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The Cognitive Neuroscience of Memory Function and Dysfunction in Schizophrenia

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Abstract

Patients with schizophrenia have pronounced deficits in memory for events, or episodic memory. These deficits severely affect patients' quality of life and functional outcome, and current medications have only a modest effect, making episodic memory an important domain for translational development of clinical trial paradigms. The current article provides a brief review of the significant progress that cognitive neuroscience has made in understanding basic mechanisms of episodic memory formation and retrieval that were presented and discussed at the first CNTRICS meeting in Washington, D.C. During that meeting a collaborative decision was made that measures of item-specific and relational memory were the most promising constructs for immediate translational development. A brief summary of research on episodic memory in schizophrenia is presented to provide a context for investigating item-specific and relational memory processes. Candidate brain regions are also discussed.

Keywords

memory; schizophrenia; cognitive; neuroscience; fmri; neuroimaging; relational; episodic; prefrontal cortex; hippocampus; medial temporal lobes

Virtually every significant act of daily living requires the ability to remember past events, or episodic memory (1). Individuals with schizophrenia have pronounced episodic memory impairments (2,3), which in turn compromise their daily living skills. These memory impairments show only modest improvement with currently available therapies for schizophrenia (4–7), and the vast majority of patients treated with our very best second generation antipsychotic drugs continue to suffer from significant memory dysfunction. Research on the assessment and treatment of episodic memory disorders is of supreme importance because memory performance is among the strongest predictors of functional outcome (8–10).

In light of its fundamental importance to the everyday life of healthy individuals and patients with schizophrenia, episodic memory was selected as one of the initial domains for the first

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meeting of the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative. The goal of this article is to provide a context for the decision to target measures of item-specific and relational memory for translation to clinical trial instruments through the CNTRICS initiative. This will be accomplished by first providing a review of the significant strides that cognitive neuroscientists have made in understanding the neural underpinnings of the cognitive processes that support episodic memory formation and retrieval. This progress includes improved understanding of the cognitive and neural mechanisms that support encoding and retrieval of specific item attributes and of relationships between items to be remembered. A brief review of the clinical literature will focus on the relative pattern of memory strengths and weaknesses experienced by patients with schizophrenia, and candidate brain regions that might be implicated in these memory failures. Although the specific neural mechanisms of episodic memory deficits in schizophrenia have not been established, existing behavioral and imaging data support the proposition that relational memory may be disproportionately affected by the illness, possibly due to focal or distributed dysfunction in the lateral prefrontal cortex (PFC) and medial temporal lobes (MTL).

Overview of Mechanisms of Long Term Memory

The ability to successfully remember a prior event is the outcome of a complex set of processes that occur at different times. During the initial experience of an event, *encoding* processes play a critical role in determining the content and subsequent accessibility of an event (Fig. 1A). Encoding of an episode will typically involve a complex combination of perception, conceptual processing, and action. However, these events usually do not occur in a vacuum—instead, in healthy individuals, cognitive control processes direct attention towards certain goal-relevant information and away from irrelevant information. The degree and kinds of control processes that are engaged during encoding can play a significant role in promoting effective memory formation (11–14). For example, in behavioral studies of memory for word lists, it has been shown that thinking about a word in terms of its surface features (e.g., the font that a word is printed in) typically results in poor memory, whereas elaborating on the item by using *relational* (e.g., making up a story to link the words) or *item-specific* (e.g., forming a distinctive mental image of the word's referent) strategies will result in a richer memory trace that is more likely to be remembered later (11,12,15–19). Whereas relational strategies involve focusing on common elements across a set of items, item-specific strategies involve focusing on distinctive attributes of specific items that are being processed. In general, it is thought that relational encoding promotes memory for associations amongst items, whereas item-specific encoding enhances the distinctiveness of specific items (15–17,20).

After encoding, a number of events can take place before one attempts to remember the corresponding event. To the extent that subsequent events are similar to the one that is previously encoded, one can expect some degree of forgetting due to interference (21). For example, it might be difficult to remember where you parked your car last Tuesday if you subsequently parked in other spaces in the same neighborhood during the intervening period. Beyond interference, accumulating evidence from neuroscience suggests that "consolidation" can also modulate whether an event will be subsequently remembered (22). For example, differences in memory performance between emotionally-arousing and neutral materials often emerge after a significant delay between encoding and retrieval, and this effect can be attenuated or eliminated by drug administration during the delay (23). Other research suggests that consolidation of certain kinds of information may be enhanced (i.e., as evidenced by reduced forgetting rates) by periods of sleep (particularly slow-wave sleep, see 24 for review), although it is unclear exactly under what conditions sleep-related consolidation effects will be observed.

