The Frontal Cortex and Working with Memory

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In numerous attempts to characterize the functional significance of the frontal cortex (FC), investigators have emphasized the structure's role in episodic memory and various memory-related processes such as working memory, temporal ordering, and meta-memory. There is little doubt that the FC is involved in memory, but it is equally clear that its role is different from that associated with structures in the medial temporal lobe (e.g., hippocampus) and diencephalon (e.g., anterior and dorsomedial thalamus). While the latter regions differ in terms of their specific contributions, there is no question as to their fundamental importance to memory processes. Damage to medial temporal lobe and diencephalic regions reliably produces profound, global anterograde amnesia that is manifested as impaired recall and recognition. By comparison, damage to the FC does not typically produce generalized memory loss and, indeed, when it comes to remembering salient or distinctive events, patients with FC damage often experience little or no difficulty. Such patients also typically perform within normal limits on tests of cued recall or recognition memory unless some organizational component is needed to facilitate performance (Moscovitch & Winocur, 1995; Wheeler et al., 1995). They are severely handicapped, however, when success-ful recall depends on self-initiated cues or when targeted information is relatively inaccessible (Moscovitch & Winocur, 1995). In other words, the FC is required if accurate memory depends on organization, search, selection, and verification in the retrieval of stored information. The important point that emerges is that the FC is less involved in memory recollection per se, than it is in mediating the strategic processes that support memory encoding, recovery, monitoring, and verification.

An equally important point, in terms of understanding FC function, is that its participation in strategic processes is not restricted to the recovery of past experiences. Indeed, there is considerable evidence that the structure uses established memories to direct other activities, such as new learning, problem solving, and behavioral planning. In previous publications, we have referred to medial temporal lobe and diencephalic systems as "raw memory" structures, because of their close and direct links to basic memory processes. By comparison, we have argued that the FC must work *with* memory to perform its diverse strategic functions by either influencing input to medial temporal lobe–diencephalic systems or by acting on output from these regions.

We have chosen the term *working-with-*

memory (WWM) to distinguish our notion from that of *working memory*, which we believe has different, and more restrictive, connotations in the literature on both human and animal memory (see Moscovitch & Winocur, 1992a, 1992b). Our idea is that strategic contributions to long-term memory are of the same type as those made to other functions, such as short-term or working memory, problem solving, attention, and response planning. Our approach to FC involvement in memory fits into a broader framework in which the FC is viewed as a central-system structure that operates on many domains of information, rather than as a domain-specific module (Moscovitch & Umiltà, 1990, 1991; Moscovitch, 1992, 1994a; Moscovitch & Winocur, 1992a, 1992b). The various central-system functions of the FC are localized in different regions. Thus, localization of function is as much a characteristic of central, frontal systems as of posterior neocortical modular systems. What distinguishes one from the other is that *modules* are defined in terms of their *content* or nature of the *representation*, such as faces, phonemes, objects, and so on, whereas *central, frontal systems* are defined in terms of their *function*, such as monitoring, searching, verification, and so on.[1]

In our framework, the medial temporal lobes, which include the hippocampus and related neocortical structures, as well as the diencephalic structures associated with them (Aggleton & Brown, 1999), are modules whose domain is conscious or explicit memory (Moscovitch, 1992, 1994a, 1995; Moscovitch & Winocur, 1992a, 1992b). They mandatorily encode and retrieve information that is consciously apprehended, and the information is stored randomly with no organizing principle except that of short-latency, temporal contiguity. As WWM structures, regions of the FC operate strategically on information delivered to the medial–temporal/diencephalic system and recovered from it, thereby conferring "intelligence" to what essentially is a "stupid" medial temporal lobe/diencephalic system. The FC is needed to implement encoding and retrieval strategies. The latter includes initiating and directing search in accordance with the demands of the task, monitoring and verifying

recovered memories, and placing them in the proper temporal–spatial context.

In our research program, we have addressed issues related to this theoretical framework from different perspectives, using human subjects as well as animal models and a variety of experimental paradigms. As part of our ongoing testing of specific hypotheses that follow from our theoretical position, we attempt to show that the FC works with other structures in performing various tasks, and that the contributions of the respective brain regions can be functionally dissociated. This chapter will focus on studies from our animal- and human-based research that reflect our general approach and provide converging evidence in support of the WWM model.

As useful as our WWM framework has been for guiding research on memory in humans and animals, in its original version it lacked the specificity that is required for subsequent developments on localization of function within the FC. When we first proposed the model (Moscovitch, 1989; Moscovitch & Winocur, 1992a), little was known about the localization of the various strategic encoding and retrieval functions, in part because the FC was not thought to play a prominent role in episodic memory. The situation has changed markedly since then, and we now have a better idea of the distribution of these functions within the FC, and the prefrontal cortex (PFC) in particular. Accordingly, in the concluding section we briefly review recent evidence regarding the localization of function within the PFC and present a revised version of our model that takes the new evidence into account.

ANIMAL STUDIES

Our overall research strategy is guided by the premise that, for the most part, cognitive tasks are multidimensional, and successful performance depends on the effective recruitment and integration of various component processes (Witherspoon & Moscovitch, 1989; Moscovitch, 1992; Winocur, 1992b; Roediger et al., 1999). For example, when presented with a complex new problem, we tend to learn specific features of that problem which, if re-

membered, will be useful when confronted again with the same problem. We and others associate this function with the hippocampus and related structures. We also learn conceptually related information that can be abstracted and strategically applied when dealing with variations of the problem, a process likely mediated by the FC (see also Miller, 2000; Chapter 18). In the normal course of events, these distinct processes are combined as part of an efficient cognitive operation, but undoubtedly they are controlled by different neural structures, and, theoretically at least, they are separable and amenable to independent measurement.

MAZE LEARNING

Our component process approach was tested in a rat model (Winocur & Moscovitch, 1990). In a test of complex maze learning, hungry rats had to avoid blind alleys in learning a specific route to a goal area where food was available. For this study, rats were subjected, in approximately equal numbers, to lesions of the FC or hippocampus, or to a control procedure in which no brain tissue was destroyed. Half the rats in each group received initial training on maze A, while the other half received no maze training. Subsequently, half the rats in each training condition were tested on maze A, while the other half were tested on a different maze (maze B). Thus, in the training condition (T), half the rats were re-tested on maze A, while the other half were tested on a

new but similar maze. In the non-training (NT) condition, all the rats experienced a maze for the first time at test.

The results, which are summarized in Table 11–1, reveal a clear dissociation between the effects of FC and hippocampal lesions. As expected, at test, control rats in the T condition performed better than NT controls, and they also did better on maze A than on maze B. On the familiar maze A, the controls were able to benefit from specific as well as general task-related information, whereas on maze B, they were able to draw only on general information.

Lesions to hippocampus or FC generally disrupted maze performance, relative to controls, but the patterns of deficit were quite different. Rats with hippocampal lesions and in the T condition made fewer errors than those in the NT condition, but within the T condition, they performed equally on mazes A and B. Thus, rats with hippocampal lesions, trained on maze A, appear to have acquired a maze-learning strategy that they were able to transfer to a similar problem. However, their failure to display additional savings when tested on maze A suggests that they remembered general information about this type of maze that would support a learning set but that, essentially, they had forgotten the specifics of their maze A training experience.

As for the groups with FC lesions, there was no significant difference between T and NT rats on the unfamiliar maze B, but rats in the T condition performed better than in the NT

Table 12–1. Errors at testing for all groups in training and no-training conditions during 60 trials of maze learning.

