The Cognitive Neuroscience of Memory Function and Dysfunction in Schizophrenia

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Patients with schizophrenia have pronounced deficits in memory for events—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 (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) 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.

Key Words: Cognitive, episodic, fMRI, hippocampus, medial temporal lobes, memory, neuroimaging, neuroscience, prefrontal cortex, relational, schizophrenia

Virtually every significant act of daily living requires the ability to remember past events—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 meeting of the CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) 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 might be disproportionately affected by the illness, possibly owing to focal or distributed dysfunction in the lateral prefrontal cortex (PFC) and medial temporal lobes (MTL).

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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 (Figure 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 toward 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. Accumulating evidence from neuroscience suggests that, beyond interference, "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

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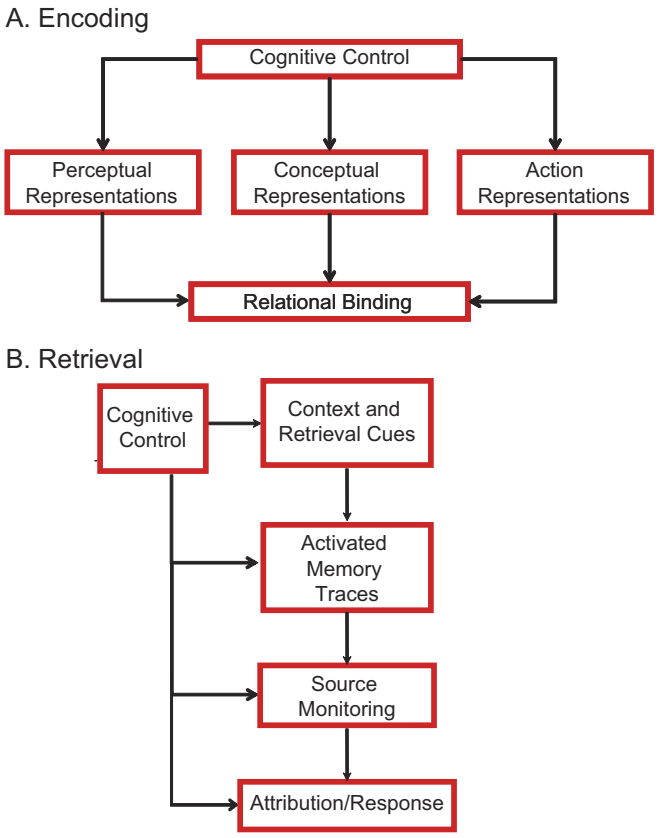

Figure 1. Schematic diagram of the processes that support memory encoding and retrieval. **(A)** Episodic memories require the binding of perceptual, conceptual, and action processes that are engaged during an event. Cognitive control processes play a particular role in determining the types of processing 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 on the basis of what is recovered.

the delay (23). Other research suggests that consolidation of certain kinds of information might be enhanced (e.g., 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") 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, because it is necessary to plan and focus on goal-relevant information. In contrast, if a specific retrieval cue is available, then these strategic factors might 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 might be automatically elicited after viewing the person's face (29). Even in this case, however, cognitive control can be helpful, because it is sometimes necessary to inhibit irrelevant information that might 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) might 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 (e.g., "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 in the preceding text, 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 in the following text, this research might 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 seem to be largely intact in most other areas of cognition (e.g., 39).

More recently, researchers have 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 amnesic patients (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 might 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 might 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 seem 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 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; Brodmann area [BA] 44, 45, and 47) might 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 functional magnetic resonance imaging (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

