

Prefrontal Cortex and Episodic Memory: Integrating Findings from Neuropsychology and Functional Brain Imaging

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INTRODUCTION

Although it has been speculated for many years that the prefrontal cortex plays a role in long-term memory for events, or episodic memory, only recently have researchers made a concerted attempt to define this role. Most theories of prefrontal function suggest that this region implements “top-down” or “executive” processes that influence a variety of domains, including memory. For example, Luria (1966) postulated a role for the frontal lobes in the regulation of voluntary attention and the organization of goal-directed behavior. Building on the work of Luria, Shallice (1982) argued that the frontal lobes are required for the attentional selection of schemes of action in novel situations. A complementary role suggested for the prefrontal cortex is the suppression of irrelevant or interfering stimuli (Brutkowski, 1965; Fuster, 1997; Knight, Staines, Swick, & Chao, 1999; Pribram, Ahumada, Hartog, & Roos, 1964; Shimamura, 1995). Teuber (1964) additionally proposed that the frontal lobes prepare sensory areas for environmental changes that will be induced by motor actions. This concept was later extended to the

generation of anticipatory behavioral sets (Fuster, 1997; Nauta, 1971). Several researchers have also postulated a central role for the prefrontal cortex in active, or working memory (Fuster, 1997; Goldman-Rakic, 1987).

It is conceivable that an impairment in any of these functions could contribute to poor performance on tests of episodic memory. What remains unclear, however, is whether the role of the prefrontal cortex in episodic memory is best characterized as an extension of the “executive functions” described above, or whether prefrontal cortex contributes to additional functions specific to the formation and retrieval of memories. Furthermore, it is unclear whether there is functional specialization within prefrontal cortex, such that different subregions implement different functions relevant to episodic memory. In the following sections, we will review findings of neuropsychological data garnered from neurological patients as well as neuroimaging studies of prefrontal activity associated with episodic memory in healthy volunteers. From these findings, we will present a model of how prefrontal cortex contributes to episodic memory.

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NEUROPSYCHOLOGICAL STUDIES

Studies of verbal learning in patients with frontal lesions indicate that these patients, although impaired, do not demonstrate the same degree of global memory impairment seen in amnesic patients with damage of the diencephalon or medial temporal lobes (Janowsky, Shimamura, Kritchevsky, & Squire, 1989). For example, several studies have shown that patients with prefrontal lesions can show normal performance on tests of recognition memory (Jetter, Poser, Freeman, & Markowitsch, 1986), cued recall (Jeri S. Janowsky et al., 1989; Swick & Knight, 1996). It should be noted that these studies had small sample sizes, and consequently may not have been sensitive enough to detect mild memory deficits. Indeed, a review of these studies by Wheeler, Stuss, & Tulving (1995) concluded that, across studies, patients with prefrontal lesions tend to show mild deficits on tests of recognition memory.

Unlike recognition and cued recall tasks that provide subjects with an external cue to drive retrieval processes, free recall tasks require subjects to initiate strategic processes to search for memory items (Moscovitch, 1992). Findings from two studies suggest that frontal lobe damage may impair the initiation of such processes (Gershberg & Shimamura, 1995; Jetter et al., 1986). In one study, patients with prefrontal lesions studied three lists of categorized words to learn (the categories from the three lists did not overlap) with the instruction that the words could be encoded by semantic category (Jetter et al., 1986). Subjects were tested on the three lists either by free-recall, cued-recall, or recognition, after a 15 minute interval, and a one-day interval. Similarly, in experiments 2 and 3 of Gershberg & Shimamura's (1995) study, subjects were tested on immediate free recall of categorized lists. In both studies, patients showed a reduced tendency to report semantically related words together during recall. Importantly, in

Experiment 3 of Gershberg and Shimamura's (1995) study, patients who were given instructions to use a semantic organizational strategy (i.e. categorize the words) at encoding, retrieval, or both showed significant improvements in free recall performance, relative to patients who received no instructions. Furthermore, patients in Jetter et al.'s (1986) study performed at the same level as controls on cued recall and recognition, even at the 1-day delay. These findings suggest that patients with prefrontal lesions can perform at or near normal levels when given strategy instructions or retrieval cues.