Maze	Hippocampal Lesion		Frontal Cortex Lesion		Control	
	T	NT	T	NT	T	NT
A (familiar)						
Mean	105.3	142.6	82.7	103.8	52.3	80.8
SE	4.6	3.8	2.8	2.6	1.8	2.3
B (unfamiliar)						
Mean	112.3	133.1	99.6	101.6	64.2	81.6
SE	4.6	5.7	3.3	2.7	2.0	2.0

T, training; NT, no training; SE, standard error.

condition rats in the NT condition on maze A. Clearly, rats with FC lesions benefited from training on maze A only when they were re-tested on the same task. This shows that, whereas rats with FC lesions were able to rec-ognize the familiar maze A, this memory did not help them on maze B.

These results are consistent with the WWM notion of FC function. Bilateral lesions to the hippocampus selectively affected rats' mem-ory for the specific and contextually defined experience associated with maze A learning, but spared procedural learning and memory that could be applied when subsequently tested on either maze A or B. In contrast, the FC-lesioned group had good memory for the salient maze A-learning experience, but were unable to use that memory in a flexible, stra-tegic way that would enable savings on an-other task, even one that was closely related to the original one.

Related work (Winocur, 1992b) has empha-sized that the impairment of FC-lesioned rats in transfer of learning is, in fact, a WWM def-icit and not simply a failure of procedural or rule learning. In one experiment, rats with hippocampus, FC, or sham lesions were trained on a problem in which they were re-quired to discriminate between circles of dif-ferent sizes. The groups did not differ in learning or remembering the original discrim-ination. However, the FC lesioned-group was severely impaired at transfering the learned discrimination to a new set of stimuli (trian-gles). Although relatively simple on the sur-face, there was a substantial strategic compo-nent to this problem in that, to transfer learning successfully, rats had to compare training and test conditions, attend to critical similarities while ignoring irrelevant differ-ences and, of course, apply previous learning to the new discrimination. All these operations required the animal to work with memory.

In the same experiment, rats with FC or hippocampus lesions, and control rats were ad-ministered a size-discrimination problem in which the stimulus pairs changed on every trial. All groups learned the rule at the same rate and showed excellent retention several weeks later. This outcome is instructive be-cause, although rats had to apply the rule to different stimuli on each trial, the require-ments quickly became routine and predictable. In this case, the transfer of information re-quired little in the way of planning or strategic operations, and no comparisons between ex-periences separated in time; as such, this trans-fer placed no demands on WWM processes.

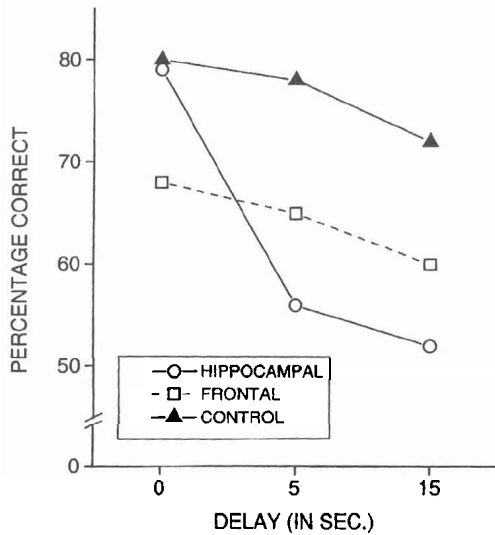## CONDITIONAL ASSOCIATIVE LEARNING

The maze-learning and transfer studies dem-onstrate the importance of FC for transferring information to new learning situations that re-quire the effective integration of past experi-ence with current task demands over extended time periods. While such tasks draw on what may be considered long-term memory, similar processes are involved in other tasks in which accurate responding depends on short-term memory. For example, in conditional associa-tive learning (CAL), in which different stimuli are associated with different responses, on each trial the subject must select, from among several alternatives, the response that is ap-propriate to the most recently presented stim-ulus. The delay between stimulus presentation and the opportunity to respond is brief and often on the order of seconds. Variations of this task have been developed for humans and nonhuman primates, with the consistent find-ing that lesions to the FC, particularly areas 6 and 8, impair performance (see Petrides & Milner, 1982, Milner & Petrides, 1984; Petri-des, 1990; 1995; chapter 3).

Impairment of CAL following FC damage has been characterized as a working memory deficit resulting from a lesion-induced inability to retain trial-specific information over the stimulus–response delay period. However, when we compared the effects of FC and hip-pocampal lesions on a rat version of CAL, the results suggested other interpretations (Win-ocur, 1991; Winocur & Eskes, 1998). In this task, one wall of a Skinner box was outfitted with a display panel, consisting of six lights placed above two retractable levers that were located on either side of the food chamber. Rats were reinforced for pressing the left lever in response to a light on the left side of the panel, and the right lever, to a light on the right side. Initially, rats were trained with the

conditional stimulus and both levers presented together on each trial. The lights were extinguished and the levers withdrawn after a response was made to allow for a 30-second intertrial interval. When responding stabilized in the 0-delay training condition, rats received five additional days of training with a 5-second stimulus–response delay, and five more days of training in which the delay was increased to 15 seconds. For the delay trial, the conditional stimulus was presented for 10 seconds and then turned off while the rats waited the prescribed delay period for the levers to reappear.

There was no difference between hippocampus-lesioned and control groups in learning the conditional rule in the 0-delay condition, but the group with FC lesions improved at a much slower rate and, as can be seen in Figure 12–1, failed to reach the performance level of the other groups even after 30 training sessions. Since there was no stimulus–response delay during training, this result shows that the FC group's deficit was not linked to the requirement that critical information be retained over a period of time. Similar patterns of performance have also been observed in FC- and hippocampus-lesioned groups in tests of delayed alternation and delayed matching-to-sample (Winocur, 1991, 1992a, 1992b).

These data argue that the deficit cannot be attributed to memory loss or to the retention components of working memory. This conclusion is reinforced by the results of the delay conditions (see Fig. 12–1). Here, we see a rapid decline in performance of the hippocampus-lesioned group, indicating that these animals were unable to remember each trial's signal even after a brief period of time. Of particular interest was the finding that increasing the stimulus–response delay did not adversely affect the performance of rats with FC lesions. As the delays increased, the performance of this group declined at the same rate as that of the control group. It should be noted that an alternative working memory interpretation of these results is that rats had to coordinate, in working memory, the signal and the response, as well as the interfering effects of past experiences, and those with FC lesions did not have the capacity to do that.

Figure 12–1. Percentage correct on the conditional associative learning test for hippocampus-lesioned, frontal cortex–lesioned, and control groups.

These results indicate that impairments on conditional learning tasks following FC lesions are neither time-dependent nor due to a straightforward memory failure, as might be argued for hippocampus-lesioned rats. More likely, the effects of FC damage were on conditional rule learning or on the process of response selection. We are not prepared to dismiss a rule-learning deficit, although, as we have seen in the transfer studies, FC lesions do not necessarily disrupt rule learning. In a recent experiment, Winocur & Eskes (1998) showed that modifying the CAL task to reduce demands on response-selection processes resulted in a significant improvement in performance in FC-lesioned rats. Our interpretation is that lesions to the FC interfered with the animal's ability to use critical information in the context of a learned rule for the purposes of accurate response selection. We view this as another expression of WWM. The CAL results highlight the point that the WWM function applies to the strategic use of specific and nonspecific memories at short as well as long delays.