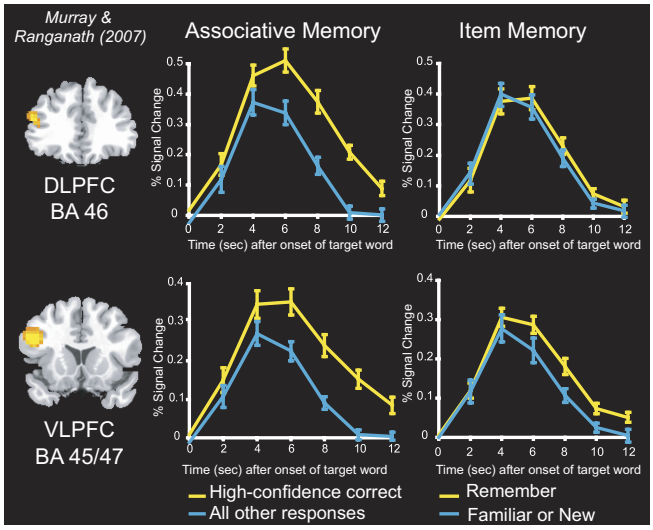

Figure 2. Results from Murray and Ranganath (66), showing that activity in dorsolateral prefrontal cortex (DLPFC) is specifically correlated with memory for associations between items. In this study, participants were scanned while encoding pairs of words, and later participants were tested on memory for the items and associations that were studied. In the left DLPFC (Brodmann area [BA] 46; top row), analyses of data on the basis of 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 ventrolateral prefrontal cortex (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 in DLPFC, activity in VLPFC was also increased during processing of items that were later remembered, as compared with subsequently forgotten items.

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 Figure 2 for an example).

The basic research summarized in the preceding text suggests that the PFC and MTL might play complementary roles in supporting normal episodic memory performance. Regions in the MTL might be critical for normal episodic memory—in particular, the perirhinal cortex might encode representations that support familiarity-based recognition, whereas the hippocampus might encode representations that support recollection. Regions in the PFC might 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 might 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 gender (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 earlier) 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 seem 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 seems that patients typically do not use semantic encoding strategies to facilitate encoding and retrieval (68,80–83). This might 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 unblocked 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 might 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 herein, however, is that selective recollection/recall deficits might simply reflect greater sensitivity of these measures, as compared with 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 in the preceding text, 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 *et al.* (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 control subjects 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 control subjects 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 control subjects 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 control subjects), 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" and "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 might exhibit selective dysfunction in the DLPFC and hippocampus, particularly on relational memory measures.

Directions for Treatment Development

The CNTRICS workgroup agreed that, on the basis of the strong evidence from basic neuroscience and psychology research, 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 coincident context, stimuli, or events). There is good reason to believe that relational memory, as described in the previous section, might be disproportionately affected in schizophrenia, whereas item-specific memory might 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. In addition to neuropsychological evidence, researchers have uncovered molecular and cellular abnormalities within the hippocampus and PFC (117–119) that might underlie the circuit-level dysfunction identified in imaging studies. Accordingly, prefrontal and hippocampal regions might 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 might be relatively preserved in schizophrenia. Thus, cognitive rehabilitation efforts might be able to build on these spared mechanisms 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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1. Tulving E (1972): Episodic and semantic memory. In: Tulving E, Donaldson W, editors. *Organization of Memory*. New York: Academic Press, 382–402.
2. Aleman A, Hijman R, de Haan EH, Kahn RS (1999): Memory impairment in schizophrenia: A meta-analysis. *Am J Psychiatry* 156:1358–1366.
3. Heinrichs RW, Zakzanis KK (1998): Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology* 12: 426–445.
4. Green JF, King DJ (1998): The effects of chlorpromazine and lorazepam on abnormal antisaccade and no-saccade distractibility. *Biol Psychiatry* 44:709–715.
5. Goldberg TE, Greenberg RD, Griffin SJ, Gold JM, Kleinman JE, Pickar D, *et al.* (1993): The effect of clozapine on cognition and psychiatric symptoms in patients with schizophrenia. *Br J Psychiatry* 162:43–48.
6. Goldberg TE, Goldman RS, Burdick KE, Malhotra AK, Lencz T, Patel RC, *et al.* (2007): Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: Is it a practice effect? *Arch Gen Psychiatry* 64:1115–1122.

