

CHAPTER 17

Frontal Lobes and Memory

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Casual observations of patients with focal frontal lobe lesions often reveal little if any cognitive impairment (Fuster, 1989; Hebb, 1945). At the same time, such patients display an assortment of cognitive deficits upon neuropsychological assessment (Janowsky et al., 1989c; Luria, 1980; Stuss & Benson, 1984). With respect to memory, focal frontal injury does not produce a severe amnesic disorder, such as that observed in patients with medial temporal damage, but it can cause more subtle, yet definable, memory deficits. These deficits take the form of an impairment in the *control* of memory (Moscovitch, 1992; Shimamura, 1995, 2000a), i.e. the prefrontal cortex appears to be crucial for the monitoring and control of memory processes, both at the time of encoding and at the time of retrieval. In this chapter, we describe patterns of memory impairment associated with focal damage to the prefrontal cortex. Specifically, we review the role of the prefrontal cortex in learning and recall, memory for contextual information, metamemory and retrieval from remote memory. We then relate these long-term memory deficits to impairments in on-line processing associated with working memory and attention. Finally, we put these deficits in the context of a more global view of prefrontal function.

LEARNING AND RECALL

Clinically, patients with focal prefrontal lesions do not exhibit an “amnesic syndrome”. This term has been reserved for the debilitating, new learning disorder associated with medial temporal damage (Gershberg & Shimamura, 1998; Squire, 1992). Moreover, standard clinical tests of learning and memory are often not sensitive to prefrontal lesions (Incisa della Rocchetta & Milner, 1993; Janowsky et al., 1989●), e.g. recognition memory in frontal patients is often not significantly different than that of controls (Janowsky et al., 1989●). Nonetheless, experimental studies of new learning in patients with frontal lobe lesions have identified specific memory deficits. The pattern of these deficits suggests that frontal patients suffer from a failure to utilize memory strategies to enhance encoding and retrieval.

Free Recall and Semantic Organization

Recall tasks require the ability to organize, encode and retrieve information with minimal external aids. Patients with prefrontal lesions exhibit significant memory impairment on tasks involving free recall of word lists (Baldo et al., in press; Dimitrov et al., 1999; Gershberg & Shimamura, 1995; Hildebrandt et al., 1998; Janowsky et al., 1989●; Stuss et al., 1994). These deficits are quite apparent on tests of delayed free recall and can also be observed on tests of cued recall, in which participants are presented with a cue at test (e.g. a category cue). However, when information is embedded within a rich, well-organized context, such as learning a story, frontal patients show relatively good recall (Incisa della Rocchetta & Milner, 1993; Janowsky et al., 1989●). Also, tasks that put minimal demands on effortful retrieval, such as word stem completion and category exemplar priming, are not sensitive to frontal lesions (Gershberg & Shimamura, 1998; Shimamura et al., 1992).

Several studies have shown that free recall impairment in frontal patients is due to a failure to make use of semantic organization inherent in list material (Hildebrandt et al., 1998; Hirst & Volpe, 1988; Jetter et al., 1986; Kopelman & Stanhope, 1998; Stuss et al., 1994). Semantic encoding has been assessed experimentally by comparing patients' memory for related vs. unrelated lists. Related lists consist of several exemplars (e.g. table, chair, uncle, mother) from different semantic categories (e.g. furniture, relatives), usually presented in a random order. In normal controls, recall for related lists is superior, because semantic associations within the list facilitate organization during learning and can act as a retrieval cue at test. In contrast, Hirst & Volpe (1988) found that frontal lobe patients did not show a benefit on related vs. unrelated lists during recall. Moreover, patients did not spontaneously use the semantic categories in the related lists to aid their performance. In a subsequent condition, frontal patients were directed to use the categories and were given explicit and lengthy instructions on how to encode related items. In this condition, frontal patients' performance rose to that of the control participants, demonstrating that frontal patients possess the ability to utilize semantic cues but do not do so spontaneously. In contrast, amnesic patients (mixed etiology) spontaneously made use of and benefited from categorization but, despite this, their performance across conditions was much lower overall compared to frontal patients and controls.

Other studies have assessed organizational strategies in frontal patients by manipulating the presence of category cues at encoding and retrieval. Incisa della Rocchetta & Milner (1993) tested patients on related lists and showed that organizational cues provided at encoding (blocked vs. random order) as well as at retrieval improved frontal patients' performance. Similarly, Gershberg & Shimamura (1995) provided category cues during learning and/or at test and found that frontal patients' performance improved significantly. These findings suggest that both encoding and retrieval are disrupted in frontal patients due to poor (spontaneous) utilization of strategic cues.