RECENT AND REMOTE MEMORY

The FC, as a WWM structure, is also involved in the recovery of remote memories. There is

growing evidence that damage to the FC in humans produces a severe retrograde amnesia that can extend back many years. This pattern contrasts with the temporally graded retrograde amnesia that has often been reported for humans and animals (Winocur, 1990; Zola-Morgan & Squire, 1990; Squire, 1992; Squire & Alvarez, 1995) with incomplete medial temporal lobe/hippocampal damage (but see Nadel & Moscovitch, 1997; Nadel et al., 2000; Rosenbaum et al., 2001).

Investigations of memory function in animals with FC damage have been concerned mainly with anterograde memory, but recently we examined the effects of FC lesions in rats on a test of anterograde and retrograde memory for a learned food preference (Winocur & Moscovitch, 1999). In this test, a subject-rat acquires the preference by interacting with a demonstrator-rat that has just eaten a particular food. Memory for the preference is indicted when the subject later prefers that food to an unfamiliar food that is presented alongside it.

In previous work with this paradigm (Winocur, 1990), rats with lesions to hippocampus or dorsomedial thalamus were tested following pre- and postoperative acquisition of the food preference. There was no effect of thalamic lesions on anterograde or retrograde memory, but the groups with hippocampal lesions exhibited clear impairment. On the anterograde test, rats with hippocampal lesions learned normally but forgot the acquired preference at an abnormally rapid rate. In the retrograde test, they suffered a temporally graded retrograde amnesia in which preferences, acquired well before surgery, were remembered better than more recently acquired ones.

When rats with FC lesions were tested on this task, there were no differences between FC and control groups in either memory condition (Winocur & Moscovitch, 1999). Although surprising at first, on further reflection, the failure of FC lesions to affect memory performance made sense. In the food-preference task, memory is assessed in what is essentially a two-choice recognition memory test, and it is well known that FC damage does not affect performance on standard tests of recognition memory (Wheeler et al., 1995;

Mangels et al., 1996). In our experience, however, aged animals with frontal lobe dysfunction (Winocur & Gagnon, 1998; Winocur & Moscovitch, 1999) and patients with Parkinson's disease (Ergis et al., 2000) who exhibit frontal symptoms do exhibit impaired recognition memory when interference is introduced by increasing the number of response alternatives and their similarity to the target. Accordingly, in a second experiment, the number of food choices was increased from two to three, so that rats had to select the sample food from three equally desirable diets.

As can be seen in Figure 12–2, in the three-choice test, rats with FC lesions, in contrast to the control groups, exhibited poor memory for the acquired food preference. The effect was especially marked in the retrograde memory test, where the FC groups showed no gradient over the delay period, and at no time did their average intake of the sample food exceed 50% of the total amount consumed. In the anterograde memory test, the group with FC lesions showed declining memory for the food preference with increased delays.

These results are interesting for several reasons. First, they represent the first clear demonstration in FC-lesioned animals of patterns of anterograde and retrograde memory loss that correspond to those reliably observed in patients with comparable damage on context-free (semantic) tests of memory (see discussion in Rosenbaum et al., 2001). Second, they confirm that the FC does not mediate basic processes related to the acquisition and retention of new information, but that the structure does play a role when the tasks are more complex and greater effort is required to perform them. Thus, in experiment 2, the increased number of alternatives placed greater demands on search and selection operations and that clearly put the group with FC lesions at a disadvantage. Third, the results provide further evidence that, under certain conditions, even recognition memory, which typically resists the effects of FC damage, can be compromised. Finally, an important finding was that anterograde amnesia at long delays correlated significantly with retrograde amnesia in rats with FC damage. This result was undoubtedly related to the fact that the antero-
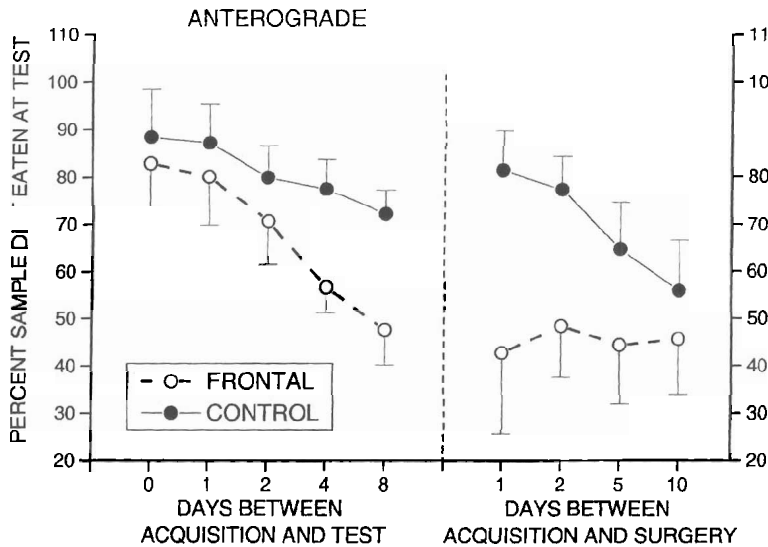
Figure 12–2. Amount of sample diet consumed by frontal cortex–lesioned and control groups, expressed as a percentage of the total amount of food consumed, at the various delays in the (three-choice) retrograde and (three-choice) anterograde amnesia tests. (*Source:* From Winocur & Moscovitch, 1999)

grade and retrograde tests were similar, and that they drew on similar FC-mediated processes.

This study provides an important example of how the FC directs goal-oriented strategies that lead to the recovery of relatively inaccessible information. In the absence of sufficient external cues, the FC is recruited to initiate appropriate search operations aimed at finding specific memory traces. Factors such as the passage of time, the number of competing associations, and difficulty in placing events in spatial–temporal context add to the complexity of the process, and place additional demands on FC. The three-choice version of the food-preference task incorporates all these factors, and its sensitivity to the effects of FC lesions, on both anterograde and retrograde measures, offers strong support for the WWM hypothesis.

SUMMARY

In this section we reviewed the results of several experiments, each involving different paradigms and each revealing deficits in rats with FC lesions that are broadly consistent with deficits seen in patients with FC damage. Although very different in terms of their cognitive demands, they all had a memory component that, in itself, posed no problems for the groups with FC lesions. They also re-

quired the animals to work *with* specific memories—whether in acquiring new responses, retrieving old ones, or in using memory in a strategic way. The results consistently show that it was the WWM function that was impaired in the FC-lesioned rats.

HUMAN STUDIES

Our studies on FC and memory in humans parallel those conducted with animal models. In both cases we try to distinguish between the contribution of the FC and other brain regions to performance on tests that have a WWM component. The studies on humans and animal were not intended to be analogous in the sense that they would resemble one another in surface structure, but rather they were designed to share processing components with each other. In fact, this approach was necessitated by the different evolutionary histories and adaptations of the organisms.

Our comparative approach is illustrated most clearly in our studies of remote memory. Because rats rely so much on olfaction, we used socially transmitted olfactory learning to examine their remote memory. In humans, it was more appropriate to rely on verbal and pictorial information to test memory for personal and public events and personalities. We used neuroimaging and lesion studies to iden-

tify the regions that are implicated in retrieval of recent and remote memories. By comparing frontal and medial temporal contributions to memory in animals and humans, as measured by corresponding tests, we hoped to develop a better appreciation of the processes mediated by these structures.

In this section on human studies, we will focus on lesion studies on memory distortion because we believe that these provide the most compelling evidence of the contribution of the FC to memory. The studies we review show that the FC contributes to acquisition of new memories and to retrieval of both recent and remote memories. In line with our view that frontal lobes make a similar contribution in all domains, we will also show that damage to the FC leads to distortion of both autobiographical memory and general knowledge. We then will turn to neuroimaging studies of recent and remote memory to identify the contribution of different regions of the FC to retrieval.