7. Harvey PD, Keefe RS (2001): Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *Am J Psychiatry* 158:176–184.
8. Green AI (2000): What is the relationship between schizophrenia and substance abuse? *Harv Ment Health Lett* 17:8.
9. Green MF (1996): What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 153:321–330.
10. Milev P, Ho BC, Arndt S, Andreasen NC (2005): Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: A longitudinal first-episode study with 7-year follow-up. *Am J Psychiatry* 162:495–506.
11. Craik F, Lockhart R (1972): Levels of processing: A framework for memory research. *J Verb Lean Verb Behav* 11:671–684.
12. Craik FI (2002): Levels of processing: Past, present, and future? *Memory* 10:305–318.
13. Atkinson R, Shiffrin R (1968): Human memory: A proposed system and its control processes. In: Spence K, Spence J, editors. *The Psychology of Learning and Motivation* New York: Academic Press, 89–105.
14. Atkinson RC, Shiffrin RM (1971): The control of short-term memory. *Sci Am* 225:82–90.
15. Hunt RR, Einstein GO (1981): Relational and item-specific information in memory. *Journal of Verbal Learning and Verbal Behavior* 20:497–514.
16. Hunt RR, McDaniel MA (1993): The enigma of organization and distinctiveness. *J Mem Lang* 32:421–445.
17. Bower GH (1970): Organizational factors in memory. *Cognit Psychol* 1:18–46.
18. Tulving E (1962): Subjective organization in free recall of "unrelated" words. *Psychol Rev* 69:344–354.
19. Blumenfeld RS, Ranganath C (2007): Prefrontal cortex and long-term memory encoding: An integrative review of findings from neuropsychology and neuroimaging. *Neuroscientist* 13:280–291.
20. Bower GH (1970): Imagery as a relational organizer in associative learning. *J Verb Learn Verb Behav* 9:529–533.
21. McGeoch JA, McDonald WT (1931): Meaningful relation and retroactive inhibition. *American Journal of Psychology* 43:579–588.
22. Milner B, Squire LR, Kandel ER (1998): Cognitive neuroscience and the study of memory. *Neuron* 20:445–468.
23. LaBar KS, Cabeza R (2006): Cognitive neuroscience of emotional memory. *Nat Rev Neurosci* 7:54–64.
24. Born J, Rasch B, Gais S (2006): Sleep to remember. *Neuroscientist* 12: 410–424.
25. Raaijmakers JGW, Shiffrin RM (1981): Search of associative memory. *Psychol Rev* 88:93–134.
26. Bartlett FC (1932): *Remembering: A Study in Experimental and Social Psychology* New York: MacMillan.
27. Johnson MK, Hashtroudi S, Lindsay DS (1993): Source monitoring. *Psychol Bull* 114:3–28.
28. Kintsch W (1970): Models for free recall and recognition. In: Norman DA, editor. *Models of Human Memory* New York: Academic Press.
29. Yonelinas AP (2002): The nature of recollection and familiarity: A review of 30 years of research. *J Mem Lang* 46:441–517.
30. Jacoby LL (1991): A process dissociation framework: Separating automatic from intentional uses of memory. *J Mem Lang* 30:513–541.
31. Ranganath C, Paller KA (1999): Frontal brain potentials during recognition are modulated by requirements to retrieve perceptual detail. *Neuron* 22:605–613.
32. Ranganath C, Paller KA (2000): Neural correlates of memory retrieval and evaluation. *Brain Res Cogn Brain Res* 9:209–222.
33. Rugg MD, Wilding EL (2000): Retrieval processing and episodic memory. *Trends Cogn Sci* 4:108–115.
34. Tulving E, Thomson DM (1973): Encoding specificity and retrieval processes in episodic memory. *Psychol Rev* 80:352–373.
35. Morris CD, Bransford JD, Franks JJ (1977): Levels of processing versus transfer appropriate processing. *Journal of Verbal Learning and Behavior* 16:519–533.
36. Schacter DL (1999): The seven sins of memory. Insights from psychology and cognitive neuroscience. *Am Psychol* 54:182–203.
37. Eichenbaum H, Yonelinas AR, Ranganath C (2007): The medial temporal lobe and recognition memory. *Annu Rev Neurosci* 30:123–152.
38. Scoville WB, Milner B (1957): Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* 20:11–21.
39. Corkin S (1984): Lasting consequences of bilateral medial temporal lobectomy: Clinical course and experimental findings in H.M. *Seminars in Neurology* 4:249–259.