Processes that occur during retrieval also play a critical role in determining whether one can successfully and accurately remember a prior event (25–28). Successful retrieval can hinge on the retrieval cues that are available and the conditions under which one is attempting to retrieve a past event. For instance, if you are attempting to *recall* where you left your keys, you would be forced to initiate a strategic search in which you generate a prior context (e.g., "I was in my office") in order to generate more specific retrieval cues (e.g., "Did I leave the keys in the desk drawer?"). Under these circumstances, cognitive control processes are critical, as it is necessary to plan and focus on goal-relevant information. On the other hand, if a specific retrieval cue is available, then these strategic factors may not be necessary. For instance, if you are attempting to *recognize* whether a face corresponds to someone you have previously met, you can rely on a sense of how familiar that person seems or recollect details (e.g., "I saw that person last night") that may be automatically elicited after viewing the person's face (29). Even in this case, however, cognitive control can be helpful, as it is sometimes necessary to inhibit irrelevant information that may be recovered (27,30–33).

It is important to emphasize that encoding and retrieval processes should not be considered in isolation, because the outcome of the retrieval process depends also on the compatibility between the information that was encoded and the cues that are available during retrieval (34,35). For example, processing what is common amongst a set of items (i.e., relational encoding) is optimal if one will have to subsequently recall the information (e.g., an essay exam). However, processing of distinctive attributes of each item (i.e., item-specific encoding) may be optimal if one must recognize specific details of these items later on (e.g., a true-false test).

Finally, assuming that some information is recovered, the next step is to use this information to make appropriate attributions. To ensure that one makes an accurate memory attribution (i.e., "I met that person at the conference", as opposed to "I met that person last night at the bar"), one must rely on "source monitoring" (27) processes that allow one to systematically evaluate the information that is recovered. This is a critical step, because failure to appropriately monitor the retrieval process can result in memory distortions (27,36).

The foregoing section provides only a brief summary of the complex set of processes that support normal episodic memory. Nonetheless, these ideas have clear implications for the study of memory in schizophrenia. Specifically, episodic memory impairments in schizophrenia could come about not only because of a failure to form or consolidate mnemonic representations of prior events, but also through impairment in a variety of "non-memory" processes. For instance, because one's memory for an event will depend on how the event was initially processed, it follows that perceptual or cognitive impairments could have secondary effects on episodic memory. As noted above, under many circumstances, episodic encoding and retrieval entails cognitive control processes that affect the ability to plan, initiate strategies, and inhibit distractions. Thus, a critical question in the study of schizophrenia is to assess the degree to which memory impairments in patients can be attributed to deficits in the ability to form new episodic memory representations and/or deficits in other cognitive processes that contribute to successful memory.

Cognitive Neuroscience of Episodic Memory

A great deal of information has been gleaned about the neural underpinnings of memory processing through studies of patients with brain damage and through functional neuroimaging studies of healthy participants. Much of this research has focused on the contributions of regions in the MTL and in the PFC. As we will describe below, this research may provide the context for understanding the specific abnormalities in long term memory mechanisms in schizophrenia.

The importance of the MTL in memory processes has been established largely through studies of patients and animals with MTL lesions (22,37). For instance, the famous patient H.M. became densely amnesic after a bilateral anterior temporal lobectomy, largely eliminating his ability to retain memories of events that occurred after the surgery (38). Despite their severe deficits in forming new episodic memories, amnesic patients can appear to be largely intact in most other areas of cognition (e.g., 39).