Semantic organization during memory encoding has also been assessed using semantic clustering measures. Given a related list of words, an effective strategy is to recall groups or clusters of items from each category. Patients with frontal lobe lesions exhibit reduced levels of semantic clustering (Baldo et al., in press; Gershberg & Shimamura, 1995). These studies have shown that reduced semantic clustering is present in both initial list-learning trials and on tests of delayed recall. Other studies, however, have not

found strong evidence for impaired semantic clustering in frontal patients (see Jetter et al., 1986; Stuss et al., 1994). One possible explanation for this discrepancy is the manner in which semantic clustering is computed. A recent study has called into question former methods for computing this factor and proposes a more sensitive formula for doing so (Stricker et al., in press). Using this method, Stricker et al. found that a group of patients with prefrontal lesions did indeed show impaired semantic clustering compared to control participants.

Other strategies for learning word lists include subjective and serial organization. Subjective organization is the tendency for an individual to cluster items across test trials, even when there is no apparent semantic association between the items, e.g. a participant might recall the words “table” and “dollar” in succession across several trials, even though these two words were never presented together in the list. Like semantic clustering, subjective organization involves reorganization or reencoding of list items. Not surprisingly, patients with frontal lobe lesions exhibit reduced subjective organization across learning trials of unrelated word lists (Eslinger & Grattan, 1994; Gershberg & Shimamura, 1995; Stuss et al., 1994). Another strategy for encoding is serial organization, or the tendency to recall words in the same order in which they were presented. Such a strategy is less effective, because it is based simply on the surface structure of list order. Patients with frontal lobe lesions and control participants do not differ in the use of serial organization (Baldo et al., in press; Gershberg & Shimamura, 1995).

In short, these findings suggest that recall deficits in frontal patients are related to their reduced use of semantic and subjective organization, both at encoding and retrieval. Moreover, these studies support the notion that the learning process itself may not be fundamentally impaired. Instead, it is the monitoring and control of information during encoding and retrieval that is compromised in these patients.

Susceptibility to Interference

Experimental studies of learning and memory have assessed the impact of interference on frontal patients' ability to retrieve newly learned information. Frontal patients have been shown to exhibit interference, as evidenced by increased intrusions and cross-list interference during recall (Baldo et al., in press; Gershberg & Shimamura, 1995; Shimamura et al., 1995). In a paired-associate paradigm, Shimamura et al. (1995) had participants learn related word pairs (e.g. “lion–hunter”). Following learning of this AB list, a second list (AC) was learned in which the same cue words were paired with different responses (e.g. “lion–circus”). Patients with frontal lobe lesions exhibited intact learning for the first set of pairs (AB list) but exhibited impairment in learning the second list (AC list), in part due to increased intrusions from the first list.

Incisa della Rocchetta & Milner (1993) assessed interference effects using a part-list-cueing paradigm, in which presentation of part of a word list at test actually disrupts normal recall. In their study, left frontal patients showed an exaggerated part-list-cueing effect, suggesting that they were most susceptible to the interference effect. In contrast, left temporal patients were minimally affected. Such findings suggest that frontal patients are impaired in their ability to select and manipulate information and that this leads to significant problems when highly salient but irrelevant information is activated.

Recognition Memory

Tests of recognition memory do not require participants to generate information, but rather rely more on familiarity. Traditionally, recognition memory has been thought to be intact in patients with frontal lesions (Janowsky et al., 1989●). Recently, however, Wheeler et al. (1995) performed a meta-analysis of studies that assessed memory performance in patients with frontal lesions. Across these studies, significant impairment was observed on tests of free recall (80% of studies), cued recall (50% of studies) and even on tests of recognition (8% of studies). They suggested that the inconsistency in findings on tests of recognition is due to the lack of statistical power in studies with small numbers of patients available for testing. Despite this inconsistency, Wheeler et al. concluded that these data were evidence for the presence of an episodic memory impairment in frontal patients, rather than simply a deficit in organizational and strategic control.

Other findings have suggested that impaired recognition (as well as recall) may be due to subclinical language impairment. Stuss et al. (1994) reported that frontal patients were impaired on an overall recognition score and that this recognition impairment correlated with the degree of anomia in left frontal patients. They hypothesized that reduced verbal elaboration at encoding (due to language deficits) was in part responsible for subsequent recognition deficits (but see Vilkki et al., 1998). In keeping with this, Vogel et al. (1987) found that aids that increased depth of processing improved memory performance in frontal patients. This factor is crucial to consider, as many left frontal patients included in studies may have been acutely aphasic and may possess a residual, although mild, anomia. Indeed, studies of new learning often report greater impairment in left than right frontal patients (Dimitrov et al., 1999).