40. Lavanex P, Amaral D (2000): Hippocampal-neocortical interaction: A hierarchy of associativity. *Hippocampus* 10:420–430.
41. Witter MP, Naber PA, van Haeften T, Machielsen WC, Rombouts SA, Barkhof F, *et al.* (2000): Cortico-hippocampal communication by way of parallel parahippocampal- subicular pathways. *Hippocampus* 10:398–410.
42. Burwell RD (2000): The parahippocampal region: Corticocortical connectivity. *Ann N Y Acad Sci* 911:25–42.
43. Yonelinas AP, Kroll NE, Quamme JR, Lazzara MM, Sauve MJ, Widaman KF, *et al.* (2002): Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity. *Nat Neurosci* 5:1236–1241.
44. Bowles B, Crupi C, Mirsattari SM, Pigott SE, Parrent AG, Pruessner JC, *et al.* (2007): Impaired familiarity with preserved recollection after anterior temporal-lobe resection that spares the hippocampus. *Proc Natl Acad Sci U S A* 104:16382–16387.
45. Fortin NJ, Wright SP, Eichenbaum H (2004): Recollection-like memory retrieval in rats is dependent on the hippocampus. *Nature* 431:188–191.
46. Sauvage MM, Fortin NJ, Owens CB, Yonelinas AP, Eichenbaum H (2008): Recognition memory: Opposite effects of hippocampal damage on recollection and familiarity. *Nat Neurosci* 11:16–18.
47. Diana RA, Yonelinas AP, Ranganath C (2007): Imaging recollection and familiarity in the medial temporal lobe: A three-component model. *Trends Cogn Sci* 11:379–386.
48. Hirst W, Volpe BT (1988): Memory strategies with brain damage. *Brain Cogn* 8:379–408.
49. Incisa della Rochetta A, Milner B (1993): Strategic search and retrieval initiation: The role of the frontal lobes. *Neuropsychologia* 31:503–524.
50. Stuss DT, Alexander MP, Palumbo CL, Buckle L, Sayer L, Pogue J (1994): Organizational strategies of patients with unilateral or bilateral frontal lobe injury in word list learning tasks. *Neuropsychology* 8:355–373.
51. Gershberg FB, Shimamura AP (1995): Impaired use of organizational strategies in free recall following frontal lobe damage. *Neuropsychologia* 33:1305–1333.
52. Kesner RP, Hopkins RO, Fineman B (1994): Item and order dissociation in humans with prefrontal cortex damage. *Neuropsychologia* 32:881–891.
53. Swick D, Knight RT (1996): Is prefrontal cortex involved in cued recall? A neuropsychological test of PET findings. *Neuropsychologia* 34:1019–1028.
54. Dimitrov M, Granetz J, Peterson M, Hollnagel C, Alexander G, Grafman J (1999): Associative learning impairments in patients with frontal lobe damage. *Brain Cogn* 41:213–230.
55. Alexander MP, Stuss DT, Fansabedian N (2003): California Verbal Learning Test: Performance by patients with focal frontal and non-frontal lesions. *Brain* 126:1493–1503.
56. Wheeler MA, Stuss DT, Tulving E (1995): Frontal lobe damage produces episodic memory impairment. *J Int Neuropsychol Soc* 1:525–536.
57. Ranganath C, Knight RT (2003): Prefrontal cortex and episodic memory: Integrating findings from neuropsychology and event-related functional neuroimaging. In: Parker A, Wilding E, Bussey T, editors. *The Cognitive Neuroscience of Memory Encoding and Retrieval.* Philadelphia: Psychology Press, 83–99.
58. Ranganath C, Blumenfeld RS (2008): Prefrontal cortex and memory. In: Byrne JH, editor. *Learning and Memory: A Comprehensive Reference*. Oxford, UK: Academic Press, 261–279.
59. Shimamura AP (1996): The role of prefrontal cortex in monitoring and controlling memory processes. In: Reder L, editor. *Implicit Memory and Metacognition.* Mahwah, New Jersey: Erlbaum, 259–274.
60. Badre D, Wagner AD (2007): Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia* 45:2883–2901.
61. Thompson-Schill SL, Bedny M, Goldberg RF (2005): The frontal lobes and the regulation of mental activity. *Curr Opin Neurobiol* 15:219–224.
62. Buckner RL (2003): Functional-anatomic correlates of control processes in memory. *J Neurosci* 23:3999–4004.
63. Wendelken C (2001): The role of mid-dorsolateral prefrontal cortex in working memory: A connectionist model. *Neurocomputing* 44–46: 1009–1016.
64. Wagner AD (1999): Working memory contributions to human learning and remembering. *Neuron* 22:19–22.