More recently, it has become appreciated that the MTL consists of multiple, functionally dissociable regions (40). At the coarsest level, one can distinguish between the perirhinal and parahippocampal cortices, the entorhinal cortex, and the hippocampus. Almost all of the cortical input to the MTL is initially directed to the perirhinal and parahippocampal cortices, which project to the entorhinal cortex, which, in turn, projects to the hippocampus (41,42). In general, hippocampal lesions in monkeys or rodents elicit modest or nonsignificant impairments on item recognition tasks, whereas perirhinal lesions severely impair recognition memory (37). More recent studies of human amnesics (43,44) and lesion studies of rats (45, 46) have suggested that the hippocampus specifically contributes to recollection of contextual information associated with an event, whereas the perirhinal cortex may be sufficient to support familiarity-based item recognition. This idea has received strong support from functional neuroimaging studies, which have consistently linked activity in the hippocampus with recollection and activity in the perirhinal cortex with familiarity (47). Collectively, these findings suggest that the perirhinal cortex might be sufficient to support near-normal performance on measures of item memory, whereas the hippocampus may be required to support recollection of information in the service of relational memory tasks.

Unlike patients with MTL damage, patients with damage restricted to the PFC typically do not exhibit an amnesic syndrome. Instead, PFC lesions most significantly affect cognitive control processes that can affect the efficacy of encoding and retrieval. On laboratory tests, such patients can appear normal under some conditions and exhibit memory impaired performance under others. In general, PFC patients will perform significantly more poorly than healthy subjects under conditions that require the engagement of control processes during encoding and retrieval. For instance, patients will do more poorly if they are asked to intentionally encode information for an upcoming test, but their performance improves if they incidentally learn the materials while performing a structured encoding task (48–51). They will also do very poorly if asked to freely recall information from a previous study episode, perform better at cued-recall, and exhibit only mild deficits on item recognition tests (50,52–56). Put another way, patients with PFC lesions tend to perform poorly in situations that require the engagement of control processes in order to select appropriate strategies or inhibit the influence of irrelevant information during encoding and retrieval (19,57–59).

Results from functional imaging studies have also emphasized the importance of the PFC for the implementation of control processes that facilitate episodic encoding and retrieval. Additionally, these studies have suggested that regions in the ventrolateral PFC (VLPFC; BA 44, 45, and 47) may implement different processes than regions in the dorsolateral PFC (DLPFC; BA 9 and 46). For instance, numerous studies have shown that activity in the VLPFC is consistently increased under conditions that require the inhibition of irrelevant information and the selection of goal-relevant information about items that are being processed (60–62). These effects are not typically observed in the DLPFC. However, DLPFC activation is increased when one must process relationships amongst items that are active in memory (19, 63).

Recent findings from event-related fMRI studies of memory encoding have linked these control processes to the ability to successfully remember different kinds of information (62,64). In these studies, participants are scanned while performing specific encoding tasks, and then a

post-scan test is administered. This allows activity during each encoding trial to be analyzed as a function of whether information from that trial was subsequently remembered. A recent review (19) of such encoding studies found that almost all of them reported that activation in VLPFC was increased for items that were subsequently remembered, as compared with items that were subsequently forgotten. In contrast, DLPFC activation is specifically increased during relational encoding tasks, and DLPFC activation is correlated with long-term memory for information about associations between items (65–67) (see Fig. 2 for an example).

The basic research summarized above suggests that the PFC and MTL might play complementary roles in supporting normal episodic memory performance. Regions in the MTL may be critical for normal episodic memory—in particular, the perirhinal cortex may encode representations that support familiarity-based recognition, whereas the hippocampus may encode representations that support recollection. Regions in the PFC may implement cognitive control processes that facilitate encoding and retrieval, with the VLPFC supporting item-specific processing and the DLPFC additionally recruited during relational encoding.

Long-term Memory Dysfunction in Schizophrenia

Although a range of cognitive and information-processing deficits have been consistently observed in schizophrenia, a meta-analysis of neuropsychological studies found that the largest effect sizes for cognitive dysfunction in schizophrenia are for verbal learning and memory (3). This suggests that there may be a more severe deficit in learning and memory against a background of less severe generalized cognitive dysfunction (68–73). This memory impairment is not accounted for by demographic variables such as education or sex (74), or by clinical variables such as medication exposure, or duration and severity of illness (2). The cognitive profile of long-term memory deficits is similar for both unmedicated first-episode and previously-treated patients (75), and remains stable over time (76). Memory impairment is also a stronger predictor of patients' functional outcome than either clinical symptoms or a range of other cognitive or demographic variables (8,9). These functional measures include activities of daily living and occupational performance (9,77,78).