Consistent with this idea, Incisa della Rochetta & Milner (1993) tested patients with unilateral frontal or hippocampal lesions and controls on recall of categorized lists. During the study phase, some categories of words were presented in blocks preceded by the name of the category, whereas others were intermixed. Next, subjects were either tested by free recall, or category cued recall. Patients with left frontal lesions were impaired in all encoding-retrieval conditions except for the blocked-category encoding, cued-recall condition. Thus, these patients were able to perform at normal levels only if given pre-organized material and presented with these organizational cues at retrieval. Collectively, the results obtained by Jetter and colleagues, Gershberg and Shimamura, and Incisa della Rochetta & Milner strongly suggest that patients with prefrontal lesions exhibit impairments in self-initiated organizational processes, that are particularly relevant to free recall performance. Furthermore, these results demonstrate that even if these processes are not initiated at encoding, patients can still benefit from organizational cues at retrieval.

Patients with prefrontal lesions appear to show particular impairments remembering the context surrounding an event, termed source memory (Johnson, Hashtroudi, & Lindsay, 1993). For instance, Janowsky and colleagues (1989) taught patients with

prefrontal lesions, age-matched controls, and younger control participants a set of 20 trivia facts (e.g., “The last name of the actor who portrayed Dr. Watson in the Sherlock Holmes series was Bruce”). Later, participants were asked to recall these facts, as well as 20 facts that were not presented during the study phase (e.g., “What was the last name of the actor who portrayed Dr. Watson in the Sherlock Holmes series ?). For each correct response, each participant was then asked to recall the most recent time the fact was learned. Although patients showed normal recall and recognition for the facts, they were impaired at recalling when the fact was learned relative to age-matched and younger controls across a two-hour and a one-week retention interval.

Results from several other studies further support the notion that patients with prefrontal lesions have poor memory for the temporal context of events. For example, Shimamura and colleagues (Shimamura, Janowsky, & Squire, 1990) found that patients with prefrontal lesions exhibited intact recognition and only mildly impaired performance on free recall for words or historical events. These patients were disproportionately impaired, however, when asked to temporally order the information they had learned. Similarly, Milner and her colleagues (Milner, Corsi, & Leonard, 1991) had patients with unilateral prefrontal lesions and controls study a series of easily visualized words, representational drawings, or abstract designs. Periodically, participants were shown cards with two previously studied stimuli, and were asked to decide which was seen more recently. Results showed that patients with left frontal lesions were impaired only on recency discrimination for words, whereas patients with right frontal lesions were impaired on all three recency tasks.

In a follow-up to this experiment, McAndrews & Milner (1991), examined whether providing salient cues as to when items occurred could help patients with prefrontal

lesions overcome their deficits in temporal organization. In this study, patients with unilateral frontal lesions and controls were presented with a series of objects, one at a time, with instructions to name each object. Interspersed among these objects were “action items,” for which the subject was additionally asked to manipulate the object in some way. Later, they made three types of recency discriminations: between action items, between items that occurred before and after an action item respectively, and between two items not separated by an action item. Patients with left and right frontal lesions were impaired at all recency discriminations except for discriminations between two action items. In contrast, healthy controls did not show any differences across the three types of tasks, despite the fact that they were performing below ceiling (approximately 80%).

One potential explanation of these findings is that there were fewer action items than non-action items, so these findings might reflect an abnormal susceptibility to interference in the patients (Shimamura, 1995). Alternately, it is possible that, because encoding in this task was intentional, control subjects may have utilized organizational strategies to distinguish the temporal position of all of the items, whereas the patients may have only been able to organize the salient and temporally distant action items from one another.

These explanations cannot completely account for results of a subsequent study by Butters and colleagues (Butters, Kaszniak, Glisky, Eslinger, & Schacter, 1994). As in McAndrews & Milner’s (1991) study, patients with prefrontal lesions and matched controls were given recency discrimination tasks with objects that were either manipulated by the subject or simply named. In other study conditions, participants either visually imaged the objects, watched the experimenter manipulate the objects, or verbally elaborated on the nature of the objects. In accord with

previous studies (McAndrews & Milner, 1991; Milner et al., 1991), patients exhibited intact recognition for the objects and impaired recency judgments for named objects, imaged objects, and described objects. Importantly, patients and controls performed equally well at making recency judgments between objects that they manipulated.

It is unlikely that failure to control interference could explain the patients' pattern of performance in this experiment, because patients potentially faced equal levels of interference for all items but were only able to perform intact recency discriminations on manipulated objects. An alternate explanation is that the object manipulation task involved the encoding of motor and somatosensory information as well as visual and cognitive information, and that patients with prefrontal lesions can perform recency discrimination when they have several sources of such information to draw upon. One interpretation of these results is that whereas normal individuals have the ability to specify the source information required to make recency judgments, patients with prefrontal lesions are limited in what they can retrieve and require representations in several modalities to make such judgments (Johnson et al., 1993).