65. Blumenfeld RS, Ranganath C (2006): Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. *J Neurosci* 26:916–925.
66. Murray LJ, Ranganath C (2007): The dorsolateral prefrontal cortex contributes to successful relational memory encoding. *J Neurosci* 27:5515–5522.
67. Summerfield C, Greene M, Wager T, Egner T, Hirsch J, Mangels J (2006): Neocortical connectivity during episodic memory formation. *PLoS Biol* 4:e128.
68. Gold JM, Randolph C, Carpenter CJ, Goldberg TE, Weinberger DR (1992): Forms of memory failure in schizophrenia. *J Abnorm Psychol* 101:487–494.
69. Gur RC, Moelter ST, Ragland JD (1999): Learning and memory in schizophrenia. In: Sharma T, Harvey P, editors. *Cognition in Schizophrenia*. Oxford: Oxford University Press.
70. McKenna PJ, Tamlyn D, Lund CE, Mortimer AM, Hammond S, Baddeley AD (1990): Amnesic syndrome in schizophrenia. *Psychol Med* 20:967–972.
71. Rund BR (1989): Distractibility and recall capability in schizophrenics. A 4 year longitudinal study of stability in cognitive performance. *Schizophr Res* 2:265–275.
72. Saykin AJ, Gur RC, Gur RE, Mozley PD, Mozley LH, Resnick SM, *et al.* (1991): Neuropsychological function in schizophrenia. Selective impairment in memory and learning. *Arch Gen Psychiatry* 48:618–624.
73. Tamlyn D, McKenna PJ, Mortimer AM, Lund CE, Hammond S, Baddeley AD (1992): Memory impairment in schizophrenia: Its extent, affiliations and neuropsychological character. *Psychol Med* 22:101–115.
74. Seidman LJ, Stone WS, Jones R, Harrison RH, Mirsky AF (1998): Comparative effects of schizophrenia and temporal lobe epilepsy on memory. *J Int Neuropsychol Soc* 4:342–352.
75. Saykin AJ, Shtasel DL, Gur RE, Kester DB, Mozley LH, Stafiniak P, *et al.* (1994): Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. *Arch Gen Psychiatry* 51:124–131.
76. Censits DM, Ragland JD, Gur RC, Gur RE (1997): Neuropsychological evidence supporting a neurodevelopmental model of schizophrenia: A longitudinal study. *Schizophr Res* 24:289–298.
77. Lysaker P, Bell M, Beam-Goulet J (1995): Wisconsin card sorting test and work performance in schizophrenia. *Psychiatry Res* 56:45–51.
78. Velligan DI, Bow-Thomas CC, Mahurin RK, Miller AL, Halgunseth LC (2000): Do specific neurocognitive deficits predict specific domains of community function in schizophrenia? *J Nerv Ment Dis* 188:518–524.
79. Heinrichs RW, Awad AG (1993): Neurocognitive subtypes of chronic schizophrenia. *Schizophr Res* 9:49–58.
80. Paulsen JS, Heaton RK, Sadek JR, Perry W, Delis DC, Braff D, *et al.* (1995): The nature of learning and memory impairments in schizophrenia. *J Int Neuropsychol Soc* 1:88–99.
81. Iddon JL, McKenna PJ, Sahakian BJ, Robbins TW (1998): Impaired generation and use of strategy in schizophrenia: Evidence from visuospatial and verbal tasks. *Psychol Med* 28:1049–1062.
82. Koh SD, Kayton L, Berry R (1973): Mnemonic organization in young nonpsychotic schizophrenics. *J Abnorm Psychol* 81:299–310.
83. Koh SD, Peterson RA (1978): Encoding orientation and the remembering of schizophrenic young adults. *J Abnorm Psychol* 87:303–313.
84. Brebion G, Amador X, Smith MJ, Gorman JM (1997): Mechanisms underlying memory impairment in schizophrenia. *Psychol Med* 27:383–393.