LESION STUDIES: REMOTE MEMORY AND MEMORY DISTORTION

The contribution of the frontal lobes to retrieval of remote memory was noted by Kopelman (1989, 1991), who found that performance on tests of remote memory in amnesia was correlated with the severity of deficits on tests of frontal lobe function. More recent studies by Levine et al. (1998) have shown that loss of remote autobiographical memories, particularly the ability to re-experience them as elements of one's personal past, is associated with damage to the inferior, right FC and the uncinate fasciculus that connects it to the anterior temporal lobe. This same region was found by Levine (personal communication) to be activated when re-experiencing or remembering an event, as opposed to "knowing" that it occurred. By comparison, performance is relatively preserved on recognition tests that are mediated primarily by the medial temporal lobes.

In contrast to Levine et al.'s patient who finds his own past unfamiliar, there are patients with the opposite disorder: they find familiarity even in novel events and stimuli

(Schacter et al., 1996a; Rapcsak et al., 1999). This overextended sense of familiarity, most noticeable when novel items belong to the same category as recently studied targets, is also observed when these patients encounter people, faces, and words for the very first time, presumably because at some level they resemble familiar stimuli. The lesion associated with this disorder has not yet been localized to a particular region in the frontal lobes, although it occurs more often with damage in the right hemisphere (but see Parkin et al., 1999, next section). There are a number of possible interpretations of this disorder, which we consider below. The overextended sense of familiarity resembles a common feature of confabulation, although the latter is a more complex form of memory distortion in which elements of old memories may be combined with one another, and with current perceptions and thoughts, to create new memories that the individual truly believes to be veridical and experiential (Dalla Barba, 1993a, 1993b). Overextended familiarity in confabulating people is apparent on tests of recognition. Correct responses to targets may be normal, but there are more false alarms either to new, related items (see Moscovitch, 1989) or to items that had once served as targets but now act as lures (Schnider et al., 1996; Schnider & Ptak, 1999). In line with their performance on laboratory tests, many confabulating patients will claim to be familiar with people and places encountered for the first time. With very good retrieval cues, FC-damaged patients are able to provide correct answers and their confabulations are diminished and even eliminated (Moscovitch, 1989).

It was observations such as these that led us to conclude that confabulations arise in conditions in which search is faulty but not empty, and in which the erroneous products of that search are not monitored well (Moscovitch, 1995). The FC is needed both to initiate and guide search and to monitor the product of that search at different levels (see Gilboa and Moscovitch, in press, for review).

Most of our knowledge of remote memory and confabulation is based on informal observation and reports of spontaneously occurring confabulation. To bring confabulation for re-

mote memory under some experimental control, Moscovitch and Melo (1997) administered an autobiographical and historical/semantic version of the Crovitz cue-word test (Crovitz & Schiffman, 1974) to confabulating and nonconfabulating amnesic patients and to their matched controls. In these tests, participants were asked to use a cue word, such as *broken* for the autobiographical version, and *assassinations* for the historical/semantic version, to retrieve, and describe in detail, either a personal memory related to that word or an historical event that also occurred before the participant was born. There are a number of interesting aspects to the results, which are noted in Figure 12–3.

First, the Crovitz test proved to be effective in eliciting confabulations under laboratory conditions, but only in people prone to confabulation outside the laboratory. Nonconfabulating amnesics and controls produced few confabulations. Second, consistent with

our idea that the FC is a central system structure that works with memory across all domains, we found that confabulation was not restricted to autobiographical memory but included knowledge of the historical events that belong to the domain of semantic memory (but see Dalla Barba, 1993a, 1993b).

A third aspect of the results is that confabulating amnesics recalled far less information, whether veridical or otherwise, than other amnesics or controls, and benefited disproportionately from prompting. It should be noted that prompts increased veridical and confabulating responses equally.

These findings indicate that although the final, proximal cause of confabulation may be defective postretrieval monitoring and verification of recovered memories, deficits in a number of preretrieval components are associated with the disorder and in all likelihood contribute to it. They include impairments in formulating the retrieval problem and in spec-
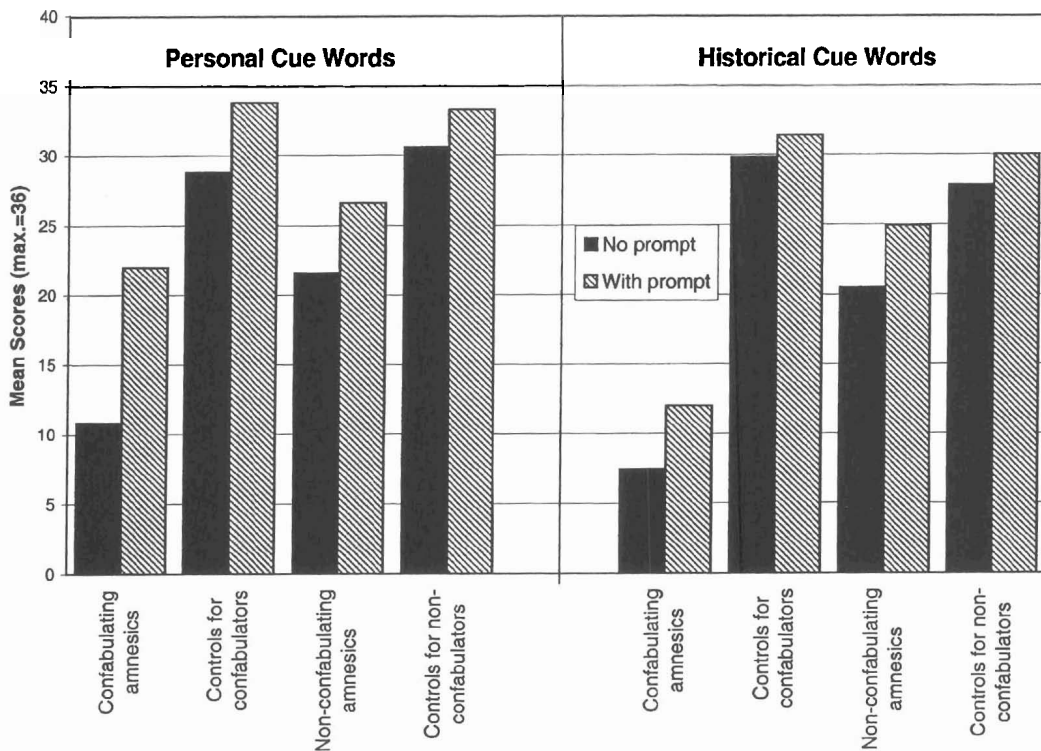
Figure 12–3. Mean score (maximum 36), with and without prompt, for confabulating and non-confabulating patients and their respective controls on the Crovitz personal and historical cue word test. (*Source:* From Moscovitch & Melo, 1997)

ifying appropriate cues. Other components that may be deficient are those guiding search and selection among alternative memory candidates and responses. Similar proposals for fractionating the retrieval process into a number of subcomponents have been advanced by Burgess and Shallice (1996) (see chapter 17), by Schacter et al. (1998a), and by Kopelman (1999). This view suggests that the nature of the confabulation errors that are observed will depend on which and how many of the subcomponents are affected. The idea is consistent with our WWM model, which assigns different components of encoding and retrieval to the FC, and raises the possibility that they are mediated by different regions in the FC (see Localization of function in Frontal Cortex and chapter 17).

