REVIEW

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Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies

Abstract Working memory refers to the short-term retention of information that is no longer accessible in the environment, and the manipulation of this information, for subsequent use in guiding behavior. In this review, we will present data from a series of event-related functional magnetic-resonance-imaging (fMRI) studies of delayed-response tasks that were designed to investigate the role of different regions of the prefrontal cortex (PFC) during different working-memory component processes. From these data, we conclude that: (1) lateral PFC is anatomically organized according to the types of cognitive operations that one performs when attempting to temporarily maintain and manipulate information; and (2) consistent with the picture that has emerged from the monkey electrophysiological literature, human lateral PFC is involved in several encoding- and response-related processes as well as mnemonic and nonmnemonic processes that are engaged during the temporary maintenance of information. Thus, lateral PFC activity cannot be ascribed to the function of a single, unitary cognitive operation.

Key words Working memory · Prefrontal cortex · Functional MRI
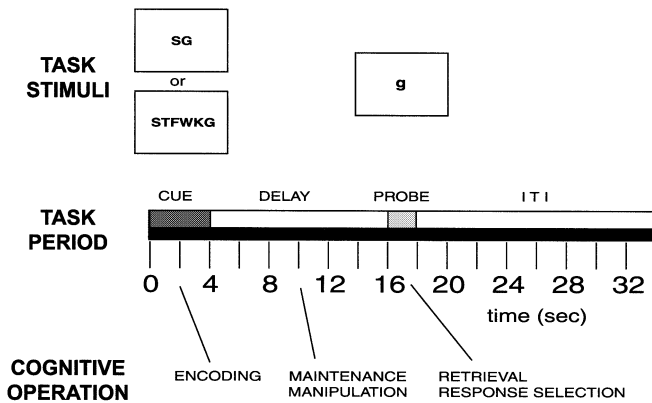
Introduction

Working memory refers to the short-term retention of information that is no longer accessible in the environment, and the manipulation of this information, for sub-

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sequent use in guiding behavior. An interacting set of processes can be recruited to maintain information in working memory and to perform operations on it. Working memory makes important contributions to many cognitive functions, such as reasoning, language comprehension, planning, and spatial processing. Important evidence for the neural basis of working memory was initially provided from animal studies (for a review, see Owen et al. 1999). For example, electrophysiological studies of awake behaving monkeys have used delayed-response tasks to study working memory. In these tasks, the monkey must keep "in mind", or actively maintain, a representation of the target stimulus [or of the anticipated probe stimulus (Rainer et al. 1999; Watanabe 1996)] over a short delay. During such tasks, neurons within the lateral prefrontal cortex (PFC) have been found to be persistently activated during the delay period when the monkey is maintaining information in memory prior to a making a motor response that is contingent on this information (Funahashi et al. 1989; Fuster and Alexander 1971). The necessity of this region for active maintenance of information over short delays has been demonstrated in monkey studies showing that lesions of the lateral PFC impair performance on these tasks (Bauer and Fuster 1976; Funahashi et al. 1993).

Using event-related functional magnetic-resonance-imaging (fMRI) designs, groups have begun to demonstrate that lateral PFC in humans is also engaged during the active maintenance of information over short delays in delayed-response tasks (Courtney et al. 1997; Zarahn et al. 1999). These studies, however, have not assessed the role of PFC during other processes that are engaged during delayed-response tasks, such as encoding processes at the time of stimulus presentation and retrieval processes at the time of probe presentation. Electrophysiological studies in monkeys performing delayed-response tasks, however, have revealed that PFC neurons can also be active during many non-delay portions of the task, and it is well established that PFC neurons can respond during any combination of target, delay, and response periods (Chafee and Goldman-Rakic 1998; Funahashi et al.

Fig. 1 Schematic illustration of a prototypical delayed-response task with proposed cognitive processes that may be engaged at each task period. *ITI* Intertrial interval

1989; Fuster et al. 1982). Thus, in addition to active maintenance, the PFC appears to be involved in processes that may include stimulus encoding, sustained attention to stimuli, manipulation of information being actively maintained, decision about a probe, preparation for a motor response, and execution of the motor response itself.

In this review, we will present data from a series of event-related fMRI studies of delayed-response tasks that were designed to investigate the role of different regions of the PFC during different component processes engaged when information is stored and temporarily manipulated during delayed-response performance (Fig. 1). This was achieved by examining the temporal dynamics of PFC activity over the course of a single trial, and isolating the variance in the fMRI signal attributable to the theoretically dissociable components of the trial [i.e., target, delay, probe (Zarahn et al. 1997)]. This capability represents an important methodological advance, because it permits direct measurement of the PFC contribution to the different processes that can contribute to working memory performance. As our review will demonstrate, event-related fMRI designs have emerged as a powerful method for the studies of human cognition that are analogous to awake, behaving monkey physiological studies.