Accordingly, these findings suggest that an important facet of memory deficits following prefrontal lesions is an inability to use and evaluate retrieved information to make memory judgments (Johnson & Raye, 1998; Moscovitch, 1989). Recent findings suggest that, in addition to contributing to poor source memory, such memory monitoring deficits may also contribute to memory distortions in patients with prefrontal damage.

For example, several studies of patients with damage to the ventromedial prefrontal cortex (following rupture of an aneurysm of the anterior communicating artery) have reported significantly elevated false alarm rates on recognition memory tests (Delbecq-Derouesne, Beauvois, & Shallice, 1990; Parkin, Yeomans,

& Bindschaedler, 1994; Parkin, Bindschaedler, Harsent, & Metzler, 1996; Rapcsak et al., 1998; Rapcsak, Reminger, Glisky, Kaszniak, & Comer, 1999; Schnider, Gutbrod, Hess, & Schroth, 1996; Schnider & Ptak, 1999; Schnider, Ptak, von Daniken, & Remonda, 2000). A similar pattern was observed in a patient with a large right frontopolar lesion (Rapcsak et al., 1999), and a patient with a right ventrolateral prefrontal lesion (Curran, Schacter, Norman, & Galluccio, 1997; Schacter, Curran, Galluccio, Milberg, & Bates, 1996).

Further evidence of a memory monitoring deficit following prefrontal damage comes from a recent study in which event-related potential (ERP) and behavioral measures of recognition memory were recorded in patients with prefrontal lesions and controls (Swick & Knight, 1999). The majority of patients in this study had lesions of the left lateral PFC caused by strokes. Results showed that patients and controls exhibited equivalent hit rates and both exhibited ERP differences between old and new items thought to index recollection (Ranganath & Paller, 1999b). Patients with prefrontal lesions exhibited significantly higher false alarm rates, however, than did controls. Based on this pattern of results, Swick and Knight (1999) concluded that episodic recollection was intact in the patients, but patients were impaired in the evaluation of new words that may have elicited some degree of familiarity.

Altogether, available neuropsychological evidence demonstrates that prefrontal cortex is essential for the implementation of strategic, goal-directed processes. These reflective processes are not essential for episodic memory, but serve to enhance memory formation, facilitate retrieval, and evaluate the appropriateness of retrieved information (Johnson, 1992). But these findings provide little evidence for the idea that prefrontal cortex implements processes specific to episodic memory.

Nonetheless, there are reasons to believe that human neuropsychological studies may underestimate the importance of prefrontal cortical regions to episodic memory. For example, the studies reviewed earlier typically had small sample sizes and were unable to subdivide patients into damage in subregions of lateral and orbital prefrontal cortex. Thus, if prefrontal regions make differential contributions to episodic memory performance, such effects might be obscured by the variability of lesion locations in group analyses.

Furthermore, most patients in these studies had unilateral lesions, so their memory performance may have been supported by compensatory activity in the nonlesioned hemisphere (Chao & Knight, 1998). Results from one study showed that when stimuli were presented to the left or right hemifields, patients exhibited recognition memory deficits and corresponding alterations in ERPs for stimuli presented contralateral to the lesioned hemisphere (Nielsen-Bohlman & Knight, 1999, see Figure 1).