LESION STUDIES: MEMORY ACQUISITION AND MEMORY DISTORTION

If memory is a reconstructive process (Bartlett, 1932), confabulation and an overextended sense of familiarity may be caused by deficits at encoding as much as by deficits at retrieval in people with FC lesions. Parkin et al. (1999) provide compelling evidence that a defect in encoding the target distinctively, rather than by its general characteristics, can lead to exaggerated false recognition in a patient with left frontal lesions. To study the effects of frontal lesions on distortion of newly acquired memories, Melo, Winocur and Moscovitch 1999) induced distortions in the laboratory. They used the Deese-Roediger-McDermott paradigm (Deese, 1959; Roediger & McDermott, 1995) to examine memory distortion in amnesic people with and without FC damage, as well as in people with FC damage without amnesia. In this paradigm, people try to remember lists of related words, such as *bed, nap, pillow, snooze,* all of which are associated to a common word, which, in this particular example, would be *sleep.* The word *sleep,* however, is not presented and serves as a *critical lure* at test. Following each list presentation, participants are asked to recall as many of the items as they can remember. Once all the lists are presented and recalled,
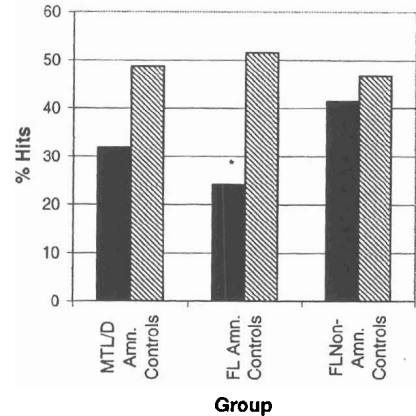

Figure 12–4. Proportion of study list words produced by patients ▧ and controls ■ °*P* < 0.05. Amn., amnesia; FL, frontal lesion; MTL/D, medial temporal lobe/diencephalon (*Source:* From Melo et al., 1999).

a break ensues, after which participants are asked to recognize the target items and distinguish them from unrelated lures and from the critical lure.

The controls behaved as normal people did in most published studies: they recalled and recognized as high a proportion of the critical lures as that of the target items, and very few of the unrelated lures (see Figs. 12–4 and 12–5). Although there are a number of explanations for this outcome, the one we prefer is that participants base their responses both on their specific (verbatim) memory for the tar-
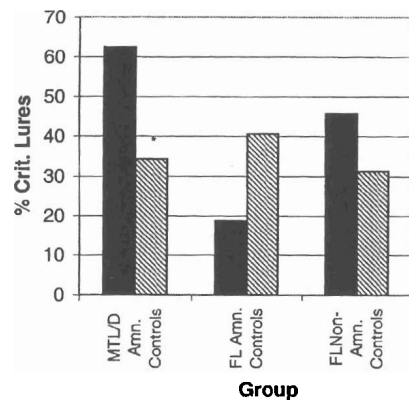

Figure 12–5. Proportion of critical lures intruded by patients ▧ and controls ■ °*P* < 0.05. Amn., amnesia; FL, frontal lesion; MTL/D, medial temporal lobe/diencephalon (*Source:* From Melo et al., 1999)

gets as well as on the gist that they extracted from them, which, in most cases, was exemplified best by the critical lure (Brainerd et al., 1995, 2000; Reyna & Brainerd, 1995; Schacter et al., 1996c, 1998b). Monitoring at retrieval for perceptual qualities of the recovered memory can be helpful in distinguishing targets from critical lures (Schacter et al., 1999), but is not a major factor unless participants are trained or instructed to attend to the relevant features.

On the basis of this analysis and our WWM framework, we predicted that amnesic patients, whose memory for the targets is poor but who can still retain the gist if tested immediately after the list is presented, will respond with a higher than normal proportion of critical lures, and a lower proportion of targets, at recall. When recognition is delayed, their memory for both targets and gist will be poor, and so they will show poorer than normal recognition of both. Patients with only lateral, FC lesions will be impaired at monitoring and so are expected to show a slight increase in recalling and recognizing critical lures, although their memory for targets will be normal. The increase should be slight because monitoring plays a minimal role in normal performance on this test (see above). Amnesics with medial temporal lobe/diencephalic (MTL/D) and FC damage suffer from a compound deficit. Their lesions typically include the ventromedial frontal lobes and basal forebrain. Consequently, their memory for the targets will be as poor as that of amnesics. Their frontal damage may not only impair their ability to monitor but may even prevent them from extracting the gist at encoding or using it to guide retrieval. As a result, their memory for targets and critical lures should be disproportionately low even when tested immediately.

The findings were consistent with our predictions (see Fig. 12–4 and 12–5). Though providing general support for the WWM model, showing different effects of MTL/D and FC lesions on performance, our results do not distinguish clearly whether the distortion in patients with FC lesions arises at encoding or retrieval. This is an issue that has yet to be resolved in all studies employing the Deese-Roediger-McDermott (DRM) paradigm. In addition, our study also suggests a degree of specialization within the FC in that patients with primarily lateral frontal lesions do not show as much distortion as those whose lesions are more medial and implicate the basal forebrain. These differences will need to be taken into account in developing the model further (see Components of Retrieval and Frontal Cortex).

LOCALIZATION OF FUNCTION IN FRONTAL CORTEX

Our initial intent in developing the WWM model was to establish its basic principles with respect to the broad range of FC functions, such as initiating and guiding retrieval of memories (which may involve cue specification and maintenance), monitoring memories, evaluation, and response selection, that are implicated in tests of episodic memory. (In addition to the studies reported here, the model was supported by studies of aging [Moscovitch & Winocur, 1992b, 1995], word fluency, [Troyer, et al., 1997; 1998a, 1998b]; and of divided attention [Moscovitch, 1994b; Troyer et al., 1999; Fernandes & Moscovitch, 2000; Moscovitch et al., in press]. Each of these component functions of the FC is likely mediated by different regions of the FC. There is growing evidence in the literature that a comprehensive model of frontal function must take regional specialization into account—and this clearly is the direction in which the field is heading. Although our research has not addressed the issue of localization of function in the FC directly, our findings indicate its importance. For example, as noted above, there is a clear dissociation of function between the lateral and ventromedial aspects of the FC in memory distortion.

One of the difficulties of the traditional neuropsychological approach to this issue is that patients rarely present with sufficiently circumscribed lesions to allow precise localization of function in large-scale studies (but see Milner and Petrides, 1984; Chapter 3; Stuss, this volume, Chapter 25). Sophisticated neu-

roimaging and controlled animal studies, however, can be used to address this issue more effectively. Our neuroimaging work on recovery of recent and remote autobiographical memory illustrates the benefits of this approach.

NEUROIMAGING STUDIES: RECENT AND REMOTE AUTOBIOGRAPHICAL MEMORY

We conducted a functional magnetic resonance imaging (fMRI) study on remote memory for autobiographical events to identify structures associated with the various component processes that are activated during retrieval (Ryan et al., 2001). We asked participants to recollect (re-experience) in as much detail as possible a personal episode that occurred either recently (within the last couple of years) or long ago (20 or more years earlier). Activation in the autobiographical memory test was compared to two baseline conditions: rest and a sentence completion test.

Two important results emerged from this study. The first was that retrieval of autobiographical memory was associated with increased hippocampal and diencephalic activity, as compared to the control conditions, regardless of whether the memory was recent or remote. Second, we also found greater activation in a number of neocortical regions, most particularly in the FC. Here, too, the extent of activation was no different for retrieval of recent memories than for that of remote memories, although Maguire (2001), in her review of this literature, has noted greater activation in the region of left, posterior ventrolateral PFC.

