al., 2006). Although this finding is reported much less often than abnormal DLPFC activation by patients, there are several reasons why it may be hard to detect MTL activation during WM tasks. First, some commonly used acquisition sequences have poor power to detect signal in this region (Wager et al., 2007). Second, the extent to which MTL is involved in WM tasks likely depends on whether the stimuli used in the task are novel (Nee et al., 2008). Finally, baseline tasks with some degree of memory load (e.g. 0-back in an *n*-back task) may also recruit MTL activation, thus leaving no apparent MTL activity in the task of interest.

Furthermore, while it may seem that findings of lower temporal lobe activation and higher DLPFC activation in controls than in patients is inconsistent with the functional connectivity results of Meyer-Lindenberg et al. (2005), it is important to keep in mind that functional connectivity analyses examine sample-wise correlations between activation of brain regions within subjects rather than the relationship between two brain regions across an entire sample within a given task condition. That is, functional connectivity examines relationships between activation of brain regions throughout the time course of a scan within individual subjects, while group-averaged differences look at the *mean* activation in each region averaged across time-courses and subjects. Thus, these two measures have no necessary relationship to each other. Instead, what the findings summarized above suggest is that, in addition to the activation of a different network of prefrontal brain regions discussed at the outset of this section, patients also demonstrate abnormal involvement of temporal lobe regions in the performance of WM tasks.

In addition to altered fronto-temporal connectivity, patients with SCZ have been shown to have reduced connectivity between prefrontal cortex and the cerebellum along with enhanced connectivity in thalamo-cortical circuits during the performance of WM tasks (Schlösser et al., 2003). Tan et al. (2006) demonstrated that patients with SCZ exhibit increased connectivity between ventrolateral prefrontal cortex and posterior parietal cortex while healthy controls exhibit increased connectivity between DLPFC and the same region of parietal cortex during WM. In addition, the strength of connectivity between these regions in both groups was predictive of performance, indicating that these increases in connectivity were important for successful WM performance. Again, these results suggest that the neural implementation of WM in patients with SCZ differs fundamentally from the implementation in control participants, either as a result of strategic differences in the way these two participant groups approach the task, or as a means of compensating for a pathological disturbance in the connectivity between regions or in the integrity (functional or structural) of the brain regions that subserve WM in healthy individuals. Finally, it is also worth noting that the results of functional connectivity analyses may be meaningfully supplemented by work using diffusion tensor imaging. That is, fractional anisotropy values acquired in the context of diffusion tensor imaging studies can be used, along with their eigenvalues, as a measure of white-matter integrity and, thus, the efficiency of connectivity along specific white-matter tracts.

5. Functional neuroimaging of long-term memory in SCZ

A substantially smaller literature has employed neuroimaging to study LTM deficits in SCZ, and there are no meta-analyses available on the neuroimaging of LTM in patients with SCZ. The experimental paradigms employed in this literature typically involve either imaging participants during both encoding and recall or recognition of words, which are sometimes collapsed into a single analysis, or imaging during recall or recognition only. Reduced activation of prefrontal cortex has been demonstrated in patients during the performance of LTM tasks (Hazlett et al., 2000; Ragland et al., 2001; Barch et al., 2002; Weiss et al., 2003; Ragland et al., 2004; Ragland et al., 2005), but increased activation of the frontal pole by patients has also frequently been reported (Heckers et al., 1998; Hazlett et al., 2000; Weiss et al., 2003; Ragland et al., 2005) in addition to increased activation of other prefrontal regions (Heckers et al., 1998; Weiss et al., 2003). It is interesting to note that Heckers et al. (1999) observed reduced prefrontal activation relative to controls only in patients with a deficit syndrome (characterized by enduring negative symptoms), raising the possibility that abnormal activation in prefrontal cortex is contingent on a specific psychopathological feature of the illness.

In addition to differences in activation of prefrontal cortex, several studies have also reported that patients exhibit reduced activation of the medial temporal lobe during performance of LTM tasks (Heckers et al., 1998; Heckers et al., 1999; Ragland et al., 2001; Barch et al., 2002; Weiss et al., 2003); however, both null findings with respect to the temporal lobe (Hazlett et al., 2000) and increased activation of this region (Ragland et al., 2004; Ragland et al., 2005) have also been reported. Thus, it remains unclear as to whether patients exhibit reliable alterations in medial temporal lobe activity during the performance of LTM tasks. One possibility is that medial temporal lobe activation (and possibly prefrontal cortex activation) by patients is partially dependent on task performance in the same manner as DLPFC activation by patients has been shown to be dependent on performance in WM tasks. While there are probably too few neuroimaging studies of LTM in patients with SCZ for a clear relationship between medial temporal lobe activation and performance to emerge in the available literature, Ragland et al. (2004) provided direct support for this view by showing that improved performance by control subjects was correlated with greater activation of right DLPFC, but improved performance by patients was instead correlated with greater activation of medial and mesial temporal lobe, orbitofrontal, superior frontal, and inferior parietal regions. Again, these data support the view that patients activate a different brain network than do control participants in order to subserve task performance.

