

# 9 Functional Neuroimaging of Working Memory

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## INTRODUCTION

Working memory is an evolving concept that refers to the short-term storage of information which is not accessible in the environment, and the set of processes that keep this information active for later use in behavior. It is a system that is critically important in cognition and seems necessary in the course of performing many other cognitive functions, such as reasoning, language comprehension, planning, and spatial processing. Animal studies initially provided important evidence for the neural basis of working memory (for review, see Fuster, 1997). 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 stimulus over a short delay. During such tasks, neurons within the prefrontal cortex (PFC) are found to be persistently activated during the delay period of a delayed-response task, when the monkey is maintaining information in memory prior to making a motor response (Funahashi et al., 1989; Fuster & Alexander, 1971). The necessity of this region for active maintenance of information over short delays has been demonstrated in monkey studies which have shown that lesions of the lateral PFC impair performance on these tasks (Bauer & Fuster, 1976; Funahashi et al., 1993).

From a psychological point of view, working memory has been conceptualized as comprising multiple components that support executive control processes as well as active maintenance of information. For example, Baddeley (1986) has proposed the existence of a "central executive system" that, based on behavioral studies of normal subjects, is a system which actively regulates the distribution of limited attentional resources and coordinates information within limited-capacity verbal and spatial memory storage buffers. The central executive system, based on the analogous supervisory attentional system introduced by Norman and Shallice (1986), is proposed to take control over cognitive processing when novel tasks are engaged and/or when existing behavioral routines have to be overridden. Both Baddeley and Shallice originally argued that an executive controller is a distinct cognitive module which is supported by the PFC, and that damage to this module, or system, accurately describes some of the behavior of patients with PFC damage. More recently, however, Baddeley has postulated that the central executive does not function as a single module and can be fractionated into subcomponents (Baddeley, 1998).

Although the concept of a "central executive" has influenced our thinking about the function of the PFC, other researchers have

or working, memory; preparatory task set, or the ability to be prepared for future action; and inhibitory control. He also has argued explicitly against the executive interpretation of PFC function, writing that "the PFC would not superimpose a steering or directing function on the remainder of the nervous system, but rather, by expanding the temporal perspectives of the system, would allow it to integrate longer, newer, and more complex structures of behavior" (Fuster, 1995 p. 172). Thus, based on the interpretation of empirical evidence from animal studies, a notion similar to that derived from computation models arises, that is, executive control is an emergent property that arises from lower-level memory functions which serve to integrate behavior.

Goldman-Rakic (1987) has also proposed a working-memory account of PFC function, according to which lateral PFC instantiates a form of working memory that she terms "representational memory." Based on evidence from both electrophysiological studies and studies of lesions of monkeys, as referenced above, Goldman-Rakic concluded that the ability to keep information in mind across short intervals depends critically on the lateral PFC. She has also suggested that this framework could be extended to explain a range of human cognitive impairments following focal frontal lesions, as well as nonfocal pathologies affecting lateral PFC (e.g. schizophrenia, Huntington's and Parkinson's diseases). Moreover, like Fuster, she has explicitly stated that "based on anatomical, physiological, and lesion evidence in both monkeys and humans, 'a central-executive' in the form of an all-purpose polymodal processor may not exist, and to the contrary, a strong case can be made for the view that the substrates of cognition reside in the parallelism of the brain's modularized information processing systems" (Goldman-Rakic, 1996).

In summary, working memory is not a unitary system and can be viewed as a set of properties that characterize how this cognitive system makes use of temporarily activated representations to guide behavior. These properties may be behaviorally and neurally dissociable. Many methods exist to examine the neural basis of working memory in humans. The lesion method, for example, has been helpful in establishing the necessity of PFC in working-memory function (e.g., Ptito et al., 1995; Venn et al., 1993). However, since injury to PFC in humans is rarely restricted in its location, using lesion studies in humans to test ideas about the necessity of a specific region of PFC for specific components of working memory is difficult. Functional neuroimaging, such as positron emission tomography (PET) or functional MRI (fMRI), provides another means of testing such ideas and will be reviewed in the next section.

It is important to realize however, that unlike lesion studies, imaging studies only support inferences about the *engagement* of a particular brain system by a cognitive process, but not about the system's *necessity* to the process (Sarter et al., 1996). That is, neuroimaging studies cannot, alone, tell us whether the function of a neural system

house an "executive controller," but instead serves processes that are simpler and more fundamental. For example, Cohen and Servan-Schreiber (1992, p. 46) have proposed a neural network model of the underlying cognitive and linguistic impairments in schizophrenia, which, they hypothesize, results from impaired function of the PFC. Their model proposes "a degradation in the ability to construct and maintain an internal representation of context, [by which] we mean information held in mind in such a form that it can be used to mediate an appropriate behavioral response." In their model, disordered performance is seen as a consequence of a change to a single low-level parameter. This simple change allows them to account for performance on a variety of tasks thought to be dependent on PFC function. In this way, it serves as a model case in understanding how behaviors that appear outwardly different may have their roots in similar fundamental processes.