Previously, fMRI and positron emission tomography (PET) investigations of working memory have employed blocked experimental designs that require the integration of a neuroimaging signal across entire blocks of each type of trial in an experiment. This approach has at least three important limitations. First, its temporal resolution is inherently poor, typically on the order of tens of seconds, and is thus ill-suited for direct measurement of working-memory-related processes, which operate on the order of seconds or milliseconds. Second, it often requires the pairing of the assumption of "pure insertion" (Sternberg 1969) with application of the logic of "cognitive subtraction" (Posner et al. 1988), a combination that may yield unreliable results (Friston et al. 1996; Zarahn et al. 1997). For example, a blocked experimental design

may contrast performance on a delayed-response task (comprised of stimulus presentation, delay, and probe components) with performance on a visual matching task (comprised of only stimulus presentation and probe components), with the subtraction of neuroimaging signal from these two conditions intended to reveal the brain regions contributing to cognitive processes *not* shared by the two – in this case, delay-related processes. The assumption guiding this design is that the *insertion* of the delay period will not interact with the stimulus presentation and probe components of the trial. Such a design was featured in the early, influential neuroimaging investigations of Jonides, Smith, and colleagues (Jonides et al. 1993; Smith et al. 1995). It has been demonstrated empirically, however, that PFC voxels that are *not* active during the delay-period of a delayed-response task can evince greater probe-related activity when the response is preceded by a delay period than when it is immediately preceded by stimulus presentation (Zarahn et al. 1997). That is, the insertion of a delay period into a visual matching task can have interactive effects on nonmnemonic parts of the task, and a conventional block-design analysis would incorrectly identify such a voxel as having delay-period activity.[1] A third limitation of blocked neuroimaging studies is that inferences derived from them are usually based on aggregate task performance and fMRI activation data. This approach has been useful for mapping the contributions of various brain regions to working memory, but does not permit the investigation of relations between behavioral (e.g., reaction time, accuracy) and physiological indices (e.g. fMRI activation) associated with working-memory task performance. In this review, we will also present data that address relations between individual differences in performance and individual differences in cortical activity.

Maintenance versus manipulation processes

In some behavioral contexts, information must be maintained in the state in which it was encoded (as when one remembers a telephone number when walking from the phone book to the telephone). Other circumstances require the manipulation of this remembered information (as when one simultaneously performs mental calculations and remembers the intermediate products). Presumably, these manipulations or additional operations entail the recruitment of additional cognitive processes not required for simple maintenance of information. One systems neuroscience model encompassing this view proposes that the ventrolateral PFC (primarily the inferior

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[1] Note that event-related designs can also rely on cognitive subtraction, as, for example, when comparing delay-period activity associated with the retention of three items versus delay-period activity associated with retention of six items, a design we will discuss in a subsequent section. A more detailed consideration of different types of neuroimaging experimental designs can be found in: Aguirre GK, D'Esposito M (1999) Experimental design for brain fMRI; in: Moonen CTW, Bandettini PA (eds) Functional MRI. Springer, Berlin Heidelberg New York, pp 369–380.

frontal gyrus, Brodmann's areas 47, 44, 45) is the site where information is initially received from posterior association areas and where organization of information held in working memory is performed, whereas dorsolateral PFC (primarily the middle frontal gyrus, areas 9 and 46) is additionally recruited only when monitoring and manipulation of information within working memory is required (Petrides 1989, 1994). Empirical support for such a dorsal/ventral organization in human PFC came from a PET study contrasting PFC activation associated with several different spatial working-memory tasks that varied manipulation and monitoring demands (Owen et al. 1996). The results were consistent with the Petrides model and have been replicated in subsequent fMRI (Owen et al. 1998) and PET (Owen et al. 1999) experiments. Interpretation of these results is complicated, however, by the complex set of subtractions and comparisons required to partial out the relative contributions of tests of delayed-response, span, self-ordered choosing, and n-back utilized in these studies – and of the control task associated with each – to measures of PFC activation. In addition to the concerns about interpreting results produced by a cognitive subtraction analysis, the blocked designs of these studies also prevented direct inference as to whether the additional monitoring-related neuroimaging signal in dorsolateral PFC was attributable to neural activity arising during encoding, delay, or probe portions of such tasks. Thus, although these studies represent important initial tests of this processing model of the anatomical organization of working memory function in PFC, they left many important questions unresolved.