To what extent does impaired recognition performance reflect problems in organizing information during encoding and retrieval? In a recent study, Baldo et al. (in press) found significant impairment in yes–no recognition memory, based on the tendency of frontal patients to false-alarm to semantically related distractors. On a forced-choice recognition procedure, however, frontal patients made no errors; but on this task, the distractor items were semantically unrelated and easily dismissed. This pattern of errors in frontal patients was distinct from that of an amnesic patient with medial temporal injury who, in addition to poor performance on yes–no recognition (worse than frontals), made several errors on the same forced-choice recognition paradigm that was trivially easy for frontal patients.

Further evidence for this dissociation comes from Swick & Knight (1999), who tested frontal and hippocampal patients on a continuous recognition memory paradigm. They reported a double dissociation, such that frontal patients exhibited a normal hit rate but an inflated false alarm rate compared to controls, while hippocampal patients exhibited a reduced hit rate (especially at long lags) but a normal false alarm rate. They concluded that frontal patients do not show a “simple” memory deficit but rather have impairments due to poor use of strategy, source monitoring errors and working memory impairments.

Severe recognition impairment following frontal injury has been reported by Schacter and colleagues in case studies of patient B.G., who incurred an extensive, right posterior frontal lesion (Curran et al., 1997; Schacter, 1996; Schacter et al., 1996). B.G. exhibited a “pathological” false recognition syndrome for semantically related distractors and would even claim to recall details of learning certain items that had not been presented. Interestingly, this false recognition syndrome was ameliorated when he studied a categorized list and the distractor items on the subsequent recognition task were from novel categories.

Schacter and colleagues concluded that B.G. exhibited an “over-responsivity to a memory signal based on the general similarity of test items to studied items” (Curran et al., 1997, p. 1047; also see Schacter, Chapter 16, this volume). Again, B.G.’s deficits demonstrate that memory impairments in frontal patients stem from an inability to control and sort newly-learned information, but that this impairment does not exist when critical cues are provided for the patient as a memory aid.

Findings on tests of recognition memory traditionally supported the view that recognition was relatively unimpaired in frontal patients. However, more recent findings suggest that this view may be incorrect, as recognition is sometimes found to be impaired, e.g. when distractors are semantically related to target items. As in new learning and recall, such recognition deficits in frontal patients are ameliorated under certain conditions. This pattern of memory impairments and residual abilities is best explained by a general deficit in strategic encoding and retrieval, rather than a fundamental learning deficit. Further support for this notion comes from evidence of similar deficits in other aspects of memory described in the following sections.

MEMORY FOR CONTEXTUAL INFORMATION

In addition to deficits in new learning and recall, frontal patients have a reduced ability to recollect contextual information (Janowsky et al., 1989a; Shimamura et al., 1990; Smith & Milner, 1988). Contextual information refers to the spatiotemporal aspects of an event (e.g. when and where you saw a recent movie), as opposed to its semantic content (e.g. the plot of a movie; see Johnson et al., 1993). Retrieving such information requires the reconstruction of episodic information from long-term memory.

The first demonstration of an impairment of this type was a study of verbal and nonverbal recency memory in frontal and temporal lobe patients (Corsi, as described in Milner, 1971). Patients with frontal lobe lesions were impaired when they had to determine which of two items was presented more recently. Specifically, left frontal patients exhibited a recency deficit for words, whereas right frontal patients exhibited a recency deficit for nonverbal stimuli. In contrast, temporal lobe patients were impaired at making old–new judgments about the items but did not exhibit disproportionate impairment on recency judgments.

Studies of temporal order memory have also supported the proposition that patients with frontal lobe damage are impaired at retrieving spatiotemporal information. Shimamura et al. (1990) tested frontal lobe patients’ memory for temporal order, using a sequence reconstruction test in which items were displayed in a random array and participants were asked to reconstruct the study order. Patients with frontal lobe lesions were significantly impaired at reconstructing the order of both recently presented word lists and at reconstructing the chronological order of public events. In a similar study, Mangels (1997) tested focal frontal patients on a series of temporal order tasks that involved both intentional and incidental learning conditions. In each condition, patients were shown a series of words and 1 min later were asked to reconstruct the word sequence. Frontal patients were impaired relative to controls in the *intentional* learning condition, but they performed as well as controls in the *incidental* learning condition, i.e. frontal patients were inferior to controls only when participants were told that their memory would later be tested. Mangels concluded that frontal patients possess the ability to form “basic temporal codes” but are not able to engage additional strategies needed to enhance performance.