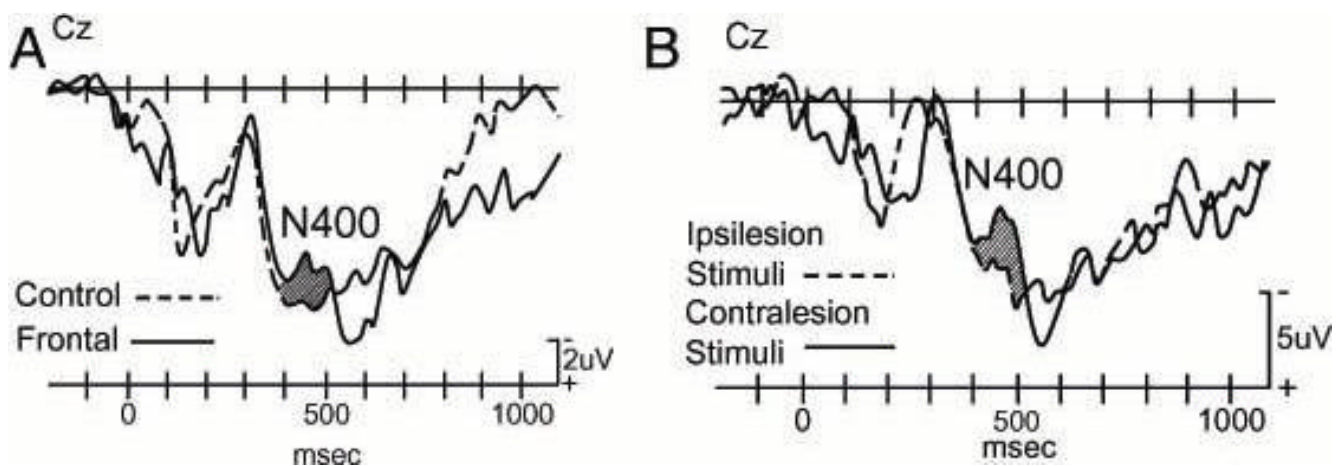


Figure 1. Results from an ERP study of recognition memory for objects in patients with lateral prefrontal lesions and matched controls. In this study, participants performed a continuous recognition task with objects presented to either the left or right hemifield. Behavioral results showed that at short delays, patients exhibited recognition impairments relative to controls for objects presented to the contralesional hemifield. (A) Patients with prefrontal lesions exhibited an enhanced N400 component for these stimuli, relative to control subjects. (B) N400 amplitudes within patients with prefrontal lesions were greater for objects presented to the contralesional than the ipsilesional hemifield. These results suggest that, although patients with unilateral prefrontal lesions may exhibit intact recognition memory under most circumstances, impairments may be more apparent when stimuli are presented directly to the lesioned hemisphere.

NEUROIMAGING STUDIES

Another important source of evidence regarding the contributions of prefrontal regions to episodic memory has come from neuroimaging studies of healthy volunteers. Although neuroimaging results cannot reveal whether prefrontal regions are necessary for episodic memory, they can reveal insights into the functional organization of the prefrontal cortex with a high degree of spatial resolution. Findings from these studies suggest that

multiple prefrontal regions exhibit dissociable patterns of activity during episodic encoding and retrieval tasks (Buckner & Petersen, 1996; Nyberg, Cabeza, & Tulving, 1996; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994; Wagner, 1999). Based on early findings from positron emission tomography (PET) studies of episodic memory, Tulving and colleagues proposed the Hemispheric Encoding Retrieval Asymmetry (HERA) model of episodic memory (Nyberg et al., 1996; Tulving et al.,

1994). According to this model, left prefrontal cortex is more involved in semantic encoding of information into episodic memory, whereas right prefrontal cortex is more involved in episodic retrieval. Subsequent research, however, revealed that both left and right prefrontal regions are active during encoding and retrieval (Buckner & Petersen, 1996; Wagner, 1999). These developments, in turn, have led to more specific hypotheses regarding functional contributions of prefrontal subregions to episodic memory processing. We will review findings of prefrontal activation during episodic encoding and retrieval and suggest how these findings might be integrated with the neuropsychological results reviewed earlier.

Several studies have reported activation in ventrolateral prefrontal cortex, including the inferior frontal gyrus (brodmann's areas [BA] 44, 45, & 47) and precentral sulcus (BAs 6 & 44) during intentional encoding (Buckner & Petersen, 1996; Wagner, 1999). Encoding activations in regions of dorsolateral prefrontal cortex in portions of the middle frontal gyrus (BAs 9 & 46) have also been reported (Ranganath, Johnson, & D'Esposito, 2000). These results suggest that activation in ventrolateral PFC tends to be lateralized according to the type of material that is encoded. For example, activation was greater in the right than the left inferior frontal and precentral gyri during encoding of faces or other nonverbal information, the opposite pattern was observed during encoding of words (Kelley et al., 1998; McDermott, Buckner, Petersen, Kelley, & Sanders, 1999; Wagner, Poldrack et al., 1998). These findings are in agreement with prior neuropsychological findings (Milner, 1971), but no imaging studies have investigated what computational differences between the hemispheres might produce such specialization (see Ivry & Robertson, 1998; Kosslyn, 1987; Marsolek, Kosslyn, & Squire, 1992, for discussion of some possibilities).