We have performed two event-related fMRI studies designed to investigate the proposed neural dissociation between processes required for the active maintenance of information in working memory and the processes engaged when this information is manipulated. In the first study (D'Esposito et al. 1999a), the behavioral paradigm was a delayed-response task in which a set of five letters was presented simultaneously, in a randomly determined order, followed immediately by an instruction cue ("FORWARD" or "ALPHABETIZE"), followed by an 8-s delay, during which only a fixation cross appeared on the screen, followed by a probe that prompted the subject to make a button-press response. Thus, subjects were presented with two types of trials (in random order) in which they were required either to: (1) *maintain* a randomly ordered sequence of five letters across a delay period, or (2) *manipulate* a comparable sequence of letters by arranging them into alphabetical order during the delay period. In both conditions, the probe consisted of a letter and a number. In the *maintenance* condition, subjects were instructed to determine whether the letter was in the ordinal position represented by the number. This condition, therefore, simply required retention of the letters in the same format as presented at the beginning of the trial. In the *manipulation* condition, subjects were instructed to determine whether that letter would be in the ordinal position represented by the number if the items

in the memory set were rearranged into alphabetical order. This condition, therefore, required subjects to transpose the order of the five items presented at the beginning of the trial during the delay period.

In each subject, activity during the delay period was found in both dorsolateral and ventrolateral PFC in both types of trials. Additionally, in each subject, dorsolateral PFC activity was significantly greater in trials during which information held in working memory was manipulated (Fig. 2). Thus, our results were broadly consistent with a hierarchical processing model of the organization of working memory function in PFC, in that they revealed a consistently greater contribution of dorsal PFC to manipulation processes than of ventral PFC.

These results differed importantly from those of previous studies (Awh et al. 1996; Owen et al. 1996, 1998, 1999; Smith et al. 1998), however, in that they provided evidence for dorsolateral PFC contribution to working-memory maintenance trials. Although our maintenance task differed methodologically from some of those of Owen and colleagues, for example, in that it may not have required "monitoring" operations to the same extent, such differences would only be expected to *lessen* the extent to which our tasks would recruit dorsolateral PFC. The results discussed here are consistent with those of at least five other studies that have shown, with several different types of stimuli, that active maintenance in working memory recruits dorsolateral PFC (Cohen et al. 1997; Courtney et al. 1997; Postle and D'Esposito 1999; Postle et al. 1999; Zarahn et al. 1999). The finding that dorsolateral PFC is engaged during active maintenance as well as during manipulation processes is the first piece of evidence that we marshal in support of our view that lateral PFC subserves several discrete working-memory-related cognitive processes.

A second event-related fMRI experiment, utilizing a variation of the same task, replicated the results of the first in that it also provided evidence for dorso- *and* ventrolateral PFC activity during the delay-period of working-memory maintenance trials, but consistently greater activity during alphabetization trials only in dorsolateral PFC (Postle et al. 1999). This second study also extended our earlier results in two important ways. First, it might have been argued the greater activity of dorsolateral PFC associated with the alphabetize condition in the earlier study (D'Esposito et al. 1999a) was due to the greater difficulty of this condition rather than to the additional mental processes required by this task. In this second experiment, however, performance on "Forward 5" (maintenance) and "Alphabetize 5" (manipulation) tasks was equivalent, thereby removing the difficulty confound from these data. (For these analyses we operationalized difficulty as performance accuracy.) We could thus unequivocally attribute to alphabetization-related processes to the increased activity that we observed in dorsolateral PFC.

The second advance represented by this task was the inclusion of a condition requiring maintenance of two

letters, a modification that permitted investigation of working-memory load effects. We found delay-specific load effects in dorsolateral PFC in only two of the five subjects participating in the experiment, and, importantly, no evidence of delay-period load effects in any voxels that evinced greater manipulation than maintenance