Kimberg and Farah (1993) have also attempted to provide a parsimonious account of the computations underlying the diverse cognitive processes, considered to be "executive" in nature, that are impaired following damage to the PFC. Their model suggests that executive dysfunction can be interpreted in terms of damage to simple working memory components, and demonstrates how disparate impairments that follow PFC damage can be due to a common underlying mechanism. In this model, the term "working memory" refers to the functions and properties of the human cognitive system that allow representations to have levels of activation appropriate to the current task. It is a memory system in that the levels of activation reflect recent events, but it is not simply the capacity to remember. Items are not "in" working memory, but they do have levels of activation that can be higher or lower. Thus, performance on a task requiring working memory is determined by levels of activation of relevant representations, and the discriminability between activation levels of relevant and irrelevant representations. In selecting among competing responses, the model contains no "central executive" but simply considers the sum of the sources of activation contributing to each potential response. Specifically, their account of PFC dysfunction postulates that damage weakens the associative contribution to the activation of working-memory representations, achieved in the simulation by attenuating the strengths of these associations. Thus, the pattern of deficits following damage to this component of working memory would reflect an inability to coactivate mutually relevant, or associated, representations. A simple implementation of this model did indeed reproduce characteristic patterns of behavior on four disparate "executive" tasks, such as the Wisconsin Card Sorting Test and the Stroop Task.

Fuster (1997) has proposed that the PFC is critically important in tasks which require the temporal integration of information. Drawing on evidence from both animal and human research, Fuster has proposed three distinct PFC functions: active,

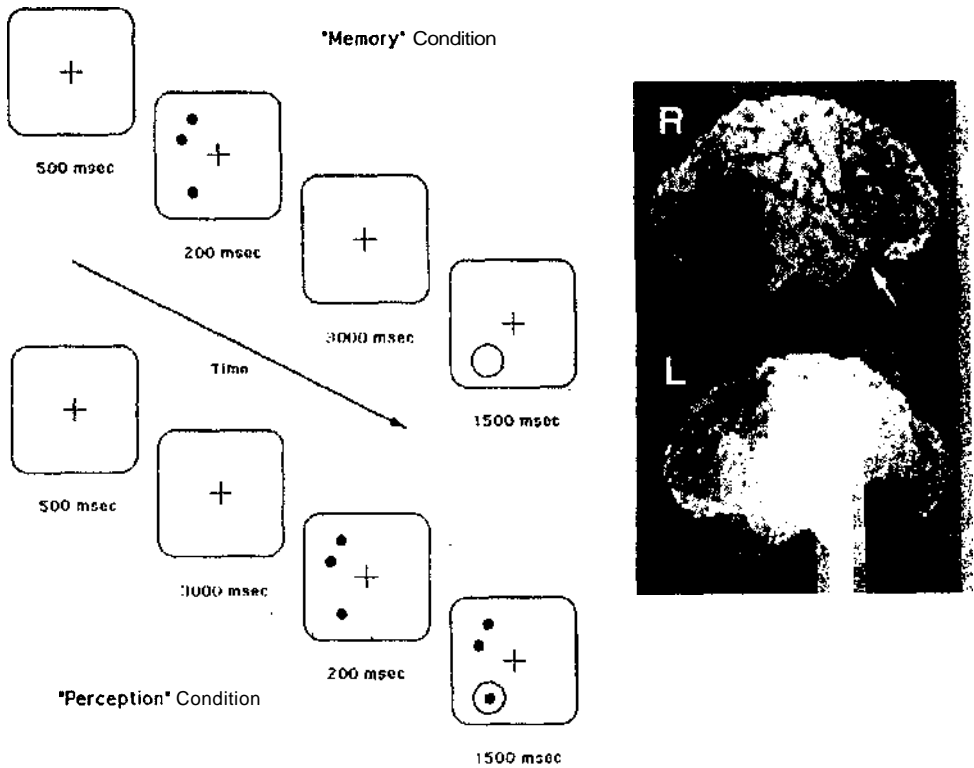
represents a neural substrate of that function, or is a nonessential process associated with that function. Moreover, this observation applies equally to all methods of physiological measurement, such as single-unit and multiunit electrophysiology, EEG, or MEG. Thus, data derived from neuroimaging studies provide one piece of converging evidence that is being accumulated to determine the neural basis of working memory.

## **FUNCTIONAL NEUROIMAGING OF WORKING MEMORY**

### **Active Maintenance Processes**

There is now a critical mass of studies (more than 30) using functional neuroimaging in humans which have demonstrated that the PFC is engaged during working-memory tasks (for review, see D'Esposito et al., 1998). Review of the details of each of these studies is beyond the scope of this chapter, but those studies which highlight the critical advancement of our understanding of the neural basis of working memory will be considered. For example, Jonides and colleagues (1993) performed the first imaging study, using PET, to show that PFC was activated during performance of a spatial working-memory task analogous to the one used in the monkey studies. In this study, subjects were presented with two types of trials (left side of figure 9.1 and color plate 18). In the memory condition, subjects were required to maintain the spatial location of three dots appearing on a visual display across a 3 sec delay. After this delay, a probe for location memory consisted of a single outline circle that either surrounded the location of one of the previous dots or did not. In the perception condition, the three dots were again presented on a visual display, but immediately following their presentation, a probe circle appeared simultaneously with the dots, and the subject merely made a perceptual judgment as to whether or not the probe encircled a dot.