An important question regarding these activations is whether they are epiphenomenal, or whether they actually reflect processes that contribute to memory encoding. Five recent event-related functional magnetic resonance imaging (fMRI) studies have reported that prefrontal activation during encoding actually predicts later memory (Aguirre, Zarahn, & D'Esposito, 1997; Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Kirchoff, Wagner, Maril, & Stern, 2000; Wagner, Schacter et al., 1998). In these studies, participants were scanned during encoding of words (Aguirre et al., 1997; Henson, Rugg et al., 1999; Wagner, Schacter et al., 1998) or scenes (Brewer et al., 1998; Kirchoff et al., 2000) and encoding activity was correlated with subsequent recognition judgments. Across these studies, encoding activation in the inferior frontal gyrus was greater for items that were subsequently remembered than for items that were forgotten. Furthermore, these subsequent memory effects were relatively right lateralized for visual scenes and left lateralized for words (Brewer et al., 1998; Henson, Rugg et al., 1999; Kirchoff et al., 2000; Wagner, Schacter et al., 1998).

How does ventrolateral PFC contribute to subsequent memory effects? One possibility is that these regions mediate "working memory" processes that act to enhance memory encoding (Aguirre et al., 1997; Wagner, 1999). For example, regions in the left inferior frontal gyrus have been associated with the selection and maintenance of semantic information (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997), associated with "deep" encoding (Craik & Lockhart, 1972). Another possibility is that ventrolateral prefrontal activity is sensitive to the novelty/familiarity of the item (Knight & Nakada, 1998) and that this information can be used to make recognition judgments (Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998). Indeed, several studies have demonstrated enhanced

ventrolateral PFC activation for novel relative to familiar stimuli (e.g., Buckner et al., 1998; Kirchoff et al., 2000; Tulving, Markowitsch, Craik, Habib, & Houle, 1996), and patients with prefrontal lesions exhibit attenuated electrophysiological responses to novel stimuli (Knight, 1984, 1997; Yamaguchi & Knight, 1991, see Figure 2). Results from a recent study

showed that intact monkeys exhibited enhanced memory for novel relative to familiar information, whereas monkeys with prefrontal lesions failed to show this effect (Parker, Wilding, & Akerman, 1998). These findings suggest that novelty-related modulations of ventrolateral prefrontal activity may play a role in episodic memory encoding.