The pattern of memory deficits in patients with schizophrenia is similar to what is seen in patients with PFC lesions (described above) or in patients with dementing disorders that affect fronto-striatal function, such as Huntington's or Parkinson's dementia. As in these other disorders, encoding and retrieval processes appear to be more impaired than long-term storage (68,79,80). Patients with schizophrenia do not show the pattern of rapid forgetting that is observed in cortical dementias such as Alzheimer's disease.

In general, the relative severity of memory deficits in schizophrenia depends on the specific conditions under which information is learned and the way in which retrieval is tested. For instance, during encoding, it appears that patients typically do not utilize semantic encoding strategies in order to facilitate encoding and retrieval (68,80–83). This may reflect an underlying failure in the self-generation of organizational strategies (81,84,85). This "strategic memory" account is supported by findings that patients can benefit from training in semantic organizational strategies (86), from being administered blocked versus un-blocked lists of words (68,84), and from engaging in "deep" semantic rather than "shallow" perceptual level of item-specific processing during encoding (87).

During retrieval, schizophrenia patients exhibit deficits more consistently on recall tests than on recognition tasks (86,88). This is not to say, however, that recognition is unimpaired—indeed, a recent meta-analysis of memory studies in schizophrenia found moderate effects on recognition performance and large effects on recall performance (2). Further exploration of recognition memory has suggested that patients with schizophrenia may rely more on familiarity, rather than recollection of the event. Consistent with this idea, one study showed

that patients exhibited intact familiarity based recognition , but recollection was severely impaired (89), although this pattern was not observed in a different study (90). This general pattern of memory deficits bears similarity to what has been observed both in patients with focal hippocampal dysfunction (37,91) and in patients with focal prefrontal lesions (58). One caveat to interpreting the results described above, however, is that selective recollection/recall deficits might simply reflect greater sensitivity of these measures, as compared to familiarity/recognition measures (92). Accordingly, one goal of the CNTRICS initiative will be to more precisely ascertain whether selective patterns of memory deficits might be obtained even when using measures that are equated for sensitivity.

Given the results described above, it is not surprising that functional imaging studies of episodic memory in schizophrenia have consistently reported abnormal patterns of activity in the MTL and PFC (93). Heckers and colleagues (94) were the first to find evidence of abnormal hippocampal recruitment during word retrieval. Unlike healthy participants who activated a right frontal-temporal network during word retrieval, schizophrenia patients had reduced hippocampal and abnormally increased frontal activation. Reductions in hippocampal volume and memory-related activation were subsequently replicated in the schizophrenia literature (see 95, for review). However, these hippocampal abnormalities were invariably accompanied by evidence of abnormal PFC recruitment (e.g., 96). This has led some to propose that memory impairment in schizophrenia might reflect abnormal functional connectivity between the PFC, the hippocampus, thalamus, and cerebellum (97). This fronto-temporal disconnection hypothesis of schizophrenia (98) has received some support through functional connectivity analysis of activity in PFC and MTL seed regions (99–102), although it should be noted that these studies are correlational and do not establish causality or directionality. Current limitations in the temporal resolution of the fMRI signal have made it difficult to determine whether episodic memory deficits in schizophrenia result from a focal deficit in a key MTL, PFC or other brain region that has upstream and downstream effects, or from a more distributed dysfunction in the integration of activity between these key brain regions.

Further insights into episodic memory deficits in schizophrenia have been gained by controlling and manipulating the types of encoding strategies to be used. Initial studies imaged patients during word retrieval and found greater right hippocampal activation in controls and greater anterior prefrontal activation (BA 10) in patients during cued recall of words that were encoded in the context of a deep (semantic) orienting task, as compared with retrieval of words that were encoded with a shallow (non-semantic) task (94,103). Interestingly, group differences in the hippocampus were due to greater patient than control hippocampal activity during baseline and shallow retrieval conditions, resulting in less of a hippocampal increase in patients when deep minus shallow retrieval was contrasted. This retrieval study was followed by a series of encoding studies. The first encoding study (104) imaged patients and controls while repeating a shallow and deep orienting task that had previously been administered outside of the scanner. Contrasts between deep minus shallow encoding revealed that patients showed reduced activation in VLPFC and increased superior temporal cortex activation. However, it was unclear whether repeating the task might have affected group differences in activity. Accordingly, subsequent encoding studies administered the shallow and deep encoding tasks for the first time in the scanner (105–107). In these studies, patients and controls showed equivalent VLPFC activation in contrasts between deep minus shallow processing, suggesting that functioning in the VLPFC could be restored by providing patients and unaffected family members with item-specific semantic processing strategies. However, in these studies patients also showed a more diffuse pattern of activation in the contrast between deep and shallow encoding (including evidence of greater MTL activation in patients than controls), suggesting that providing patients with an item-specific encoding strategy does not fully normalize brain responses.