Other studies have shown that patients with frontal lobe lesions are impaired in another aspect of temporal coding, viz. frequency estimation; i.e. estimating how often an event has occurred. Smith & Milner (1988) showed that patients with right and left frontal, but not temporal, lesions were impaired on a test of frequency estimation using abstract designs. Importantly, a recognition test demonstrated an impairment only in right temporal lobe patients, which suggested that the performance of patients with frontal lobe lesions could not be attributed to an impairment of discrimination or recognition of the designs.

Source memory (i.e. recalling the source of learned information) has also been shown to be disproportionately impaired in patients with frontal lobe lesions. In one study, participants were asked a series of trivial questions (e.g. "What is the name of the dog on the Cracker Jacks box?"; Janowsky et al., 1989a). On those questions that they could not answer correctly, participants were given the correct answer (e.g. "Bingo") and asked to repeat and memorize it. Several days later, participants returned and were tested on the previously learned items, along with new (filler) items. They were tested for their ability to recall the answer to each question and to determine the source of the information (i.e. whether they heard it during the experimental session or at some other time). Patients with frontal lobe lesions were not impaired on tests of item recall or recognition. They were, however, poor at determining the source of a correctly answered question. That is, they made source errors by stating that filler items were learned during the previous session and by misattributing information learned during the previous session to their own general knowledge.

To what extent does impaired source memory in frontal patients reflect a basic deficit in representing source and temporal information? Some have suggested that episodic memory (and thus, contextual information) is an inherent property of the prefrontal cortex (Tulving et al., 1994; Wheeler et al., 1995). Alternatively, it may be that retrieval of contextual information, like free recall, requires extensive manipulation and control of memory processes. Findings by Mangels (1997), demonstrating intact memory for temporal order under incidental learning conditions, show that when strategic processing is reduced, frontal patients do not exhibit deficits in temporal order memory. Also, McAndrews & Milner (1991) addressed this issue by facilitating attentional control in frontal patients during learning. Participants were presented with objects and asked to perform a task with each one (e.g. "bounce the ball"). Later, participants were given a recency judgment test in which pairs of objects were presented, and they were asked to determine which of the two was presented more recently. Patients with frontal lobe lesions exhibited intact recency memory for manipulated stimuli but impaired performance for objects that were shown but not manipulated. In sum, these findings suggest that patients with frontal lobe lesions have the capacity to retrieve contextual, spatiotemporal information, depending on the attentional demands during learning.

METACOGNITION AND MEMORY

Metacognition refers to the ability to reflect upon one's own thoughts, memories, and knowledge (see Metcalfe & Shimamura, 1994). This ability depends in part on the status of the prefrontal cortex (Janowsky et al., 1989b; Metcalfe & Shimamura, 1994; Shimamura, 2000b). Similar to other aspects of memory discussed thus far, metacognition depends upon strategic, explicit retrieval of information from long-term memory.

Hirst & Volpe (1988, Experiment 1) tested metacognition by questioning patients about memory strategies (e.g. how would they go about learning a list of categorizable words) and by having patients judge the relative difficulty of different memory tasks. This experiment revealed that frontal lobe patients were not very sophisticated in their metacognitive knowledge and had little awareness of their memory deficits, e.g. they did not realize the importance of item repetition or extra study time. In contrast, amnesic patients were relatively sophisticated in their knowledge of memory strategies and were aware of their deficits.

A well-studied technique that involves the use of metacognitive processes is the “feeling-of-knowing” paradigm. In this paradigm, participants make predictions about future performance on a memory test. In one study, Janowsky et al. (1989b) assessed feeling-of-knowing judgments in patients with frontal lesions and amnesic patients (including Korsakoff patients). Participants learned sentences such as, “Mary’s garden was full of marigolds”. Following a retention interval (5 min–3 days), patients were shown the sentences with the final word missing and were asked to supply that word. If they could not recall the word, they rated how likely they could recognize the word if given some choices. Frontal patients performed like controls at the short delay but exhibited impaired feeling-of-knowing at long (1–3 days) delays. That is, they were not accurate at predicting the likelihood that they could recall the target word.