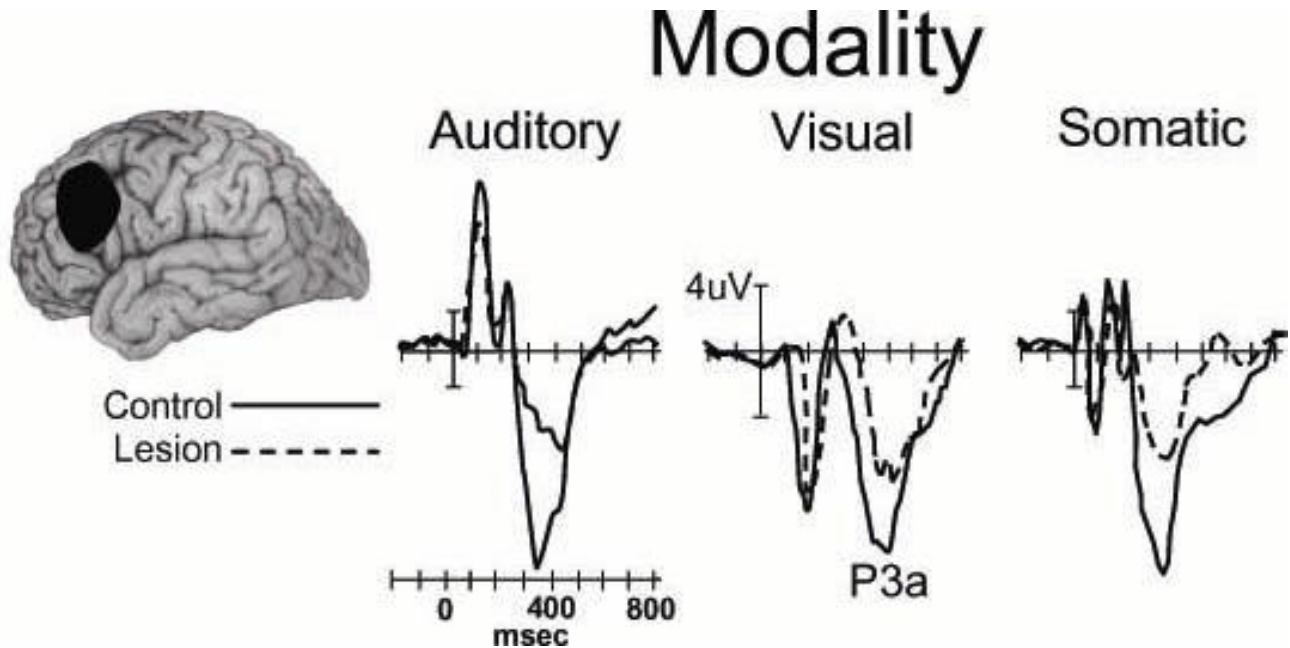


Figure 2. Electrophysiological evidence for attenuated responses to novel stimuli in patients with prefrontal damage (Knight, 1997). In these experiments, event-related brain potentials were recorded while patients with prefrontal damage and matched controls performed target detection tasks. In the auditory modality, targets and repeated nontarget stimuli were pure tones, and occasionally, irrelevant, novel distractors (e.g., a dog bark, a ringing bell, etc.) were presented. In the visual modality, targets and repeated nontarget stimuli were pure upright and inverted triangles, and occasionally, irrelevant, novel distractors, such as line drawings of objects or complex patterns were presented. In the somatosensory modality, targets and repeated nontarget stimuli were taps to the finger and occasional novel distractors consisted of brief random shocks to the median nerve. Novel stimuli across all modalities elicited a potential identifiable as the novelty P300, or the P3a. The magnitude of this potential was attenuated in patients with prefrontal damage, whereas electrophysiological responses to target and repeated nontargets were intact.

Although it is unclear precisely how ventrolateral prefrontal regions contribute to encoding, it is clear that these regions are also robustly activated during memory retrieval. For example, in one study, Ranganath, Johnson, & D'Esposito (Ranganath et al., 2000) used rapid presentation event-related fMRI to examine prefrontal activation during encoding and retrieval of objects. As shown in Figure 3, the same regions of the inferior frontal gyrus were

activated during both encoding and retrieval. Furthermore, region in the right middle frontal gyrus was activated during both tasks. Although activation was more extensive and robust in the retrieval condition, these results suggest that dorsolateral and ventrolateral prefrontal regions implement cognitive processes that can be tapped by encoding and retrieval tasks.

In addition to dorsolateral and ventrolateral PFC, results from several studies suggest that anterior prefrontal regions (BA 10/46) spanning the anterior middle, medial, and superior frontal gyri are particularly activated during retrieval tasks (Buckner & Petersen, 1996; Wagner, 1999). Unlike ventrolateral prefrontal regions, dorsolateral and anterior PFC activation does not appear to reliably lateralize according to the type of

material that is being processed (McDermott et al., 1999). Instead, the laterality of activation in these regions may be more dependent on the type of retrieval task that is being performed and the baseline against which this activity is compared (Nolde, Johnson, & D'Esposito, 1998; Nolde, Johnson, & Raye, 1998; Ranganath et al., 2000; Rugg, Fletcher, Chua, & Dolan, 1999).