activity (Postle et al. 1999). We did find, in contrast, consistent delay-period load effects in all subjects in left posterior perisylvian cortex. Group analyses revealed a double-dissociation, with greater load-than-alphabetization activity in left posterior perisylvian regions, and greater alphabetization-than-load activity in PFC, indicating that the neurophysiological factors underlying manipulation and storage differed qualitatively, not just quantitatively (Postle et al. 1999). These results, therefore, provide the first evidence that the manipulation-related processes ascribed to dorsolateral PFC are fundamentally nonmnemonic in nature. That is, whereas they play an important role in the exercise of executive control of working memory, they do not govern the maintenance or storage per se of the information held in working memory. We believe that many manipulation-related processes may also be recruited to support non-working-memory behaviors. This result has implications not only for hierarchical processing models of the organization of working-memory function in PFC, but also for the interpretation of "load effects" observed in PFC in experiments that parametrically manipulate the number of items maintained in an n-back task (Braver et al. 1997; Cohen et al. 1997; Jonides et al. 1997), suggesting that these effects may be attributable to nonmnemonic processes contributing to performance of these tasks and not the to information-storage or -maintenance processes. This last proposal received support from the results of the next study we will describe, an examination of load-effects in item-recognition working memory.
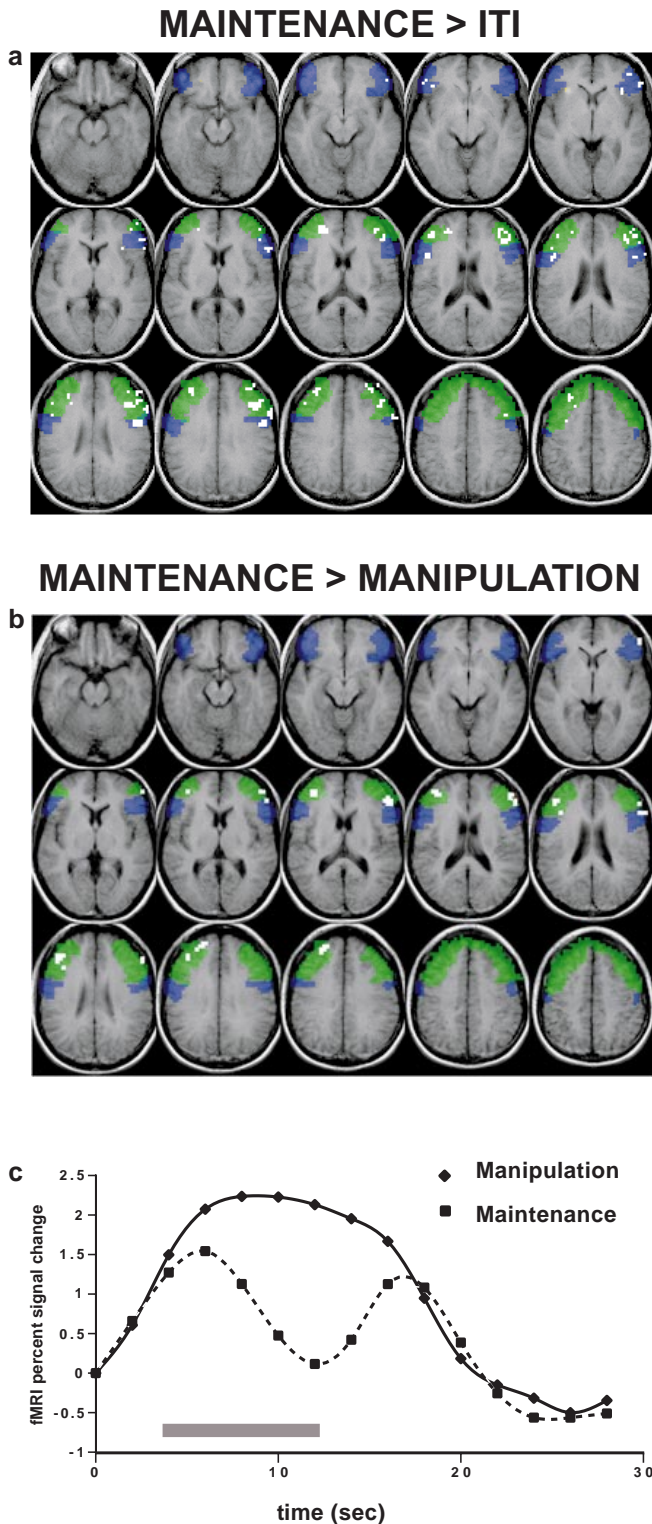
The effect of load on encoding, maintenance, and retrieval processes

Recently, two studies have shown that dorsolateral PFC recruitment increases in parallel to increased memory load during performance of tasks with no overt requirements to manipulate information held in working memory (Manoach et al. 1997; Rypma et al. 1999). For exam-

Fig. 2 a Representative subject *t*-map illustrating the voxels demonstrating significant delay-period activity (versus baseline) during maintenance trials, during which the subject maintained a representation of five letters in the order in which they were presented. **b** A *t*-map from the same subject illustrating the voxels demonstrating significantly greater delay-period activity during manipulation ("alphabetize 5 letters") than maintenance trials. The *green-shaded* ROI represents ventrolateral PFC (inferior frontal gyrus) and the *blue-shaded* ROI represents dorsolateral PFC (middle frontal gyrus). Maintenance-related activity (**a**) is seen in both ventrolateral and dorsolateral PFC, whereas manipulation activity is greater than the maintenance activity only in dorsolateral PFC (**b**). **c** The trial-averaged time series from the voxels highlighted in **b**. Note the two peaks in the maintenance condition correspond to the stimulus presentation and the probe periods of the trial. In the manipulation condition, in contrast, these voxels maintained a high level of activity throughout the delay period. The *solid bar* along the horizontal axis represents the duration of the delay period