One interpretation of these results is that retention and retrieval of autobiographical memories, both recent and remote, depend on the interaction of medial temporal/diencephalic regions with the FC. This interpretation is consistent with the WWM model, and also supports the multiple trace theory (MTT) of memory proposed by Nadel and Moscovitch (1997, 1998).[2]

Within the FC, areas 6 (premotor cortex), 9, 46 (mid-dorsolateral FC), and 47 (ventrolateral FC) were activated, as well as areas 44

and 45, indicating widespread FC involvement in the retrieval of autobiographical memories. These results are consistent with those of Fink et al. (1996) Levine (personal communication), and Gilboa, Winocur, Grady & Moscovitch (in preparation) who found greater right PFC activation in some of these regions during recognition of personal autobiographical memory than of semantic memories or information associated with another person. In the WWM model, we assume that each of these activated regions serves a different function. We are drawing on the human and animal literature to speculate about the function of each of these regions and are attempting to develop the model further. We are doing so with the knowledge that the function of some of these regions is understood better than that of others, and that even for those that are relatively well understood, there is some debate as to how best to characterize the functions, as is obvious by comparing most of the chapters in this volume. We also hope that this model will serve as a useful guide for future research.

COMPONENTS OF RETRIEVAL AND FRONTAL CORTEX

One of the core ideas of WWM is that regions of the FC that are implicated in memory retrieval are described best in terms of their function or general cognitive operation, rather than in terms of information content or the domain in which they operate. Thus, when the same functions are performed, the same general regions of FC that are activated during retrieval of recent and remote memory are also activated during tests of working memory, problem solving, or even during tests of perception. There is some dispute, however, as to whether smaller, local, or lateralized regions within the more general area are activated differentially depending on whether the material is spatial, verbal, or pictorial (see Moscovitch & Umiltà, 1990; Footnote 1; and Chapters 3, 5, 11, 15, and 18).

In considering the components of retrieval, we deliberately made little reference to lateralization of function in the frontal lobes. Doing so enabled us to focus on the function of

the various subregions without entering the debate concerning lateralization.

Area 6 (Premotor Cortex): Response Selection and Inhibition

The area that was most consistently activated in our neuroimaging study was area 6 (premotor cortex), the likely homologue of the FC lesion that led to equal deficits in remote and recent memory in rats (Winocur & Moscovitch, 1999). Activation of area 6 is likely associated with memory-based response selection. Damage to this region leads to deficits on tests of CAL in monkeys (Petrides, 1982; see Chapter 3). and in humans (Petrides & Milner, 1982; Milner & Petrides, 1984) and is activated during tests of CAL in normal people (Petrides, 1995; see Chapter 3). In a series of studies, Winocur found that lesions to the FC that consistently destroyed all or most of the premotor area disrupted performance on a variety of conditional learning tasks (CAL, delayed alternation: Winocur, 1991; matching-to-sample; Winocur, 1992a) that required accurate response selection from among competing alternatives. Of particular importance is Winocur and Eskes' finding (1998, see Conditional Associative Learning, above) that deficits in CAL are reduced in rats with FC lesions in the region of the premotor cortex when response selection is not an overriding factor. Similarly, on the socially acquired food preference-test (Winocur & Moscovitch, 1999), remote and recent memory were impaired only when the number of alternatives was increased from two to three. Response selection clearly is an important factor in retrieval of autobiographical memory in which the appropriate event and corresponding details must be selected from a variety of other similar items.

Response selection (or inhibition of alternative responses) also seems to play a role in performing some implicit tests of memory, such as stem completion, whose performance is related to frontal function in older adults (Winocur et al., 1996). The correlation between tests of stem completion and frontal function are found only when there are many multiple solutions to the stems (Nyberg et al.,

1997) and not on tests of fragment completion with only one solution (see also Gabrieli et al., 1999). Consistent with this interpretation is some suggestive evidence that the premotor area is one of several FC structures activated when normal subjects select primed responses in tests of word-stem completion (e.g., Buckner et al., 1995).

Areas 9 and 46 (Mid-dorsolateral Frontal Cortex): Monitoring and Manipulation of Information Held in Mind (Working Memory)

The mid-dorsolateral PFC (areas 9 and 46) is implicated in tests that require manipulation of information that is being actively maintained such as in animal and human tests of working memory (Petrides, 1995). Thus, activation of this region is associated with increasing complexity of operations in tests of memory and problem solving (Christoff & Gabrieli, 2000; Duncan & Owen, 2000; Petrides, 2000; Postle & D'Esposito, 2000; see Chapters 3 and 18). This area is also implicated in tests of long-term memory such as free recall, in which one must keep track of responses in order not to repeat them (Stuss et al., 1994; Fletcher et. al., 1998; Henson et al., 2000). As might be expected, area 9 is also activated on tests of temporal order in humans (Cabeza et al., 1997). It is very likely that manipulation of information, which relies on monitoring and maintaining temporal order, is also crucial for recounting events that have a narrative structure, such as autobiographical memories, which may explain why this region was activated during retrieval in our neuroimaging study.

Work with animals provides converging evidence that areas 9 and 46 play a crucial role in monitoring information that derives from temporally ordered events. Damage to this region in monkeys and its homologue in rats (dorsomedial prefrontal cortex) reliably produces deficits on tests of working memory (Becker et al., 1980; Petrides, 1991, 2000; Granon & Poucet, 1995) and self-ordered pointing (Petrides, 1989), as well as on ordering item and spatial information (Kesner & Holbrook, 1987). All of these studies have or-

dering and response-selection components, but a study by Delatour and Gisquet-Verrier (2001) showed that lesions to this area affect response selection only when tasks place high demands on ordering processes. These investigators compared rats with lesions to dorsomedial prefrontal cortex on two response alternation tasks—one in which correct behavioral sequencing required the use of temporally ordered information and a second in which explicit cues specified the correct response on each trial. Both tasks required the selection of a correct response but the lesioned rats were impaired only on the former task where response selection was directly linked to temporal patterning.

Ventrolateral Frontal Cortex (Area 47): Cue Specification and/or Maintenance at Retrieval and at Encoding

The mid-ventrolateral FC (area 47) has been implicated in tests of recognition independently of the number of items held in memory or the operations performed on them (Henson et al., 2000; Fletcher & Henson, 2001). A number of investigators have proposed that this region is crucial for using distinctive retrieval cues to specify information that needs to be recovered from long-term memory (Wagner, 1999; Henson et al., 2000; Fletcher & Henson, 2001), as in detailed recall of specific autobiographical events, and possibly also for encoding information distinctively enough to discriminate targets from similar lures (Brewer et al., 1998; Wagner et al., 1998; Parkin et al., 1999). Thus, poor cue specification, with an overreliance on gist as seen in our memory distortion study (Melo et al., 1999), may be responsible for the overextended sense of familiarity observed in some patients with ventral FC lesions, with lesions on the left being associated with encoding deficits (Parkin et al., 1999) and lesions on the right with deficits at retrieval (Schacter et al., 1996a). This disorder may also be linked to dysfunction in the ventromedial area, which is adjacent to area 47 and often difficult to isolate functionally in lesion or activation studies (see next section). Sufficiently poor cue specification also leads to errors of omission on tests of re-

call, a common feature of frontal lobe amnesias (Moscovitch & Melo, 1997). Such an impairment, associated with lesions to area 47 and the uncinate fasciculus, which projects from this region to the temporal lobes, could also account for the loss of a sense of recollection that accompanies autobiographical memory (see Levine et al., 1998). This disorder is opposite the one associated with confabulation in which subjects experience a sense of recollection that is virtually indistinguishable for true and false memories and is likely related to damage to ventromedial PFC (see next section). Thus, cue specification is a necessary early step in accessing stored memories.