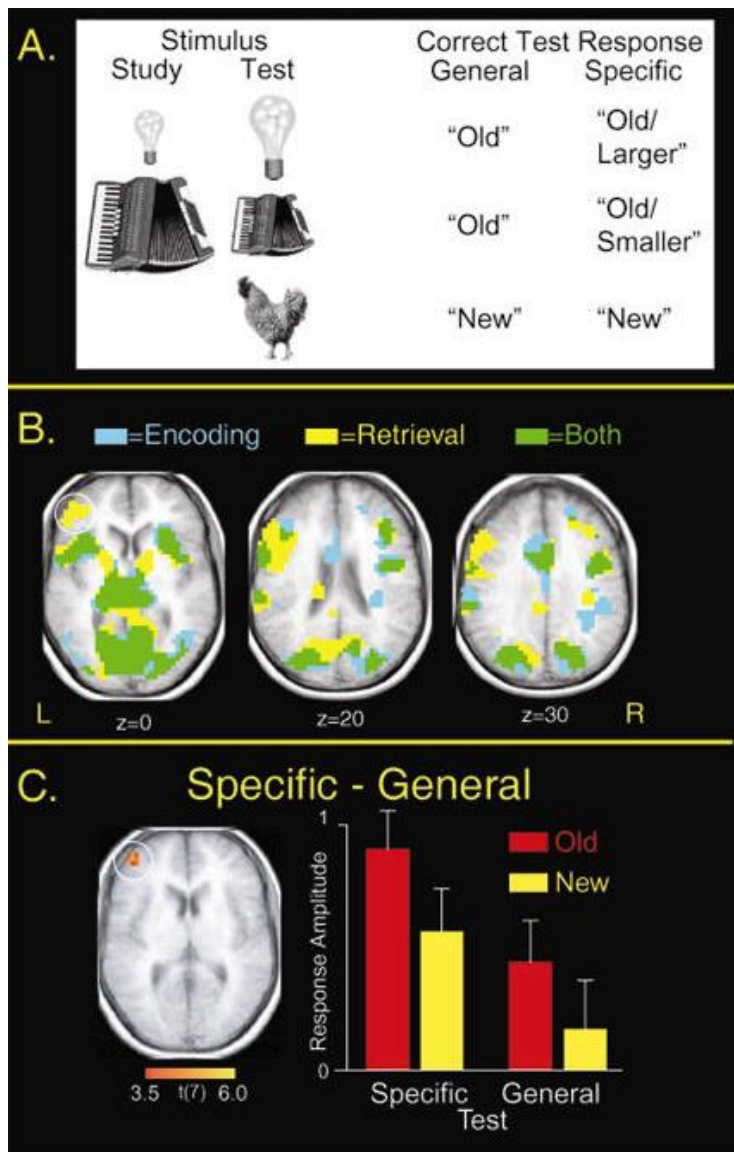


Figure 3. Results from a rapid presentation event-related fMRI study of episodic encoding and retrieval (Ranganath et al., 2000). (A) Examples of study and test stimuli and appropriate responses for each test condition. (B) Voxels were characterized according to whether they were reliably activated during encoding trials (blue), retrieval trials (yellow), or both (green). As shown in the figure, bilateral regions in anterior and posterior inferior frontal gyri (BAs 44, 45, & 47), and right superior frontal gyus (BA 9) were active during both trial types. (C) The circled region in left anterior prefrontal cortex was significantly more active during specific test trials than during general test trials. At right, a bar graph shows response amplitudes within this region in response to old and new objects in each test condition. Activation in the left anterior hippocampus (not shown) exhibited a similar pattern, suggesting that interactions between anterior prefrontal and hippocampal regions were critical for the monitoring and evaluation of specific memory characteristics in the specific test. Figure adapted from Ranganath, Johnson, & D'Esposito (2000).

For example, in their review of the neuroimaging literature, Nolde, Johnson, and Raye (1998) observed that relatively simple memory retrieval tasks revealed right-lateralized prefrontal activation, but more demanding retrieval tasks were more likely to reveal left-lateralized or bilateral activation in dorsalateral and anterior PFC (see Ranganath & Paller, 1999a, 1999b; 2000, for relevant electrophysiological evidence). Interestingly, the types of retrieval tasks that elicited left-lateralized prefrontal activation bear strong resemblance to the types of source memory tests that are sensitive to prefrontal damage (Henson, Shallice, & Dolan, 1999; S. F. Nolde et al., 1998; S.F. Nolde et al., 1998; Ranganath et al., 2000; Rugg et al., 1999). The findings of anterior prefrontal activation during blocked-trial studies of source memory could reflect a role for this region in the recollection of source information or in making the specific memory attributions required by such tasks (Donaldson & Buckner, 1999; Ranganath & Paller, 1999b).

In one event-related fMRI study, Ranganath, Johnson, and D'Esposito (2000) examined prefrontal responses during item and source memory tests to differentiate between these explanations. Eight volunteers in this study were scanned during encoding of objects and during retrieval tests that included size-changed versions of studied objects and unstudied objects. During the "general test", instructions were to disregard the size changes and indicate whether each object was old or new. During the "specific test", instructions were to additionally specify whether each studied object was enlarged or reduced. Although test conditions were blocked, responses to old and new objects within each test block could be separately examined, because the sequence of old and new items in each test and the inter-trial interval was randomized. Results showed that a region of the left anterior prefrontal cortex was more active during specific than general test trials, for both old and new objects. Because

differences were seen for both old and new objects, it was unlikely that activation in this region solely reflected retrieval of learned information. Furthermore, because accuracy rates and response times for new objects were virtually identical between the two test conditions, this result could not be attributed to global difficulty or time-on-task differences. Instead, these results suggest that left anterior PFC was implementing processes critical for the monitoring and evaluation of specific memory characteristics at retrieval.