As in the basic cognitive neuroscience literature (19), the majority of imaging studies of memory in schizophrenia have used item-specific, rather than relational encoding tasks, making them relatively insensitive to modulation of DLPFC activity. However, a number of schizophrenia studies have begun to examine higher-level associative memory tasks that are more likely to depend on control processes mediated by the DLPFC and on relational binding processes mediated by the hippocampus. One approach has been the use a transitive inference (TI) paradigm (108–112) to contrast relational inferences (e.g., if "A>B" & "B>C", then "A>C") with item-specific recognition memory (e.g., is "A" old or new?). Initial behavioral studies documented a differential patient impairment in the TI condition (113). In a subsequent fMRI study (109), overall TI performance was intact in schizophrenia, although patients did have a selective deficit on TI trials in which the two items in each pair had an equal reinforcement history (BD pairs), in contrast to the remaining TI trials composed of items with unequal reinforcement histories. When all TI trials were contrasted with all non-TI trials, patients had unimpaired pre-supplementary motor and VLPFC activation, and reduced activation in the anterior cingulate gyrus and right parietal cortex. When TI BD pairs were contrasted with all remaining TI pairs, patients again had reduced right parietal activation and also reduced left hippocampal activation (109). A second approach (114) was to examine activation during tests of memory for object pairs that could either be solved on the basis of familiarity-based recognition (i.e., new vs. old pair) or required memory for previously studied associations (i.e., intact vs. rearranged pairs). Consistent with the TI results, performance impairments were specific to the associative memory task, and were accompanied by reduced left prefrontal and anterior cingulate activation during encoding and left DLPFC and right VLPFC during retrieval.

In sum, schizophrenia clearly affects MTL structure and function, with strong evidence of reduced hippocampal volume and disrupted hippocampal modulation during associative and non-associative retrieval tasks (95,115). However, MTL dysfunction is frequently accompanied by PFC dysfunction, particularly when control processing demands are increased. Provision of semantic processing strategies can help to restore item-specific control processes, dramatically improve recognition performance, and re-engage VLPFC. However, patients continue to show a more diffuse pattern of activation even when encoding strategies are controlled, and may exhibit selective dysfunction in the DLPFC and hippocampus, particularly on relational memory measures.

Directions for Treatment Development

Based on the strong evidence from basic neuroscience and psychology research, the CNTRICS workgroup agreed that research on memory in schizophrenia should consider differentiating between measures of item-specific memory (i.e., memory for individual stimuli irrespective of contemporaneously presented context or elements) and measures of relational memory (i.e., memory for stimuli/elements and how they were associated with conincident context, stimuli or events). As described above, there is good reason to believe that relational memory may be disproportionately affected in schizophrenia, whereas item-specific memory may be relatively spared (when differences in encoding strategy are controlled). However, this opens up a new question: what are the precise mechanisms of relational memory impairment in schizophrenia?

Integrating the basic and clinical cognitive neuroscience literatures suggests that the PFC and hippocampus are candidate brain regions for developing a mechanistic understanding of memory impairment in schizophrenia that can be targeted for development of cognitive enhancing agents. Like patients with lesions to the hippocampus or PFC, patients with schizophrenia are most impaired on relational memory measures, whereas familiarity-based item recognition is relatively spared (116). Another similarity is that patients with schizophrenia, like patients with frontal dysfunction, do not spontaneously engage effective

strategies during initial learning (68,80–83), but memory performance in these patients can benefit greatly if elaborative strategies are provided. This suggests a deficit in cognitive control processes that modulate the efficacy of encoding, perhaps in addition to a fundamental deficit in patients' ability to form new episodic memories. Beyond neuropsychological evidence, researchers have uncovered molecular and cellular abnormalities within the hippocampus and PFC (117–119), that may underlie the circuit-level dysfunction identified in imaging studies. Accordingly, prefrontal and hippocampal regions may be excellent targets for pharmacological interventions (e.g., 120).