Consistent with the idea that the function of area 47 is cue specification, monkeys with lesions to the ventrolateral cortex, like humans, have difficulty choosing between novel and familiar items (Petrides, 2000). In rats, the deficit manifests itself on tests that require flexibility in response to cues that change their significance within the same context. For example, in a test of alternation behavior conducted in a cross-maze, rats were able to alternate on the basis of spatial location or on the basis of their own prior response. However, having learned one rule for alternation, lesioned animals were unable to shift to another one in the same context (Ragozzino et al., 1999). This deficit is similar to one Schnider et al., (2000) proposed to account for confabulation (discussed in next section) and may also be associated with ventromedial lesions.

Ventromedial Frontal Cortex (Areas 11, 13, 25): Felt-Rightness for Anomoly or Rejection

The lesions most commonly associated with confabulation are found in the ventromedial FC and basal forebrain, which include areas 11, 13, and 25 (and possibly 32, although its role seems to be associated more with conflict resolution), so it is puzzling that they were not activated in our neuroimaging study on retrieval of recent and remote memories. One possibile explanation is that the location of the areas makes them difficult to observe on neuroimaging studies, particularly those studies using fMRI. We should note, however, that

on PET scans, the comparison sentence-completion task may also activate the same or adjacent regions of FC (see Elliot et al., 2000), thus even if this region could have been imaged on fMRI, no difference would have been detected between the memory and baseline, sentence-completion task. We will return to this point shortly.

In a PET study, Schnider and colleagues (2000) showed that the ventromedial FC is crucial for temporal segregation (see also Pribram & Tubbs, 1967; Schacter, 1987), so that currently relevant memories can be differentiated from memories that may have been relevant once but are no longer. Temporal confusion, however, may not be the primary cause of confabulation but secondary to some other aspect of strategic retrieval mediated by the ventromedial FC (see Moscovitch 1989, 1995).

The hypothesis we favour is derived from studies on the effects of ventromedial FC lesions on emotion, risk taking, and social awareness and interaction (Bechara et al., 2000a, 2000b). Patients with ventromedial FC lesions have difficulty taking into account the emotional and social consequences of their actions so that they can plan appropriately and maximize their rewards in the long run. They are described as being "cognitively [but not motorically] impulsive," as not being able to appreciate the *"felt-rightness,"* of a response in relation to the goals of a task, regardless of whether the domain is social (Bechara et al., 2000a, 2000b) or cognitive (Elliot et al., 2000).

From the point of view of memory retrieval, felt-rightness is an intuitive, rapid endorsement or rejection of recovered memories with respect to the goals of the memory task. "Cognitive impulsivity" in the memory domain, manifested as the absence of a mechanism for felt-rightness, leads to the hasty acceptance of any strong, recovered memory as appropriate to the goals of the memory task, even if it is not. The extensive, direct connections of the ventromedial PFC to the hippocampus, amygdala, and adjacent structures in the medial temporal lobes, and to the temporal pole, make it ideally situated to play a prominent role in the first, postecphoric stages of memory retrieval from the MTL. Both elements,

the content of the memory and the overall context in which it is made, are crucial. This early, rapid (intuitive) decision to reject an item as incorrect is necessarily a first stage of retrieval that likely precedes the more thorough, cognitive check on the memory's plausibility, which occurs under conditions of uncertainty or when the initial response is incompatible with other knowledge or memories.

This hypothesis receives some support from a PET study (Moroz 1999) on memory for words coded in relation to oneself and in relation to another person. In this study, an investigator might ask, for example, "Does the word *modest* apply to you" (self)? "Does it apply to the current Prime Minister of Canada" (other)? Moroz (1999), working with us, found that different regions of the FC were activated depending on whether a target item elicited a "remember" or a "know" response at retrieval, regardless of whether it was related to the self or to another (Craik et al., 1999). "Remember" responses are associated with a contextually rich memory for an item, an indication that the person re-experienced the event at retrieval. A "know" response indicates only familiarity that the event occurred. Typically, "remember" responses are much faster and of higher confidence than "know" responses, which are more tentative, as they were in our study. "Remember" responses were positively correlated with activation in a neural network that included the anterior cingulate, which is part of the ventromedial PFC, and related limbic structures. "Know" responses, on the other hand, being less certain and requiring more monitoring, were correlated with activation in the mid-dorsolateral PFC [left (Brodmann's area 6/9/46) > right (Brodmann's area 9, 47)]. Similar results were reported by Henson et al (1999) in their study on remembering and knowing.

Area 10 (Anterior Prefrontal Cortex): Felt-Rightness for Acceptance or Endorsement

This region is also often implicated during retrieval of episodic memory, but its function has yet to be determined with any great degree of confidence. Some investigators equate

activation of area 10 on the right with retrieval mode (LePage et al., 1998) or with recovery of episodic memories (Tulving et al., 1994). In a recent review of the literature, Henson et al. (2000; Fletcher & Henson, 2001) suggested that area 10 is activated during successful (correct) retrieval of episodic (Henson et al., 2000; Fletcher & Henson, 2001) or semantic (Rugg et al., 1998) information. If their conjecture is correct, area 10 may work in concert with the ventromedial PFC to set *context-dependent* criteria of felt-rightness for correct acceptance (area 10) or rejection (ventromedial) of retrieved information, be it episodic or semantic. That area 10 may be activated equally by retrieval of episodic and semantic memory may also explain why we did not observe greater activation in this area during retrieval of autobiographical memories than during retrieval of semantic memories in the baseline, sentence-completion task.

There is no dearth of alternative proposals for the function of area 10. Fletcher and Henson (2001) have proposed that area 10 may act as a superordinate supervisory system needed to maintain complex plans in mind for coordinating retrieval operations handled by other regions such as the ventrolateral FC and dorsolateral FC. That may account for evidence that activation of this region is task-sensitive. Our own proposal of *context dependent criterion setting* would provide an equally plausible explanation of these effects. Yet another alternative is Christoff and Gabrieli's (2000) suggestion that this region is concerned with monitoring of self-generated, as opposed to externally generated, information, which is the province of the dorsolateral FC. The latter proposal seems at variance with evidence of dorsolateral FC involvement on tests of monitoring such as free recall and random number generation, all of which involve self-generated information. A final possibility is that this region implicated the "sense of self," which is a crucial component of episodic (autobiographical) memory that underlies the ability to re-experience the past (Craik et al., 1999; Levine et al., 1998; Moroz, 1999; Mosocovitch, 2000; Wheeler et al., 1997). All of these proposals, have some merit, and although all, including ours, are frankly speculative at this stage of

investigation, they are useful in that they provide clear hypotheses that can be tested in future studies.

SEQUENCE OF INTERACTION AMONG COMPONENTS

As yet, we know little about the sequence of interaction among the various regions of the FC at encoding and retrieval. By considering the functions we have assigned to these regions in the previous section, it is possible to derive some suggestions about the processing sequence at retrieval (see Fig. 12–6).

Retrieval is initiated with the establishment of a retrieval mode, which includes setting the goals of the task and initiating a retrieval strategy if external or internal cues cannot elicit a memory directly. Assuming that the function of the dorsolateral PFC is manipulation of information in working memory, then it is more suited than any of the other areas to coordinate these strategic activities and to monitor their outcome. In animal models, this process would involve learning the goals of the task and coordinating the activities necessary to achieve them.