Finally, fronto-temporal connectivity has also been shown to be disturbed in patients with SCZ during the performance of a LTM task. Wolf et al. (2007a) demonstrated that patients exhibit reduced functional connectivity between DLPFC and parahippocampal and superior temporal cortices compared to control participants, and instead show a pattern of connectivity between ventrolateral

Table 1
Summary of patient vs. control differences in functional imaging studies of working and long-term memory.

				Activation differences						
				DLPFC		MTL[a]		Other temporal		
Study	Task	PET/fMRI	Stimuli	L	R	L	R	L	R	Other
				Working memory						
Barch et al., 2001	AX-CPT	fMRI	Letters	−	n.s.	n.s.	n.s.	n.s.	n.s.	
Barch et al., 2002*	*n*-back	fMRI	Word and face	n.s.	−	−	n.s.	n.s.	n.s.	
Callicott et al., 1998	*n*-back	fMRI	Number/location	−	−	n.s.	n.s.	n.s.	n.s.	
Callicott et al., 2000	*n*-back	fMRI	Number/location	n.s.	+	n.s.	−	−STG	n.s.	
Callicott et al., 2003	*n*-back	fMRI	Number/location	−	−	n.s.	n.s.	n.s.	n.s.	DLPFC activation differences depended on performance; better performing patients exhibited regions of greater activation in DLPFC
Honey et al., 2002	*n*-back	fMRI	Letter	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	
Johnson et al., 2006*	Sternberg	fMRI	Letter	−[b]	n.s.	+[c]	+[c]	n.s.	n.s.	Medium load
Johnson et al., 2006*	Sternberg	fMRI	Letter	−[c]	−[c]	n.s.	n.s.	n.s.	n.s.	High load
Karlsgodt et al., 2007	Sternberg	fMRI	Letter							Positive linear relationship between DLPFC activation and performance in patients
Manoach et al., 2000	Sternberg	fMRI	Number	+	n.s.	n.s.	n.s.	+ITG[d]	+STG[d]	
Meisenzahl et al., 2006	*n*-back	fMRI	Letter	n.s.	−	n.s.	n.s.	+STG	+STG	
Meyer-Lindenberg et al., 2001	*n*-back	PET	Number/location	−	−	n.s.	+	+STG	n.s.	Patients exhibited greater variability in maintaining activation of a task-related brain network
Meyer-Lindenberg et al., 2005	*n*-back	PET	Number/location	n.s.	−	n.s.	n.s.	n.s.	n.s.	Patients but not controls showed functional connectivity between DLPFC and hippocampal formation
Perlstein et al., 2001	*n*-back	fMRI	Letter	n.s.	−	n.s.	n.s.	n.s.	n.s.	
Schlösser et al., 2003	*n*-back	fMRI	Letter							Patients exhibited reduced prefrontal-cerebellar and enhanced thalamo-cortical connectivity relative to controls
Schlösser et al., 2007	Sternberg	fMRI	Letter	−	−	n.s.	n.s.	n.s.	n.s.	Reduced DLPFC activation in patients predicted by adjacent white-matter abnormalities (measured with DTI)
Tan et al., 2006	*n*-back	fMRI	Number/location							Performance was predicted by DLPFC activation in controls and by VLPFC activation in patients; controls exhibited functional connectivity between DLPFC and PPC while patients exhibited connectivity between VLPFC and PPC
Walter et al., 2003	*n*-back	fMRI	Letter and location	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	
Walter et al., 2007	Novel[e]	fMRI	Letter	n.s.	n.s.	+	+	+STG	+STG	
Wolf et al., 2007b	Novel[e]	fMRI	Letter	n.s.	n.s.	+	+	+STG	+STG	Reported differences were found at intermediate but not high WM load
				Long-term memory						
Barch et al., 2002*	Encoding	fMRI	Word and face	n.s.	−	−	n.s.	n.s.	n.s.	
Barch et al., 2002*	Recognition	fMRI	Word and face	n.s.	−	n.s.	n.s.	n.s.	n.s.	
Fletcher et al., 1999	Encoding and recall	PET	Word							Patients failed to show normal DLPFC and ACC modulation of temporal cortex activation
Hazlett et al., 2000	SVLT	PET	Word	−	−	n.s.	n.s.	n.s.	n.s.	
Heckers et al., 1998	Recall	PET	Word	n.s.	n.s.	n.s.	−	n.s.	−STG	
Heckers et al., 1999	Recall	PET	Word	−	−	n.s	n.s	n.s	n.s	Patients with a deficit syndrome exhibited reduced right DLPFC and right STG and MTG activation compared to non-deficit patients
Ragland et al., 2001*	Encoding	PET	Word	−	n.s.	n.s.	n.s.	−STG	n.s	
Ragland et al., 2001*	Recognition	PET	Word	−	n.s.	−	n.s.	n.s.	n.s.	
Ragland et al., 2004	Encoding and recognition	fMRI	Word	−	−	+	+	+ITG	+MTG	
Ragland et al., 2005	Encoding and recognition	fMRI	Word	n.s.	n.s.	+	n.s.	n.s.	n.s.	
Weiss et al., 2003	Retrieval	PET	Word	n.s.	n.s.	n.s.	−	n.s.	n.s.	Patients also exhibited reduced activation in left BA 47
Wolf et al., 2007a[f]	Encoding and recognition	fMRI	Word							Patients exhibited reduced connectivity between DLPFC and MTL and STG and increased connectivity between VLPFC and MTL and STG