Another interesting finding to come from imaging studies of memory in schizophrenia (105–107) is that instructing patients to use item-specific encoding strategies can improve memory performance and restore normal activation patterns in VLPFC, even though DLPFC and MTL activation remains abnormal. Thus, VLPFC-dependent processes that support elaborative encoding of specific items may be relatively preserved in schizophrenia. Thus, cognitive rehabilitation efforts might be able to build on these spared mechanisms in order to improve the efficiency of memory encoding in patients with schizophrenia.

In summary, the present review points to the importance of understanding memory dysfunction in schizophrenia. Available evidence suggests that relational memory might be a particular area to be targeted in diagnostic and treatment efforts. Further research directed at this question could lead to the development of new treatments that increase engagement or integration of PFC and MTL regions, thereby improving patients' memory performance, and also improving their long-term functional outcome (9,10,121).

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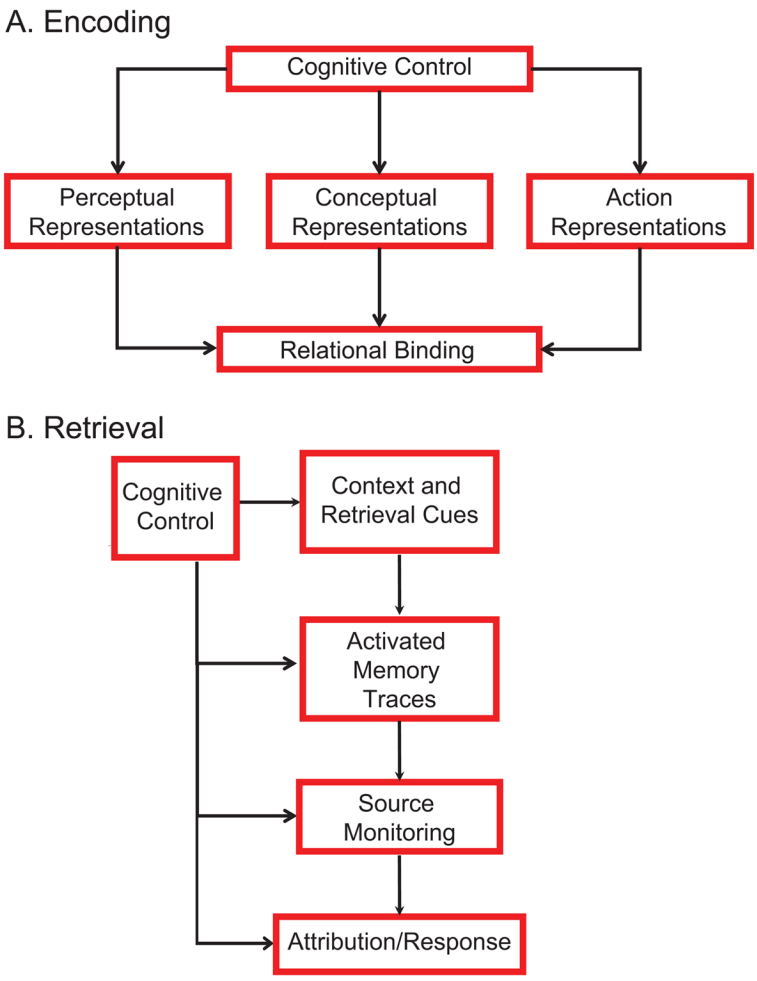

Figure 1.

Schematic diagram of the processes that support memory encoding and retrieval. (A) Episodic memories require the binding of perceptual, conceptual, and action processes that are engaged during an event. Cognitive control processes play a particular role in determining the types of processing that will be engaged, as well as the types of information to be suppressed. (B) During retrieval, contextual cues, along with more specific retrieval cues can elicit the recovery of episodic information. Cognitive control processes play a critical role in generation of retrieval cues, filtering of recovered information, and selection of criteria that will be used to make attributions based on what is recovered.