Fig. 3 A scatter plot of the numbers of suprathreshold voxels during the "Response Period" of a delayed response task in dorsal prefrontal cortex (PFC; *dotted line, squares*; slope =1.34, r^2=0.76, P<0.05) and ventral PFC (*solid line, circles*; slope =0.36, r^2=0.18) plotted against reaction-time slopes. Also shown are axial slices of activation patterns in the two representative subjects with the lowest and highest reaction-time (*RT*) slopes
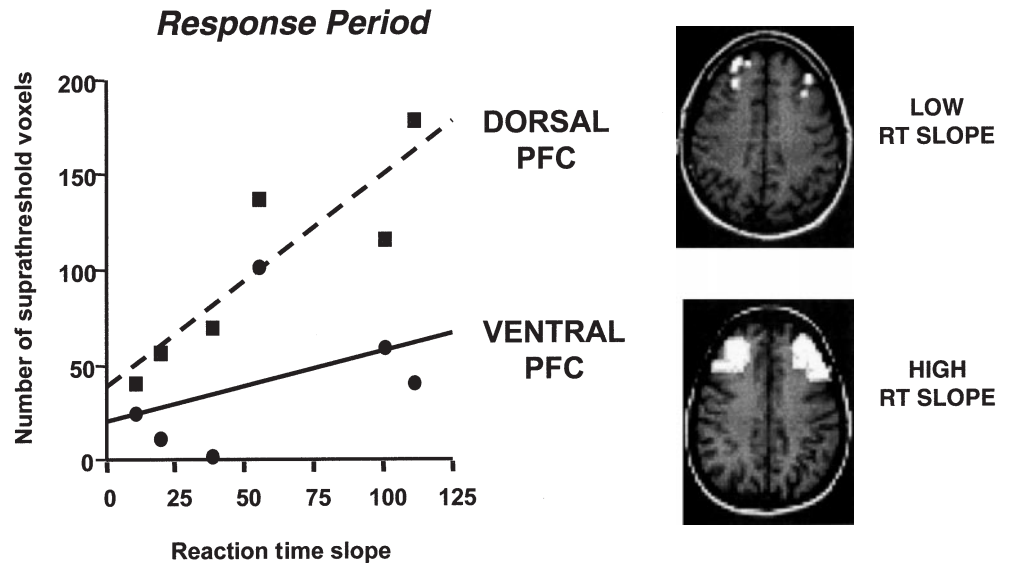
ple, Rypma and colleagues (1999) observed activation in dorsolateral PFC in a Sternberg-type item-recognition task in which subjects were required to maintain one, three, or six letters in working memory for 5 s. When subjects were required to maintain three letters in working memory, relative to one letter, activation in frontal regions was limited to left ventrolateral PFC (BA 44). However, when subjects were required to maintain six letters, relative to one letter, the additional activation of dorsolateral PFC was observed. Rypma and colleagues proposed that dorsolateral PFC may be recruited during maintenance tasks in which subjects must actively maintain information loads that approach or exceed short-term memory capacity. According to this view, the same dorsolateral PFC circuits important for manipulation of information in working memory may be recruited for the mediation of strategic processes necessary for the maintenance of a high load of information. Alternative interpretations of the Rypma et al. (1999) and Manoach et al. (1997) results were possible, however, because both featured blocked designs that didn't permit identification of the specific component processes that were sensitive to the load manipulation.

In an event-related fMRI study intended to elucidate the relative contributions of target, delay, and probe task periods to PFC activation in item-recognition working-memory performance, we asked subjects to maintain either two or six letters across an unfilled delay period and found that the effects of increased memory load were observed only in dorsolateral PFC, lateralized to the right hemisphere, and were observed only in the *encoding* period of the task (Rypma and D'Esposito 1999). Consistent with the results of Postle et al. (1999), described earlier, *delay*-period load effects were only seen in left posterior cortex. These results suggested that the load-sensitive processes in dorsolateral PFC that were identified in earlier block design studies (Manoach et al. 1997; Rypma et al. 1999) contribute to encoding processes, but

not to the maintenance of information in working memory. It may be that initial encoding of information requires cognitive operations (e.g., monitoring the contents of working memory, updating and coordination of multiple memory buffers) that are similar to those required in the "manipulation" tasks described previously. Additional experiments are required to test this possibility.

Because we observed considerable inter-subject variability in fMRI signal magnitude and activation extent, we performed additional analyses to explore possible relations between individual differences in PFC physiological measures and task performance. For this analysis, we operationalized performance of each individual subject in terms of their memory retrieval *rate*, the interpolated slope obtained when plotting reaction time (RT) against memory load (two- vs. six-letter trials). The RT slope is believed to index memory-retrieval (or "scanning") rate when subjects must make a yes/no judgment about the membership of a probe stimulus to the memory set (Sternberg 1966). Further, memory-retrieval rate may vary with the efficiency of memory-scanning processes. We operationalized PFC activity as the number of voxels identified with a load-independent contrast selective for voxels evincing delay-period activity during two-letter and six-letter trials. Linear-regression analyses were then applied to data from each trial component and from two PFC regions of interest (e.g., dorsolateral and ventrolateral) to test for relationships between performance and activity.

