The Cognitive Neuroscience of Memory Function and Dysfunction in Schizophrenia

Charan Ranganath, Michael J. Minzenberg, and J. Daniel Ragland

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).

From the Center for Neuroscience and Department of Psychology (CR); and the Department of Psychiatry and Behavioral Sciences (MJM, JDR), University of California at Davis, Davis, California.

Address reprint requests to Charan Ranganath, Ph.D., UC Davis Center for Neuroscience, 1544 Newton Ct., Davis, CA 95618; E-mail: cranganath@ucdavis.edu.

Received January 23, 2008; revised March 11, 2008; accepted April 1, 2008.

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

0006-3223/08/$34.00
doi:10.1016/j.biopsych.2008.04.011

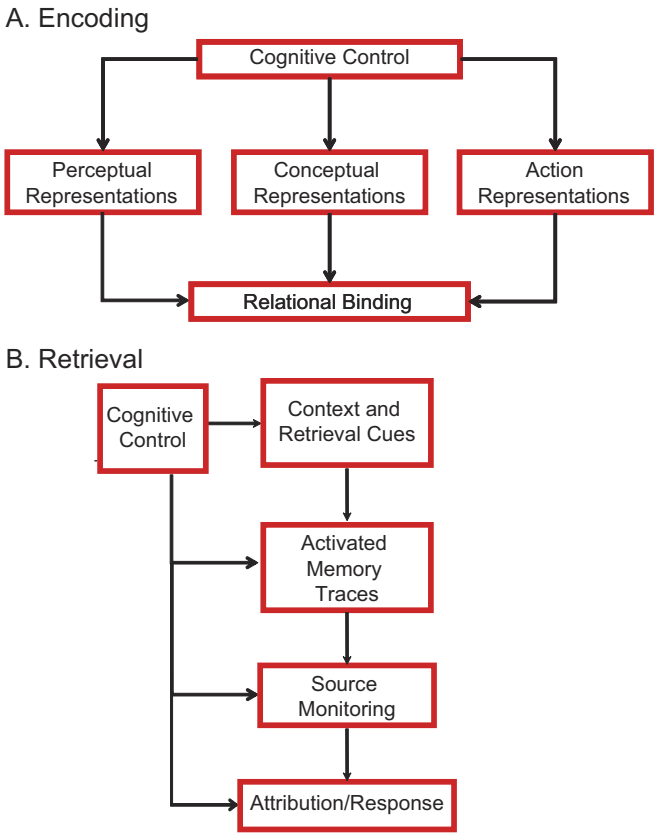

Figure 1. Schematic diagram of the processes that support memory encoding and retrieval. **(A)** Episodic memories require the binding of perceptual, conceptual, and action processes that are engaged during an event. Cognitive control processes play a particular role in determining the types of processing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