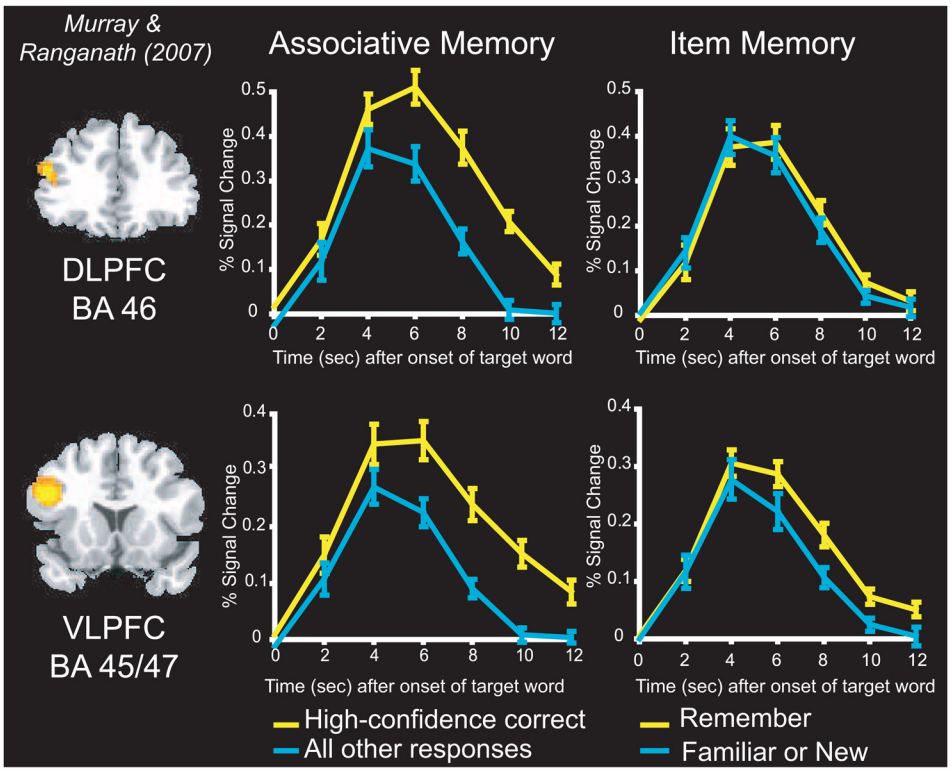

Figure 2.

Results from Murray & Ranganath (66), showing that activity in dorsolateral prefrontal cortex (DLPFC) is specifically correlated with memory for associations between items. In this study, participants were scanned while encoding pairs of words, and later participants were tested on memory for the items and associations that were studied. In the left DLPFC (Brodmann's area [BA] 46; top row), analyses of data based on associative memory accuracy (left graph) showed that activity during encoding was greater for pairs that were subsequently remembered (yellow trace), as compared with pair associations that were later forgotten (blue trace). However, when trials were analyzed as a function of accurate recognition of the items in each pair (right graph), no significant differences were observed between subsequently remembered (yellow trace) and subsequently forgotten (blue trace) items. Activity in VLPFC (BA 45/47; bottom row) was also enhanced during processing of pairs that were subsequently remembered, as compared with pairs that were forgotten. However, unlike DLPFC, activity in VLPFC was also increased during processing of items that were later remembered, as compared with subsequently forgotten items.

Table 1

Schizophrenia versus Control Group Differences in PFC or MTL Activation During Functional Imaging Studies of Episodic memory