Another way of testing metacognition is by asking individuals to make inferences using basic knowledge. Shallice & Evans (1978) used questions such as, “How tall is a bus?” or “How long is the average man’s necktie?”. Since such answers are rarely known directly, they involve estimations based on strategic analysis of memory and inferential reasoning. Shallice & Evans assessed frontal and nonfrontal patients on a series of such cognitive estimation questions, as well as on arithmetic and nonverbal reasoning tests. They found that frontal patients were impaired on the cognitive estimation questions but not on the latter two tests, which suggested that general problem-solving ability could not account for their metacognitive deficit. Similarly, Smith & Milner (1984) found that patients with frontal lesions were impaired in their ability to make reasonable estimations of prices of objects. The largest impairment was observed in right frontal patients, and performance on the task correlated with lesion size in left frontal patients.

Metacognition has been construed specifically as the monitoring and control of information processing (see Nelson & Narens, 1994; Shimamura, 1994, 2000b). Findings from patients with frontal lobe lesions suggest that they lack such an ability to use and manipulate memories. These deficits may be part of a general deficit in selecting, organizing and manipulating information in working memory, e.g. in an attempt to recall some information, one might retrieve partial information and, based on this information, decide to spend extra time trying to develop associative strategies to retrieve further information. Frontal patients’ poor metacognitive awareness, coupled with retrieval deficits discussed above, make such an effortful search unlikely to be successful.

RETRIEVAL FROM REMOTE MEMORY

In most studies of memory, such as list-learning experiments, it is difficult to distinguish between deficits at the time of learning from deficits at the time of retrieval. One way to isolate retrieval deficits is to assess memory for remote information that was presumably learned before the onset of neurological damage, e.g. Mangels et al. (1996) tested frontal

patients' recall and recognition for remote public events (e.g. "Who killed John Lennon?") and for the names of famous faces. Frontal patients performed more poorly than controls on free recall for public events, but they exhibited normal performance on a four-choice recognition task (e.g. "Was it John Hinkley, Sarah Jane Moore, Mark Chapman or David Roth?"). On the famous faces test, frontal patients were impaired on both free recall of the names of famous people and cued (phonemic and semantic) recall, but again, there was no difference between frontal patients and controls on a four-choice recognition task. Interestingly, unlike in amnesia, where retrieval is often better for very remote information vs. information learned closer to the time of injury, frontal patients exhibited a consistent recall deficit across all time periods tested. Similar findings were reported by Kopelman et al. (1999), who found that frontal patients were impaired at retrieval for autobiographical and news events and that cueing and recognition tasks improved performance.

Similar retrieval deficits have been observed in other modalities. Baldo & Shimamura (1995) tested frontal patients' ability to recall and recognize the names of common odors (e.g. smoke, cinnamon, orange). Frontal patients were significantly worse than controls at retrieving the names of odors, especially when odors were presented monorhinally to the lesioned hemisphere. In contrast to recall performance, frontal patients' performance improved significantly with a recognition task, i.e. when they were given a choice of four odor names from which to choose.

Another way of assessing retrieval from remote memory is analysis of performance on fluency tasks. Fluency tasks require patients to make a strategic search through memory for words that meet certain criteria, e.g. words belonging to a particular category (e.g. "animals") or words beginning with a particular letter. A large number of studies have shown that both letter and category fluency are disrupted in patients with right and left frontal lesions (Baldo & Shimamura, 1998; Benton, 1968; Janowsky et al., 1989; Miceli et al., 1981; Miller, 1984; Milner, 1964; Perret, 1974).

Like new learning, fluency deficits appear to be due to an impairment in strategic retrieval rather than to a loss of semantic knowledge (Baldo et al., 1997), e.g. Troyer et al. (1998) showed that frontal patients' impaired performance on fluency tasks was due to their tendency to perseverate on a subcategory, rather than switch to a new subcategory to enhance output (e.g. normals might switch from land animals to water animals to birds to maximize their output). Importantly, Baldo et al. showed that, while frontal patients were impaired at retrieval of animal names on a category fluency task, the same patients exhibited a normal "semantic space" of animal names using a triadic comparison task. This finding supports the notion that frontal patients' semantic networks are generally intact, despite their poor retrieval. When left and right frontal patients were analyzed separately for the quality of their responses, right frontal patients tended to produce more typical word profiles, while left frontal patients generated highly atypical word profiles (Schwartz & Baldo, in press). These results suggested that the left frontal lobe is more involved in the retrieval of highly typical associations, while right frontal processes support more remote and/or idiosyncratic associations.