85. Stone M, Gabrieli JD, Stebbins GT, Sullivan EV (1998): Working and strategic memory deficits in schizophrenia. *Neuropsychology* 12:278–288.
86. McClain L (1983): Encoding and retrieval in schizophrenics' free recall. *J Nerv Ment Dis* 171:471–479.
87. Ragland JD, Moelter ST, McGrath C, Hill SK, Gur RE, Bilker WB, *et al.* (2003): Levels-of-processing effect on word recognition in schizophrenia. *Biol Psychiatry* 54:1154–1161.
88. Heaton R, Paulsen JS, McAdams LA, Kuck J, Zisook S, Braff D, *et al.* (1994): Neuropsychological deficits in schizophrenics. Relationship to age, chronicity, and dementia. *Arch Gen Psychiatry* 51:469–476.
89. Danion JM, Rizzo L, Bruant A (1999): Functional mechanisms underlying impaired recognition memory and conscious awareness in patients with schizophrenia. *Arch Gen Psychiatry* 56:639–644.
90. Weiss AP, Goff DC, Duff M, Roffman JL, Schacter DL (2008): Distinguishing familiarity-based from source-based memory performance in patients with schizophrenia. *Schizophr Res* 99:208–217.
91. Aggleton JP, Brown MW (1999): Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behav Brain Sci* 22:425–444.
92. Chapman LJ, Chapman JP (1973): Problems in the measurement of cognitive deficit. *Psychol Bull* 79:380–385.
93. Achim AM, Lepage M (2005): Episodic memory-related activation in schizophrenia: meta-analysis. *Br J Psychiatry* 187:500–509.
94. Heckers S, Rauch SL, Goff D, Savage CR, Schacter DL, Fischman AJ, *et al.* (1998): Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. *Nat Neurosci* 1:318–323.
95. Preston AR, Shohamy D, Tamminga CA, Wagner AD (2005): Hippocampal function, declarative memory, and schizophrenia: Anatomic and functional neuroimaging considerations. *Curr Neurol Neurosci Rep* 5:249–256.
96. Ragland JD, Gur RC, Valdez J, Turetsky BI, Elliott M, Kohler C, *et al.* (2004): Event-related fMRI of frontotemporal activity during word encoding and recognition in schizophrenia. *Am J Psychiatry* 161:1004–1015.
97. Weiss AP, Heckers S (2001): Neuroimaging of declarative memory in schizophrenia. *Scand J Psychol* 42:239–250.
98. Friston KJ, Frith CD (1995): Schizophrenia: A disconnection syndrome? *Clin Neurosci* 3:89–97.
99. Wolf DH, Gur RC, Valdez JN, Loughead J, Elliott MA, Gur RE, Ragland JD (2007): Alterations of fronto-temporal connectivity during word encoding in schizophrenia. *Psychiatry Res* 154:221–232.
100. Meyer-Lindenberg A, Poline JB, Kohn PD, Holt JL, Egan MF, Weinberger DR, *et al.* (2001): Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. *Am J Psychiatry* 158:1809–1817.
101. Meyer-Lindenberg AS, Olsen RK, Kohn PD, Brown T, Egan MF, Weinberger DR, *et al.* (2005): Regionally specific disturbance of dorsolateral prefrontal-hippocampal functional connectivity in schizophrenia. *Arch Gen Psychiatry* 62:379–386.
102. Boksman K, Theberge J, Williamson P, Drost DJ, Malla A, Densmore M, *et al.* (2005): A 4.0-T fMRI study of brain connectivity during word fluency in first-episode schizophrenia. *Schizophr Res* 75:247–263.
103. Weiss AP, Schacter DL, Goff DC, Rauch SL, Alpert NM, Fischman AJ, *et al.* (2003): Impaired hippocampal recruitment during normal modulation of memory performance in schizophrenia. *Biol Psychiatry* 53:48–55.