NEUROPSYCHOLOGY AND NEUROIMAGING: INTEGRATING THE EVIDENCE

In summary, the neuropsychological and neuroimaging evidence we have reviewed converge on the idea that prefrontal cortex is not necessary for episodic encoding or retrieval. Instead, discrete prefrontal regions implement high level cognitive processes that can serve to enhance memory encoding and subsequent memory attributions. The degree to which these functions are tapped to perform the "Gestalt" functions that we refer to as episodic encoding or retrieval will depend on the task context. For example, ventrolateral prefrontal regions in the inferior frontal gyrus and precentral sulcus (BA 6, 44, 45, & 47) are robustly activated during both encoding and retrieval tasks, with the laterality of activation dependent on the type of information that is being processed. Importantly, transient ventrolateral prefrontal activity has been observed during tasks that tax attentional selection or inhibition processes (Corbetta et al., 1998; D'Esposito, Postle, Jonides, & Smith, 1998), whereas more sustained activity in this region has been observed during working memory tasks (D'Esposito, Postle, & Rypma, 2000). In light of the attentional deficits observed in patients with ventrolateral prefrontal damage (Barcelo, Suwazono, & Knight, 2000; Knight, 1984, 1997; Knight, Scabini, & Woods, 1989; Knight et al., 1999),

we propose that this region implements top-down control signals to bias processing in more posterior cortical regions (Knight et al., 1989, Barcelo et al 2000; Miller, Erickson, & Desimone, 1996). Accordingly, activation of this region during episodic memory tasks may reflect selection and maintenance of relevant attributes of study items and test cues (Ranganath & D'Esposito, 2000; Ranganath & Paller, 1999a, 1999b, 2000)

Unlike ventrolateral PFC, dorsolateral and anterior PFC may be more reliably activated during episodic retrieval than encoding tasks. Furthermore, this activity can be reliably enhanced by increasing the specificity of memory judgments at retrieval. Interestingly, a similar pattern of dorsolateral prefrontal activation is evident in studies of working memory—that is, dorsolateral PFC is sometimes active during working memory tasks that require simple maintenance, but activation in this region is further enhanced during tasks that require this information to be manipulated (D'Esposito, Postle, Ballard, & Lease, 1999; Postle, Berger, & D'Esposito, 1999). Accordingly, it has been suggested that dorsolateral PFC acts to monitor and manipulate active memory representations (D'Esposito et al., 2000; Petrides, 1996), and that activity in this region may also exhibit a transient or sustained time course (D'Esposito et al., 2000; Ranganath & D'Esposito, 2000; Ranganath et al., 2000), depending on task demands. These processes may be essential when specific attributes of retrieval cues must be compared with information retrieved from memory (S. F. Nolde et al., 1998; Ranganath et al., 2000; Ranganath & Paller, 1999b, 2000).

Our review also suggests important directions for new research regarding prefrontal contributions to memory. For example, although left and right dorsolateral and anterior prefrontal regions exhibit different patterns of activation across episodic retrieval tasks (S.F. Nolde et al., 1998), it is unclear precisely what these differences reflect. Another unresolved

question is whether anterior and dorsolateral prefrontal regions make distinct contributions to episodic retrieval (Ranganath et al., 2000).

Finally, perhaps the most important unresolved question in the literature is how regions in orbital prefrontal cortex (BA 11, 12, 13, 14) contribute to episodic memory. Unfortunately, little systematic work has been done to address this question in either the neuroimaging or neuropsychological literature. Given that this area of prefrontal cortex has extensive interconnections with medial and anterior temporal and retrosplenial cortical regions thought to be essential for memory formation, there is reason to believe this region may also play a special role in mnemonic processing—perhaps more so for emotionally charged material. Furthermore, some neuropsychological results suggest that amnesic patients with orbital prefrontal damage exhibit memory distortions, including spontaneous confabulation (Johnson, Hayes, D'Esposito, & Raye, in press; Moscovitch & Melo, 1997; Schnider, 2000; Schnider & Ptak, 1999; Schnider, von Daniken, & Gutbrod, 1996). Evidence from PET studies also suggests that orbital PFC is active during episodic memory tasks (Cabeza & Nyberg, 2000), particularly when previously relevant information retrieved from memory must be suppressed (Schnider, Treyer, & Buck, 2000). Unfortunately, most of the fMRI studies reviewed earlier were insensitive to orbital frontal activity, because of signal loss caused by susceptibility artifact. Recent fMRI methods have been developed, however, to image this region (Sobel et al., 1997). Application of these methods to event-related fMRI studies of episodic memory will undoubtedly help to identify the functional characteristics of this region.

In conclusion, neuropsychological and neuroimaging findings offer complementary and convergent perspectives on prefrontal contributions episodic memory. There is no module for episodic encoding or retrieval in

prefrontal cortex. Instead, results suggest that anterior, dorsolateral, and ventrolateral prefrontal regions implement strategic operations at encoding and retrieval. Depending on the experimental context, different subregions of prefrontal cortex are engaged to enable successful memory performance.

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