The results of these individual differences analyses indicated that, in the dorsolateral PFC, retrieval rate and fMRI activation were positively correlated (r^2=0.76; P<0.05), but only at the time of response (Fig. 3). This correlation corresponded to an increase of 1.34 activated voxels per millisecond of increase in retrieval rate and accounted for 76% of the variance (Rypma and D'Esposito 1999). These results suggest two conclusions. First, because increased retrieval rate corresponds to less effi-

cient working-memory scanning, poorer performers on this task may have recruited broader networks within dorsolateral PFC to compensate for inefficient working-memory scanning processes. Second, the finding of a significant brain-behavior link only in dorsolateral PFC (and not ventrolateral PFC), and only during response (and not during other task periods), suggests that this region of PFC represents an important substrate of memory scanning, a retrieval process that is initiated with the onset of the probe stimulus.

The effect of proactive interference on encoding, maintenance, and retrieval processes

Although the previously described study characterized the neural substrate of one component process (or set of processes) recruited in association with the onset of the probe stimulus in a delayed-response task, there are certainly many other processes engaged during this portion of the task, candidates among them including: shifting attention among items held in working memory (Garavan 1998; McElree 1998); inhibition of prepotent responses (Diamond 1990); mediation of proactive interference (Jonides et al. 1998); coordination of multiple task performance (D'Esposito et al. 1995); response preparation (D'Esposito et al. 2000); and motor execution. An important empirical question is the extent to which each of these theoretically dissociable, probe-related processes relies on the same neural substrate. To begin to approach this problem, we chose to focus on another memory-related phenomenon, proactive interference (PI), whose existence is measured by RTs. Like the previous study, this experiment illustrates the advantages of the *temporal resolution* of an event-related experimental design over that of a block design.

Using event-related fMRI, we scanned subjects as they performed a four-letter item-recognition task, during which they judged whether or not the probe was from the target set of four consonant letters. The task was designed such that we controlled the amount of PI associated with the probe stimulus on each trial. Two types of trials were of greatest interest: those with "Recent Negative" probes that matched a letter from the target set of the two previous, but not the present trial (and thus featured a high level of PI), and those with "Nonrecent Negative" probes that did not match a target letter from any of these trials. We hypothesized that a correct response to a "Recent Negative" probe would engage interference-resolution processes, possibly inhibition of the tendency to respond "yes" based on the sheer familiarity of the probe (which had been rehearsed extensively on the two previous trials). A correct response to a "Nonrecent Negative" probe, by contrast, would minimize demands on interference resolution, reflecting the absence of PI from the previous trials. We predicted that interference-resolution processes associated with "Recent Negative" trails would manifest themselves in brain activation and behavioral data. A previous study indicat-
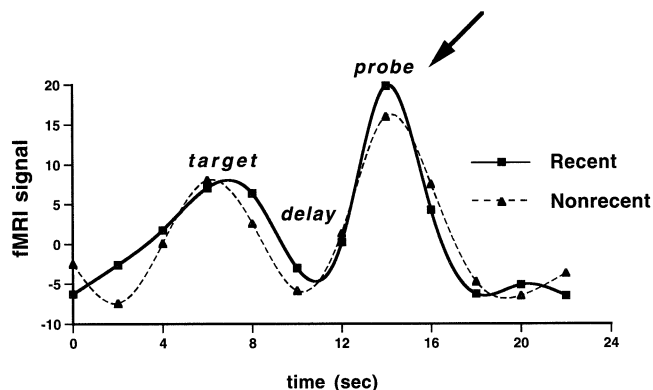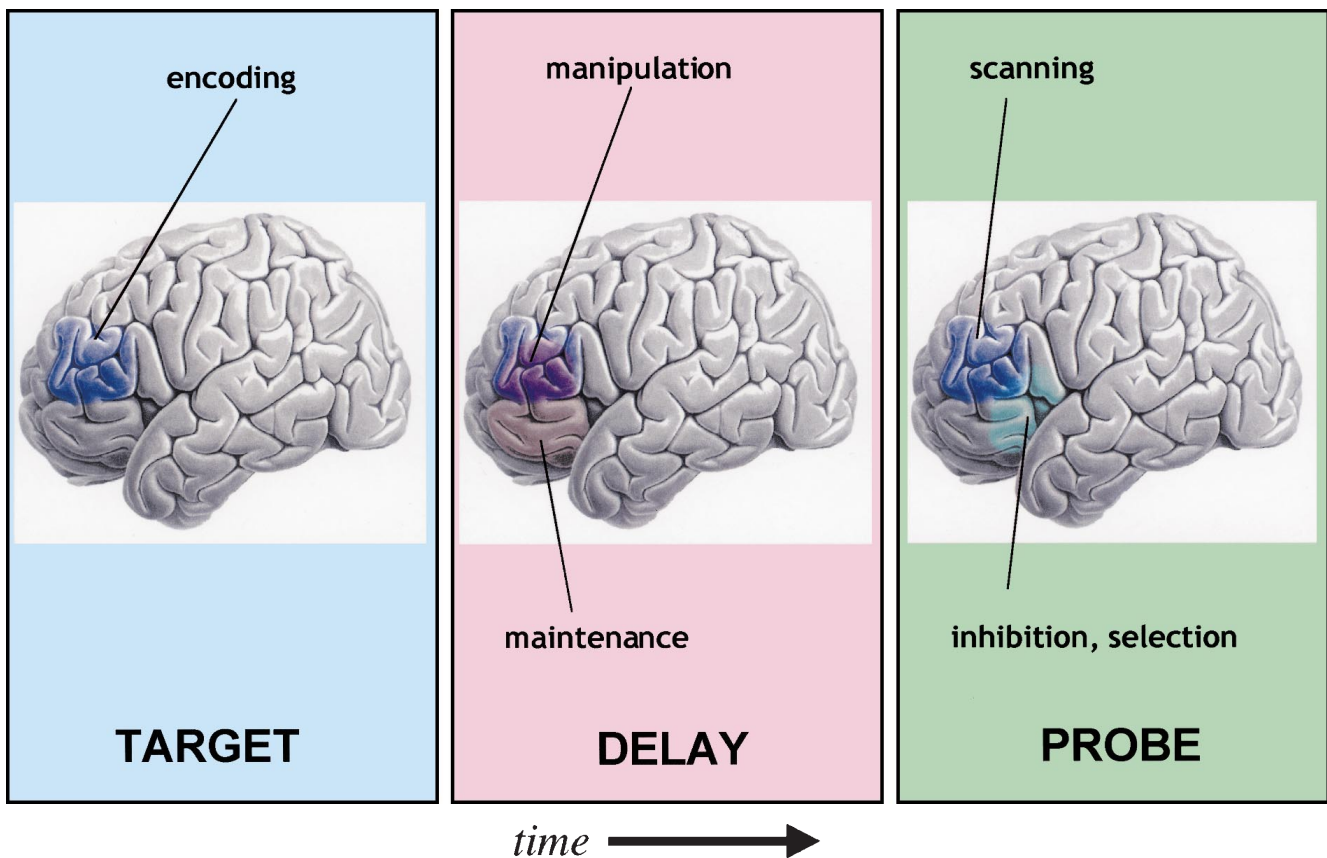