Author	Task	Contrast	CON>SCZ	SCZ>CON
Achim 07	Word List Recognition	Arbitrary > Semantically-related Word pairs	bilat Hpc, bilat PHipG, bilat Entorhinal	n/a
		Recog > nonrecog	n/a	lPCG
Andreasen 96 (PET)	Story Recall	Recall of Practiced Story vs baseline	lAntFr, rMedFr	n/a
Assaf 06	Verbal Object Recall	Recall>Nonrecall	n/a	rDLPFC, rIFG, bilatPre- SMA/ dACC, vACC, lPCG
Barch 02	Verbal/Face Recognition	Encoding > Baseline	rDLPFC (9); lHpc/ PHipG (words only)	SMA (6)
		Recognition > Baseline	rDLPFC, Medial PFG (8)	SMA (6)
Bonner- Jackson 05	LOP (Words, Faces)	Deep >Shallow	n/a	lIFG (BA45), rIFG (45), lMFG (BA 10); Perf-matched subgroups: lIFG
Crespo- Facorro 99 (PET)	Word List Recall	Practiced List > Baseline	lDLPFC (46), lSMA (6), bilatMedFG (32), rMedFG (43), rPreMot (6)	n/a
		Novel List > baseline	lIFG (44), rt ACC (32/34)	n/a
Crespo- Facorro 01 (PET)	Word Recognition	Novel Recog > Practiced Recog	Bilat SFG (8), rMFG/ IFG (46/10), lPCG (6), bilat rACC (24/32), bilat OFG (11,13), rGRect (14)	n/a
Heckers 98 (PET)	Word List Recall	High Recall > Low Recall	rHpc	rPFC (10)
Heinze 06	Word List Recall	Forgot > Recall	rHpc	rIFG (47)
		Recall > Forgot	n/a	rIFG
Hofer 03a	Word List Recog	Encoding > Baseline	rPFC (10,9)	n/a
		Recognition > Baseline	L PFC (46,6), rPFC (46)	n/a
Hofer 03b	Word List Recog	Encoding > Baseline	rPFC (10)	n/a
		Recog > Baseline	lPFC (46,9,8,4), rPFC (9)	Bilat Ant PFC (10), lPFC (6)
Lepage 06	Visual Object Pair and Item Recog	Assoc > Item Encoding	L MFG (9), ACC (24), PCG (6)	n/a
		Assoc > Item Recog	lMFG (46), rIFG (47), rMedFG (8)	n/a
Ragland 05	LOP Words	Deep > Shallow Encoding	n/a	lHpc
		Deep > Shallow Recog	n/a	lMFG (10)
Ragland 04	Word List Recog	Encoding > Baseline	rMFG (46), lMFG/ PCG (9,6)	lPCG (4), l PHipG (19), rPHipG (30)
		Recog > Baseline	lMFG (10), rPCG (6)	rMFG (11), lPCG (4,6), lMedFG (6)
Ragland 01	Word List Recog	Encoding > baseline	lPFC (45,8,9)	n/a
		Recog > Baseline	lPFC (46,8,9,32)	n/a
Ragland 98 (PET)	Paired Assoc Recognition	Recog > Baseline	Inf IFG, OFG	DLPFC
Weiss 06	Word List Recognition	Correct New Item Rejection: Long Delay > Short Delay	n/a	lPFC (46), rPFC (47,9), lSMA (6)
Weiss 03	Word-Stem Retrieval Memory: Semantically vs Perceptually- Encoded	Retrieval of Semantically-Encoded > Perceptually-Encoded	rMTL	lPFC (47), FrPole (10), lOFC (11)
		Retrieval of Semantically-Encoded > Baseline	lPFC (47), rHpc	Fr Pole (10), lOFC (11)
		Repeat-Encoding (High Recall) > Baseline	Bilat PFC (47)	n/a

Summary from all English-language peer-reviewed reports (as of 02/27/08) of schizophrenia patients (SCZ) and healthy comparison subjects (CON) performing episodic memory tasks, of all statistically-significant between-group differences for prefrontal cortical regions (PFC) and/or medial temporal lobe regions (MTL). Studies included only if reporting whole-brain analysis, and significant PFC and/or MTL group differences. All are functional magnetic resonance imaging studies unless otherwise indicated. LOP, levels-of-processing; PET, positron emission tomography; l, left hemisphere; r, right hemisphere; bilat, bilateral; AntFr, anterior frontal; Med Fr, medial frontal; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; SMA,

supplemental motor area; ACC, anterior cingulate cortex; vACC, ventral anterior cingulate cortex;; rACC, rostral anterior cingulate cortex; PCG, precentral gyrus; Hpc, hippocampus; PHipG, parahippocampal gyrus; Medial PFG, medial prefrontal gyrus; MFG, middle frontal gyrus; PreMot, premotor cortex; SFG, superior frontal gyrus; OFG, orbitofrontal gyrus; GRect, gyrus rectus. Brodmann Areas indicated in parentheses.