Note. Studies marked with an asterisk appear more than once in the table. Plus signs indicate greater activation by patients, minus signs indicate less activation by patients, and n.s. indicates no significant difference between groups. Studies for which group differences are not reported either did not test or did not report on between-group activation differences. ACC = anterior cingulate cortex; AX-CPT = AX version of the continuous performance test; DLPFC = dorsolateral prefrontal cortex; DTI =diffusion tensor imaging; fMRI = functional Magnetic Resonance Imaging; ITG = inferior temporal gyrus; L = left; MTG = middle temporal gyrus; MTL = medial temporal lobe; PET = Positron Emission Tomography; PPC = posterior parietal cortex; R = right; STG = superior temporal gyrus; SVLT = Serial Verbal Learning Test; VLPFC = ventrolateral prefrontal cortex.

[a] Includes results for the hippocampus and parahippocampal gyrus.

[b] Results for encoding phase.

[c] Results for retrieval/probe phase.

[d] Results based on significant task-baseline difference in patients but not in controls, rather than a direct between-group test of activation differences.

[e] In this task three letters are presented on each trial, and the letters to be remembered are indicated by their luminance (set size varies from one to three). A probe is then presented and participants must indicate whether the probe follows one of the target letters in the alphabet.

[f] Data from Ragland et al., 2005.

prefrontal cortex (VLPFC) and these same temporal lobe regions that was not observed in normal subjects during the performance of their task. Furthermore, connectivity between DLPFC (but not VLPFC) and temporal cortex was predictive of better task performance in control participants, while no observed connectivity pattern was predictive of better performance in the patient group. In addition, disturbed connectivity between prefrontal, cingulate, and superior temporal cortex in SCZ during performance of a LTM task was described in an early report by another group of authors (Fletcher et al., 1999).

6. A common basis for working and long-term memory deficits in SCZ

From the preceding discussion it is clear that patients with SCZ exhibit abnormal activation of prefrontal cortex and temporal lobe structures during the performance of both WM and LTM tasks, as summarized in Table 1. While the precise nature of these deficits remains unclear due to inconsistent findings, the available data are most consistent with the view that patients activate a different network of brain regions than controls in both types of task due to an as yet unspecified deficit in the functional network deployed by healthy subjects during these tasks. It is also likely that alternative-network activation by patients is not restricted to memory tasks, as altered fronto-temporal connectivity has been observed in verbal fluency (Frith et al., 1995; Yurgelun-Todd et al., 1996) and other tasks (Katz et al., 1996; Lawrie et al., 2002), although some studies have failed to replicate this finding (Spence et al., 2000).

While the similarities between functional activation differences between patients and controls in both WM and LTM tasks described above – patterns of both decreased and increased activation of prefrontal and medial temporal lobe brain regions, modulation of these activation patterns by task performance, and disturbed fronto-temporal connectivity – are merely suggestive, there is some direct evidence that the same neural substrate underlies the deficit in performance and abnormal patterns of activation in both WM and LTM tasks. First, there is behavioral evidence that WM capacity in patients can completely account for deficits in LTM recall (Stone et al., 1998). Second, the only neuroimaging study to investigate both WM and LTM in the same group of patients and controls found that the same region of right DLPFC, as well as a hippocampal/parahippocampal region, exhibited reduced activation in both the WM and LTM tasks (Barch et al., 2002). Furthermore, there were no regions in which patients exhibited reduced activation during the LTM task but not the WM task, further suggesting that the functional deficit in these tasks is the same. While reduced activation of DLPFC and the medial temporal lobe is by no means a ubiquitous finding in studies of either WM or LTM, the view that patients with SCZ activate an alternative network in order to subserve task performance in both WM and LTM predicts that *within a single sample* the functional activation differences between patients and controls should be equivalent for both WM and LTM tasks, as observed by Barch et al.