Fig. 4 The trial-averaged time series data for a representative subject extracted from voxels within the left inferior frontal gyrus (Brodmann's area 45) demonstrating a main effect for the probe period across both "Recent Negative" and "Nonrecent Negative" trials. Activity in the two conditions differed statistically only during the probe portion of the task (*arrow*)

ed that "Recent Negative" trials are associated with an RT cost believed to reflect the operation of a process or set of processes that detect and resolve PI (Jonides et al. 1998), and behavioral results from our study also revealed a small, but reliable RT effect.

The Jonides et al. (1998) study was a PET study that found that Brodmann's area 45 in left ventrolateral PFC demonstrated greater activation in association with "Recent Negative" trials. Because this study used a blocked design that averaged signals across all components of trials in each condition of the delayed-response task, however, it was unsuitable for investigation of temporal dynamics of the inhibitory processes ascribed to the observed PFC activation. For example, rather than reflecting a temporally discrete response-related process that was sensitive to PI, this neuroimaging effect could have occurred during stimulus presentation, delay, or retrieval components of trials in which PI was present, or in any combination of these three. Importantly, the PI-related activity reported by Jonides and colleagues (1998) could have also reflected a state-dependent mental "set" that persisted steadily during blocks of trials that featured high stimulus overlap, as might be expected if subjects adopted a different behavioral strategy for blocks that featured a high proportion of stimulus overlap across trials (Johnson et al. 1997). Our event-related design, in contrast, although employing a similar behavioral paradigm as Jonides et al. (1998), featured randomization of trial types that obviated the possible contamination of our data with context-dependent effects that can manifest themselves when trials representing a particular experimental treatment are blocked together.

The physiological data from our task confirmed that there were no differences in PFC between the two trial types in target presentation or delay-period activation, but that there was significantly greater probe-related activation for "Recent Negative" than "Nonrecent Negative" trials within left ventrolateral PFC, but not in other regions of PFC (Fig. 4). These findings spatially and

temporally characterized a physiological PI effect that was reliable across subjects, and that was associated with a mean RT cost of 32 ms produced by our PI manipulation. Further investigation of these effects needs to be carried out to determine whether the process(es) indexed by these effects are best characterized as response inhibition (Jonides et al. 1998), selection among candidate memoranda (Thompson-Schill et al. 1997), probe discrimination (McElree and Dosher 1987; Monsell 1978), or an as yet unarticulated alternative. But, regardless of what subsequent studies tell us about the computational nature of the processes underlying this PI effect, we have already established that it is supported by a different region of PFC than that which supports memory-scanning-related processes that are also associated with the probe/response component of working-memory-task performance.