As this review indicates, patients with frontal lobe lesions exhibit marked impairment on a variety of tests involving long-term memory. Deficits are observed on tests involving list learning, source memory, metacognition and retrieval of information from remote memory. However, frontal patients can exhibit intact memory when the demands on attention are reduced and/or retrieval strategies are provided (Hirst & Volpe, 1988; Mangels, 1997; McAndrews & Milner, 1991).

WORKING MEMORY

Frontal patients exhibit deficits on tests of new learning and retrieval when there are high demands on monitoring and controlling memory. As such, these deficits in long-term memory can be construed as directly related to deficits in the executive control of working memory. In a seminal analysis of working memory, Baddeley (1986) characterized frontal lobe impairment as a “dysexecutive” syndrome and offered a concise interpretation of the relationship between working memory and long-term memory disorders associated with frontal lobe damage (see also Moscovitch, 1992,1994).

It is well documented that patients with frontal lobe lesions exhibit deficits in the on-line control of information in short-term memory. Such working memory processes have been tested using a variety of stimuli, including digits, locations, colors and sounds (Baldo & Shimamura, 2000; Chao & Knight, 1996; Freedman & Oscar-Berman, 1986; Goldman & Rosvold, 1970; Jacobsen, 1936; Mishkin & Pribram, 1956; Petrides et al., 1993; Ptito et al., 1995). These findings are consistent with experimental studies of prefrontal damage in monkeys using delayed response paradigms (Fuster, 1989; Goldman-Rakic, 1987; Jacobsen, 1936). In the delayed response task, food is concealed in one of two locations and, after a brief delay, the animal selects the location in which the food reward was placed. Jacobsen (1936) first showed that performance on this task is impaired after bilateral lesions of prefrontal cortex but not after temporal, premotor, postcentral or parietal lesions.

Several studies have used delayed response paradigms to assess working memory in neurologic patients. One of the first studies, however, reported negative results. Ghent et al. (1962) tested frontal patients' ability to recall (following a short delay) the angle of tilt of visual and tactile stimuli, as well as their own body tilt. In addition, they tested short-term memory for digit and block design sequences. Patients with frontal damage were not impaired on any of these tasks. In contrast, Lewinsohn et al. (1972) reported that patients with frontal damage were impaired on a similar series of tasks, in which patients had to match visual, auditory, and tactile stimuli. Importantly, unlike the study by Ghent et al., this study required participants to count out loud during the delay interval to prevent rehearsal. Freedman & Oscar-Berman (1986) showed that patients with bilateral frontal lobe lesions were impaired on two types of simple delayed response tasks, the classic delayed response task and a delayed alternation task, in which the target alternated between two spatial locations. These researchers suggested that negative results from previous studies (e.g. Ghent et al., 1962) were due to the fact that they did not use populations with bilateral lesions.

A similar finding was reported by Milner et al. (1985), who used a delayed match-to-sample task with a 60 s delay. In one condition, all objects in a block of trials were different; in another condition, some objects were repeated on subsequent trials. Patients with frontal damage were only impaired in the latter condition, namely when objects appeared more than once. Milner et al. concluded that this impairment was due to interference arising from the repetition of objects and to patients' inability to segregate trials into temporally-unique events. These findings are consistent with deficits in spatiotemporal coding and increased susceptibility to interference, as discussed above.

More complex tasks of working memory have also been shown to be sensitive to frontal lobe impairment. These tasks require not only maintenance but also manipulation of information in working memory, e.g. in the self-ordered task developed by Petrides & Milner (1982), participants are presented with a matrix of stimuli (e.g. words or abstract designs);

these stimuli are presented in different positions across trials and, on each trial, participants are asked to point to a different item. Thus, the participant must not only maintain information in working memory but must also update information on each trial. Petrides & Milner found that the patients with left frontal lesions were impaired on both verbal and nonverbal conditions of the self-ordered task, while patients with right frontal lesions were moderately impaired in a nonverbal condition. Petrides & Milner thus suggested that the left frontal lobe is crucial for mediating verbal rehearsal and manipulating information in working memory. In both neuroimaging and animal studies, Petrides (1998) has identified the dorsolateral prefrontal cortex (areas 9 and 46) as critical for performance on the self-ordered pointing task.