Once the retrieval strategy is in place and initiated, the ventrolateral PFC is recruited. As noted earlier, its role is to specify and describe the cues needed to gain access to the MTL and maintain the information until the memory is recovered. The involvement of the ventrolateral PFC in this process begins at encoding and is reiterated at retrieval, where cue distinctiveness is a crucial factor in performance (Moscovitch & Craik, 1976). This cue information is transmitted to the MTL where it interacts with a code or index that elicits a (consciously apprehended) memory trace. If the cue is not specific or distinctive enough to interact with the MTL code and activate a memory trace, the process is repeated until an adequate cue is found and a memory is recovered, or the process is terminated.

It is also possible that a cue can activate the MTL directly, rather than via the ventrolateral PFC, if the cue is highly specific and strongly related to the information represented in the MTL code. In our component process model,

Figure 12–6. Flow diagram for interactions among medial temporal cortex and regions of frontal cortex during retrieval of episodic memories. DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex. The DLPFC is represented twice in the diagram to indicate its involvement in different processes at different points in the sequence.
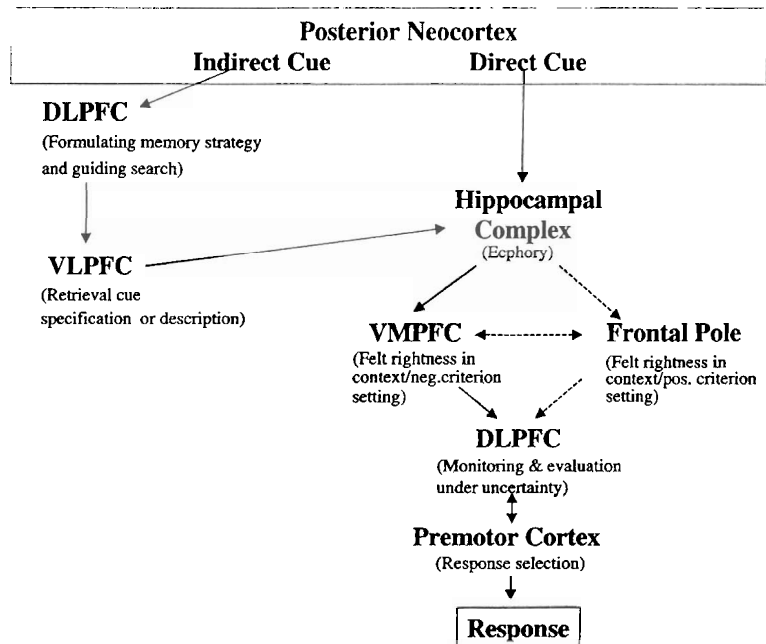
we refer to this direct process as *associative-cue dependent* (Moscovitch, 1992; Moscovitch & Winocur, 1992a, 1992b).

Once a memory is recovered, the information it represents is delivered to the ventromedial PFC. Although it is difficult to distinguish between the contribution of the ventrolateral and ventromedial regions to memory in lesion and neuroimaging studies, we have assigned different functions to them. Based on information about the goals of the task from dorsolateral PFC and about cues from ventrolateral PFC (and possibly context from Area 10), the ventromedial cortex automatically and immediately signals whether recovered memory traces satisfy those goals and are consistent with the cues in that particular context. It signals the felt-rightness of the recovered memory rather than the results of a considered evaluation. Because damage to ventromedial cortex leads to indiscriminate acceptance of recovered memories, its likely role is inhibitory in setting criteria (rejection).

In cases of uncertainty, the setting criteria may also implicate area 10, where it plays a reciprocal role of signaling acceptance or endorsement (excitatory) rather than rejection

(inhibitory) before the recovered memory is subjected to further processing. In those latter circumstances, the dorsolateral PFC is recruited to engage strategic verification processes, that would involve a host of regions in the FC, including the ventrolateral region, and posterior neocortex. These regions would then supply relevant information about the recovered memory, such as its perceptual characteristics (Johnson et al., 1996; Schacter et al., 1996b) and its compatibility with other knowledge about the event in question, that would influence the decision to accept or reject the recovered memory.

Response selection, mediated by area 6 (premotor motor cortex) is a crucial element in the retrieval process, although it is difficult to know where to place it in the sequence. It can either operate early in the process to help select among alternative strategies or cues with which to probe memory, or later to select among possible responses to memories that were recovered, or both. If the required information is not recovered or accepted, the retrieval processing sequence may be repeated or the search terminated.

We have focused on retrieval, but some of the same regions likely also operate at encod-

ing. In particular, areas 9 and 46 (DLPFC) are implicated at encoding to direct attention and establish encoding strategies (area 46) that will make the target distinctive (area 47, ventrolateral), thereby influencing its stored representation in MTL and, ultimately, making it more easily retrievable via specific cues laid down at encoding.

CONCLUSION

When we first proposed our WWM model, our goal was to provide a framework for distinguishing medial temporal from frontal contributions to memory (Moscovitch, 1989, 1992; Moscovitch & Winocur, 1992a, 1992b; Winocur, 1992b). In particular, we wished to place studies on memory in the context of a more general framework of modules and central systems (Moscovitch & Umiltà, 1990, 1991). In reviewing the literature at the time, we noted that there was ample evidence that the FC was crucial for performance on some tests of long-term, episodic memory, but with one or two exceptions (Shallice, 1988; Petrides, 1989), there was no theoretical framework that integrated those observations. Most of the focus in memory research was still on the medial temporal lobes. On the basis of our review, we proposed that the medial temporal lobes are "stupid" modules that obligatorily, and relatively automatically, encode and retrieve information that is consciously apprehended, whereas the frontal lobes act as "intelligent" central system structures that work with memory delivered to the medial temporal lobes or recovered from it. We proposed that as central system structures, the frontal lobes are needed for strategic aspects of encoding and retrieval. These include organizing input at encoding and initiating and directing search at retrieval, as well as monitoring and verifying the memories to see that they fit with the goals of the task and to place the recovered memories in their proper temporal–spatial context. At the time of that initial proposal, there was little evidence to assign each of these strategic operations to different regions of the FC, and we thought we had gone far enough in distinguishing between the strategic

function of the FC and the modular functions of the medial temporal lobes. The decade of research since our proposal has generally supported our idea that the frontal lobes are WWM structures and we have extended it by attempting to identify the regions in the FC that mediate the different components of WWM. Although a consensus has yet to be reached about what the various components are and where they are localized, there is sufficient evidence to formulate, as we did in the previous section, hypotheses about the function of different regions of the FC, in general, and more particularly, about their role in memory encoding and retrieval. Recognizing that some of the hypotheses are more speculative than others, and that further work is necessary, particularly with respect to developing animal models, we offer an updated version of the WWM model, based on these hypotheses. Like the previous version, the new version is a component process model that is concerned as much with the interaction among the components as it is with assignment, and localization, of function. We believe the model helps integrate the findings we reviewed and provides a framework for future research.

ACKNOWLEDGMENTS

NOTES

1. Given the specificity of connections from other structures to the FC, there may well be some domain specificity at a very local level within each region of the FC (see Moscovitch & Umiltà, 1990, p 21; Miller, 2000; Petrides, 2000).
2. The multiple trace theory (MTT) argues against the traditional view that, as memories become consolidated, the role of the hippocampal complex in memory retention and retrieval diminishes with time whereas that of the neocortex increases. According to the MTT and the results we obtained, the hippocampal complex is impli-

cated regardless of the age of the memory. However, supported by evidence such as that obtained in the food-preference study (see Recent and Remote Memory, above), proponents of the traditional view have offered alternative interpretations. Indeed, the question as to whether the hippocampal complex is needed for retention and recovery of remote memories is currently under intensive debate in both the human and animal literature (Moscovitch & Nadel, 1998, 1999; Rosenbaum et al., 2001).

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