Conclusions

Lateral PFC in humans is clearly recruited during many different cognitive processes that are engaged by the performance of delayed-response tasks. Moreover, lateral PFC seems to be functionally organized according to the types of cognitive operations that one performs when attempting to maintain and manipulate information over short periods of time. Figure 5 schematically summarizes the findings of the studies that were presented in this paper. When the amount of to-be-remembered information presented at the beginning of a delayed-response trial approaches or exceeds short-term memory capacity (e.g., Waugh and Norman 1965), dorsolateral PFC is preferentially engaged. Dorsolateral PFC-supported processes may facilitate the efficient encoding of information. During the subsequent delay interval, when no information is accessible to the subject, both ventro- and dorsolateral PFC are recruited. If manipulation of this information is additionally required during the delay period, dorsolateral PFC is recruited to an additional extent. Upon the presentation of the probe stimulus, when a subject is required to make a response based on what was presented at the beginning of the trial, dorsolateral PFC is again engaged, presumably as the subject scans the information that was retained across the trial and chooses an appropriate motor response. Furthermore, the extent of activation of dorsolateral PFC is correlated with the efficiency of this scanning process. That is, faster memory scanning results in less PFC activation. If, at the time of the probe, there is PI from previously remembered information, a more ventral region of left PFC is engaged to adjudicate the conflict caused by this interference. Together, the results of these studies highlight the temporal dynamics of PFC function during working memory task performance. One strong conclusion that can be drawn

from these data is that lateral PFC activity cannot be ascribed to the function of a single, unitary cognitive operation. Consistent with the picture that has emerged from the monkey electrophysiological literature, human PFC is involved in several encoding- and response-related processes, as well as to mnemonic and nonmnemonic processes that are engaged during the temporary maintenance and manipulation of information.

It is important to emphasize the types of inferences that can be drawn from our review of functional MRI studies of PFC. It is the nature of all physiological studies of the nervous system (including single- and multiunit electrophysiology, EEG, MEG, measures of glucose metabolism, and, important for the present purposes, hemodynamic measures such as fMRI) that they support inferences about the *association* of a particular brain system with a cognitive process. Thus, functional neuroimaging is an *observational*, *correlative* method (Sarter et al. 1996). The inference of *necessity* of a brain region to a given cognitive function cannot be made without a demonstration that the inactivation of this region disrupts the function in question. But interpretation of neuropsychological data is subject to a different set of caveats. Among them, lesion localization is difficult in human studies, the interruption of fibers of passage by a brain insult is difficult to assess, and the lesioned area may contribute in a nonspecific way to the normal functioning of a distal region that is itself the true neural substrate of the function in question. When lesion and functional neuroimaging studies are combined, however, a stronger level of inference can result. One type of combination might be that: (1) lesions to a cortical area impair a given cognitive process, and that (2) the cognitive process evokes changes in neural activity in the same cortical area in intact subjects. The inference that the neuroanatomical area is computationally necessary for the cognitive process is now rendered less vulnerable to the limitations of either method in isolation.

Few studies of patients with focal lesions of PFC performing delayed-response tasks have been reported. In a recent review of such studies, we found that some groups of patients with PFC lesions can be impaired on delayed-response tasks, and that these deficits tend to be more prominent when patients perform delayed-response tasks that include distraction during the delay (D'Esposito and Postle 1999). We also found that patients with lateral PFC lesions are generally not impaired on tests of working-memory span [i.e., digit span and block (spatial) span (D'Esposito and Postle 1999)]. This evidence from human lesion studies, combined with the results from some of the fMRI studies that we have summarized in this review, allow us to draw several conclusions and form new hypotheses about the function of lateral PFC. First, lateral PFC does not seem to make a *necessary* contribution to simple working-memory storage. Second, lateral PFC, and specifically dorsolateral, is likely necessary for the manipulation of information. Third, dorsolateral PFC may only make necessary contributions to the maintenance of information

when this information must be shielded from concurrent distracting stimuli (Chao and Knight 1998). Fourth, dorsolateral PFC makes an important contribution to working-memory encoding processes (Rypma and D'Esposito 1999). Finally, lateral PFC may make an important contribution to *probe*-related processes on tests of delayed response, among these memory scanning (Rypma and D'Esposito 1999) and interference resolution processes (D'Esposito et al. 1999b). Thus, the improved inferential power and the improved temporal resolution of event-related fMRI, combined with an analysis of the human neuropsychological literature, have permitted us to articulate a model of the organization of working memory functions of PFC (Fig. 5) that is more precise, at a mechanistic and at a temporal level, than currently existing models (e.g., Petrides 1989, 1994; Smith and Jonides 1999)

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