A series of studies by Owen et al. (1990, 1995, 1996) have shown that patients with frontal lobe lesions are impaired on a complex spatial working memory paradigm. In this task, participants attempted to determine in which of several locations a token was hidden. A strategy measure was computed, based on the assumption that the optimal strategy (the one most controls employ) is to begin each search in the same location. Owen and colleagues showed that patients with frontal lobe lesions were impaired on this spatial working memory task, not because of a short-term memory deficit *per se*, but rather because of a deficient searching strategy. In contrast, Owen et al. (1996) found that frontal lobe patients had normal spatial spans. Such a pattern of findings suggests that the prefrontal cortex subserves more complex working memory functions than simply maintaining information in short-term memory.

A recent study (Baldo, in preparation) assessed frontal patients and controls on a two-back working memory paradigm, similar to that used in recent functional neuroimaging studies (e.g. Awh et al., 1996). In this type of task, participants are presented with a continuous series of stimuli and they have to decide whether the current stimulus is the same as that presented two trials previously. In this way, participants have to keep updating in working memory what the comparison (two-back) stimulus was. Patients and controls were tested on three conditions of the two-back task, where the stimuli were visually presented words, nonwords and phonologically similar words (e.g. lap, sat, back, pat, etc.). Frontal patients were impaired compared to controls across all three conditions of the two-back task, making a large percentage of errors that consisted mostly of false alarms.

In short, a large body of literature supports the association between working memory and frontal cortex. Findings suggest that patients with frontal lobe lesions exhibit deficits, not simply in the maintenance of information but more so in the manipulation and updating of information in working memory.

NEUROIMAGING FINDINGS: CORROBORATION AND EXTENSION

Over the past decade, our understanding of memory processes has benefited significantly from advances in functional neuroimaging. Techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have allowed us to identify neural networks that are particularly active during memory tasks (D'Esposito, 2000; D'Esposito et al., 2000; Poldrack & Gabrieli, 1997). A number of neuroimaging studies have corroborated findings from memory studies with focal frontal patients. Others have offered a more detailed analysis of the cortical and subcortical networks that support mnemonic processes.

In terms of new learning and long-term memory, neuroimaging studies have shown that the dorsolateral prefrontal cortex plays a critical role in organizational processes (e.g. during list learning), while the ventral prefrontal cortex is activated during encoding more generally (Fletcher et al., 1998). Other studies have shown that source memory judgments activate left and bilateral prefrontal regions, while simple recognition judgments activate a subset of these regions (Rugg et al., 1999). Individual and retrospective analyses of PET data have suggested that the left prefrontal cortex is preferentially activated during encoding of episodic memories, while retrieval of episodic information is associated with bilateral but predominantly right prefrontal activation (Andreasen et al., 1995; Lepage et al., 2000; Tulving et al., 1994; but see Swick & Knight, 1996).

In terms of working memory, many neuroimaging studies have demonstrated that the lateral prefrontal cortex is activated as part of a large network of cortical regions (D'Esposito et al., 2000; Smith & Jonides, 1999). Some studies have reported a distinction between right and left hemisphere activation for spatial vs. object working memory, respectively (e.g. Smith et al., 1995), while others have not observed such a clear distinction (e.g. McCarthy et al., 1996). Other studies have focused on the neural components of verbal working memory and have reported activation of Broca's area, as well as the dorsolateral prefrontal cortex, with such tasks (Awh et al., 1996; Fiez et al., 1996; Grasby et al., 1993; Paulesu et al., 1993).

Activation of the prefrontal regions has also been observed with more complex, "executive" tasks associated with the frontal lobe, e.g. self-ordered and dual-task paradigms (Petrides & Milner, 1982; Moscovitch, 1994; Petrides et al., 1993). D'Esposito et al. (1995) reported significant activation of area 46 bilaterally when participants performed two tasks simultaneously (mental rotation and semantic judgment), but observed no frontal activation when they performed either of these tasks alone. D'Esposito et al. concluded that the prefrontal cortex is necessary for the allocation of attentional resources under such demanding conditions. Moreover, Prabhakaran et al. (2000) reported that the prefrontal cortex (especially the right) was activated preferentially when participants had to maintain in working memory integrated spatial and nonspatial information (e.g. holding in mind *what AND where* a stimulus was), while the posterior regions supported maintenance of nonintegrated information (e.g. holding in mind *what OR where* a stimulus was).

While functional neuroimaging studies can elaborate on brain regions implicated in focal lesion studies, it is important to distinguish between regions that play critical roles in memory and regions that are merely correlated with memory tasks. Ideally, functional neuroimaging and focal lesion studies will continue to complement each other, as neuroimaging studies detect large networks of cortical and subcortical regions involved in memory, and patient studies provide information about the extent to which those regions are critical to mnemonic processes.