104. Kubicki M, McCarley RW, Nestor PG, Huh T, Kikinis R, Shenton ME, *et al.* (2003): An fMRI study of semantic processing in men with schizophrenia. *Neuroimage* 20:1923–1933.
105. Ragland JD, Gur RC, Valdez JN, Loughead J, Elliott M, Kohler C, *et al.* (2005): Levels-of-processing effect on frontotemporal function in schizophrenia during word encoding and recognition. *Am J Psychiatry* 162:1840–1848.
106. Bonner-Jackson A, Csernansky JG, Barch DM (2007): Levels-of-processing effects in first-degree relatives of individuals with schizophrenia. *Biol Psychiatry* 61:1141–1147.
107. Bonner-Jackson A, Haut K, Csernansky JG, Barch DM (2005): The influence of encoding strategy on episodic memory and cortical activity in schizophrenia. *Biol Psychiatry* 58:47–55.
108. Preston AR, Shrager Y, Dudukovic NM, Gabrieli JD (2004): Hippocampal contribution to the novel use of relational information in declarative memory. *Hippocampus* 14:148–152.
109. Ongur D, Cullen TJ, Wolf DH, Rohan M, Barreira P, Zalesak M, *et al.* (2006): The neural basis of relational memory deficits in schizophrenia. *Arch Gen Psychiatry* 63:356–365.
110. Nagode JC, Pardo JV (2002): Human hippocampal activation during transitive inference. *Neuroreport* 13:939–944.
111. Acuna BD, Sanes JN, Donoghue JP (2002): Cognitive mechanisms of transitive inference. *Exp Brain Res* 146:1–10.
112. Heckers S, Zalesak M, Weiss AP, Ditman T, Titone D (2004): Hippocampal activation during transitive inference in humans. *Hippocampus* 14:141–142.
113. Titone D, Ditman T, Holzman PS, Eichenbaum H, Levy DL (2004): Transitive inference in schizophrenia: Impairments in relational memory organization. *Schizophr Res* 68:235–247.
114. Lepage M, Montoya A, Pelletier M, Achim AM, Menear M, Lal S (2006): Associative memory encoding and recognition in schizophrenia: An event-related fMRI study. *Biol Psychiatry* 60:1215–1223.
115. Heckers S (2001): Neuroimaging studies of the hippocampus in schizophrenia. *Hippocampus* 11:520–528.
116. Boyer P, Phillips JL, Rousseau FL, Ilivitsky S (2007): Hippocampal abnormalities and memory deficits: New evidence of a strong pathophysiological link in schizophrenia. *Brain Res Rev* 54:92–112.

117. Coyle JT, Tsai G (2004): NMDA receptor function, neuroplasticity, and the pathophysiology of schizophrenia. *Int Rev Neurobiol* 59: 491–515.
118. Benes FM, Berretta S (2001): GABAergic interneurons: Implications for understanding schizophrenia and bipolar disorder. *Neuropsychopharmacology* 25:1–27.
119. Benes FM, Todtenkopf MS, Kostoulakos P (2001): GluR5,6,7 subunit immunoreactivity on apical pyramidal cell dendrites in hippocampus of schizophrenics and manic depressives. *Hippocampus* 11: 482–491.
120. Minzenberg MJ, Carter CS (2007): Modafinil: A review of neurochemical actions and effects on cognition [published online ahead of print August 22]. *Neuropsychopharmacology*.
121. Lysaker PH, Buck KD (2007): Neurocognitive deficits as a barrier to psychosocial function in schizophrenia: Effects on learning, coping, & self-concept. *J Psychosoc Nurs Ment Health Serv* 45:24–30.