Perhaps the best evidence that WM and LTM deficits in SCZ share a common neural substrate comes from a large-scale Finnish twin study of the genetics of SCZ, which demonstrated overrepresentation of two haplotypes, involving the disrupted-in-SCZ (DISC1) and translin-associated factor X (TRAX) genes, in patients (Cannon et al., 2005). The DISC1/TRAX haplotypes were not only associated with schizophrenic illness, but were also correlated with reduced gray matter volume in the hippocampus and superior and middle frontal gyri, as well as performance on LTM and WM tasks. Given that the DISC1 and TRAX genes have known effects on neuronal migration and synaptogenesis (Cannon et al.), which are thought to be disordered in SCZ (for review, see Green, 1998), these findings provide a plausible neurobiological substrate for a functional disturbance of brain regions known to be involved in the performance of WM and LTM tasks, and which have been observed to show abnormal patterns of activation in functional neuroimaging studies of patients with SCZ.

Finally, it is critical to note that deficits in both WM and LTM have been shown to be a trait marker of SCZ (Rund, 1998), and both deficits are present in individuals at high risk for developing SCZ (Erlenmeyer-Kimling et al., 2000; Joyce et al., 2002; Wood et al., 2003; Saperstein et al., 2006) as well as in first-episode patients (Pantelis et al., 2003; Hill et al., 2004). While these data do not provide direct evidence for the notion that deficits in WM and LTM have the same pathophysiological substrate, the stable presence of both deficits in individuals with SCZ prior to illness onset and throughout the disease course is suggestive of a common underlying cause. Intriguingly, Pantelis et al. (2003) have shown that amongst high-risk individuals, those that go on to develop psychosis have reduced volume in medial and lateral temporal cortices, as well as the inferior frontal and cingulate cortex. One possibility is that early impairment of DLPFC disrupts the top-down modulation of encoding processes and MTL function (see de Fockert et al., 2001; Gazzely et al., 2005; Axmacher et al., 2008), a notion that is supported by the finding that some of the variance in LTM deficits in patients can be accounted for by difficulties in early perceptual encoding (Holthausen et al., 2003). While speculative, such a model could account for deficits in both WM and LTM, as well as data on abnormal activation of prefrontal and MTL regions, and altered functional connectivity between these regions. Thus, abnormal activation of both prefrontal and temporal regions, as well as abnormal connectivity between them, could arise as a result of dysfunction within a specific region, such as the DLPFC, that results in a disruption of the entire network of regions deployed to carry out WM and LTM tasks.

7. Conclusion

While it is important not to overstate the case for a common neurophysiological underpinning of WM and LTM deficits in SCZ, given that direct evidence for this claim is still quite limited, the evidence discussed in this article suggests that these deficits share a common neural substrate. Indeed, at present the parsimonious view is one which posits a shared basis for all memory deficits in the disorder. As a result, it could be argued that deficits in WM and LTM tasks in patients with SCZ should be assumed to reflect the same functional disturbance unless strong evidence of a dissociation between these deficits is provided.

The view outlined here suggests a number of directions for future work in this area, and makes clear predictions that can confirm or disconfirm the notion that a common functional abnormality underlies patient performance deficits in both WM and LTM tasks. Most obviously, studies examining activation differences between patients and controls on both types of task within the same sample (along the lines of the work of Barch et al., 2002) should demonstrate very similar alterations in the pattern of brain activation by patients with SCZ in both task types, although the specific abnormalities observed may vary between samples and with the precise nature of the tasks employed in a given study. Furthermore, the nature of differential brain activation between patients and controls in both types of task should be predicted by differences in task performance, as task performance is arguably the best available explanation for the considerable variation in activation differences between groups in studies of both WM and LTM, as described above. Critically, the LTM and WM tasks employed should be matched as closely as possible in terms of design (especially with respect to the stimulus materials used), with the critical difference being only in terms of delay between target and probe stimuli. Finally, additional research on patterns of functional connectivity in patients and controls during the performance of these tasks should continue to reveal commonalities between disordered connectivity patterns in patients in both WM and LTM tasks, particularly given existing hypotheses that a fundamental dysfunction in SCZ is abnormal functional connectivity between temporal and prefrontal cortices (e.g. Friston, 1998).

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