DYNAMIC FILTERING THEORY OF FRONTAL LOBE FUNCTION

Deficits in executive control appear to play a role in memory impairments observed in patients with frontal lobe lesions. Shimamura (1995, 2000a) developed dynamic filtering theory as a way of linking cognitive dysfunction associated with prefrontal damage to an impairment in a neurobiological gating mechanism. This view suggests that the prefrontal

cortex acts to filter or gate to neural activity arising in posterior cortical regions. This filtering mechanism increases activity selected by the prefrontal cortex and at the same time actively inhibits extraneous or irrelevant activity. In essence, dynamic filtering increases the signal-to-noise ratio by enabling top-down control of information processing. This gating mechanism can account for four basic aspects of executive control—selecting, maintaining, updating and rerouting (Shimamura, 2000a). When these processes are disrupted following frontal injury, the result is executive dyscontrol that then leads to deficits in a number of areas, including memory.

A number of studies have provided physiological evidence for the role of the prefrontal cortex in dynamic filtering and inhibitory gating, e.g. Knight and colleagues have reported a series of studies in which they recorded event related potentials (ERPs) in patients with frontal lobe lesions (Knight et al., 1989, 1999; Yamaguchi & Knight, 1990). They have shown that frontal lobe patients exhibit exaggerated ERPs to sensory information, e.g. auditory and somatosensory stimuli, suggesting that prefrontal cortex damage leads to some form of “disinhibition” in responding to environmental stimuli, i.e. frontal lobe lesions resulted in the failure to gate activity arising in posterior cortex. Moreover, patients with frontal lesions did not show normal inhibition of irrelevant stimuli (as measured by ERPs) when they were attending to target stimuli. Further support for this theory comes from neuroimaging studies with normal individuals. In a PET study of word finding (Frith et al., 1991), increased activity in the dorsolateral prefrontal cortex correlated with decreased activity in posterior cortical regions. Also, an fMRI study reported that inhibitory mechanisms were associated with dorsolateral prefrontal cortex activation in a go–no go task (Konishi et al., 1999; see also Dolan & Fletcher, 1997).

Behavioral findings are also consistent with the dynamic filtering hypothesis (Bartus & Levere, 1977; Blake et al., 1966; Knight & Grabowecky, 1995; Malmö, 1942; Shimamura, 1995, 2000a). Early studies of the prefrontal cortex noted that both monkeys and humans with frontal lesions were highly susceptible to extraneous stimuli (Brickner, 1936; Jacobsen, 1936). Jacobsen observed the following:

The operated animal seems more distractable in contrast to the sustained, directed behaviour of the normal subject. Behaviour, instead of being directed by a balance of immediate, recent and temporally remote stimulation, is dominated by present external stimuli and the stable habit systems . . . the mnemonic influence of immediately past experience is lacking (p. 52).

A number of experimental findings in both animals and humans have corroborated these behavioral observations (Baldo & Shimamura, 2000; Bartus & Levere, 1977; Chao & Knight, 1996; Malmö, 1942; Ptito et al., 1995), e.g. working memory studies have shown that patients with frontal lobe lesions are disproportionately impaired when there is some form of distraction during the delay interval. This delay period interference may be in the form of irrelevant auditory distractors (Chao & Knight, 1996) or a secondary task (Baldo & Shimamura, 2000; Ptito et al., 1995). Other support for the failure to inhibit extraneous information comes from studies of response inhibition, as frontal patients show increased interference on go–no go tasks (Drewe, 1975) and the Stroop effect (Perret, 1974).

In short, both physiological and behavioral evidence are consistent with the notion that a basic disruption of inhibitory gating results from frontal injury, and that such disruption can result in impaired performance in a number of domains, including memory.

CONCLUSIONS

Over the past decade, resurgent interest in the role of the frontal lobes in memory has led to extraordinary advances. Neuropsychological and neuroimaging studies indicate that prefrontal cortex contributes to a variety of memory processes, including learning, recall, source memory, metacognition and remote retrieval. These long-term memory mechanisms place heavy demands on executive processes, such as working memory and attention, which are also compromised in this patient group. With respect to global processing, the prefrontal cortex appears to act as a gating mechanism that monitors and controls information processing represented in other brain regions. Future studies will need to better characterize the complex, dynamic relationship between the prefrontal cortex and the medial temporal regions in order to have a more complete understanding of the neurobiological substrates and cognitive mechanisms underlying human memory.

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