The rationale of this study was that "subtraction" of images obtained during the perceptual condition from images obtained from the memory condition would reveal brain regions which require the storage of spatial information during the retention interval, and not sensorimotor components of the task. Comparison of the block of trials with a delay period to a block of trials without a delay period produced activation within PFC (right side of figure 9.1) as well as in occipital, parietal, and premotor cortices. The location of the PFC activation in this study was within right Brodmann's area 47 (inferior frontal gyrus), which is inferior to proposed homologous regions to the principal sulcus (area 46), the site of spatial working memory in monkeys (Funahashi et al., 1989, 1993). Nevertheless, this study was an important



**Figure 9.1**

(Left) The spatial working-memory task used in the Jonides et al. (1993) PET study. (Right) A surface rendering of the activated regions. While arrow points to significant activation in right ventral prefrontal cortex, Brodmann's area 47. (See color plate 18.)

demonstration that human PFC, like monkey PFC, may be critical for maintaining internal representations across time. Subsequently, numerous other imaging studies have utilized delayed-response tasks with requirements for storage of spatial (e.g., Anderson et al., 1994; Baker et al., 1996; Goldberg et al., 1996; O'Sullivan et al., 1995; Smith et al., 1995; Sweeney et al., 1996) as well as nonspatial (i.e., letters, words, faces, objects) information (e.g., Baker et al., 1996; Becker et al., 1994; Paulcsu et al., 1993; Salmon et al., 1996; Smith et al., 1995, 1996; Swam et al., 1995). Also, many studies have been performed using more complex types of working-memory tasks, such as n-back tasks (e.g., Cohen et al., 1994; McCarthy et al., 1994; Owen et al., 1996; Petrides, Alivisatos, Evans, et al., 1993; Petrides, Alivisatos, Meyer, et al., 1993; Salmon et al., 1996; Smith et al., 1996). Consistent across these studies is the demonstration of lat-

the inference that a region displayed delay-correlated increases in neural activity when in actuality it did not.

To overcome these potential problems, a new class of designs called “event-related” fMRI have been developed that do not rely on cognitive subtraction (for review, see D’Esposito, Zarahn, et al., 1998; Rosen et al., 1998). These designs allow one to detect changes in fMRI signal evoked by neural events associated with single behavioral trials as opposed to blocks of such trials. Event-related fMRI designs are somewhat analogous to designs employed in event-related potential (ERP) studies, in that the functional responses occurring during different temporal portions within the trial can be analyzed.

As mentioned, spatial delayed-response tasks typically have a stimulus presentation period, an ensuing delay (of a few seconds), and a choice period. Changes in single-unit neural activity have been observed during each of these task components in electrophysiological studies of nonhuman primates. For example, Fuster and colleagues (1982), using a visual delayed-response task, observed that responses of single PFC neurons to the initial stimulus presentation ended within a few hundred milliseconds of stimulus offset. They also observed changes in firing rate in single neurons in lateral PFC during the delay period that were sustained for several seconds. If these results also characterize human PFC function, it should be possible with an event-related fMRI design to resolve temporally functional changes correlated with the delay period from those correlated with the stimulus presentation/early delay period.

The logic of one implementation of an event-related fMRI design (Zarahn et al., 1997) is illustrated in figure 9.2. A single behavioral trial may be hypothesized to be associated with one brief neural event, or with several brief neural events that are sub-component processes engaged within a trial (i.e., encoding or retrieval in a delayed-response task). A neural event will cause a brief fMRI signal change, which is called the hemodynamic response. If we wish to detect and differentiate the fMRI signal evoked by a series of sequential neural events (such as the presentation of the stimulus and, seconds later, the execution of the response), one method would be to statistically model the evoked fMRI signal, using a pair of hemodynamic responses as covariates, each shifted to the time period where the event of interest is thought to occur. Importantly, a combination of hemodynamic responses could theoretically be used to model any neural event, even if the event is sustained, such as delay-period activity.

Analyzing in the manner described above, during the performance of a spatial delayed-response task we observed that several brain regions, including PFC, consistently displayed activity which correlated with the delay period across subjects (Zarahn et al., 1996, 1999). This finding suggests that these regions may be involved

eral PFC activation in a comparison between blocks of trials designed to have greater memory requirements than a matched control task.

A potential problem in interpretation of an imaging study such as that of Jonides et al. (1993), or the many others that were subsequently reported, is that each relies on the assumptions of the method of cognitive subtraction. Cognitive subtraction attempts to correlate brain activity with specific processes by pairing two tasks that are assumed to be matched perfectly for every sensory, motor, and cognitive process except the process of interest (Posner et al., 1988). For example, Jonides et al. assumed that the only difference between the two experimental conditions was the delay period and, therefore, the process of memory storage. Although the application of cognitive subtraction to imaging was a major innovation when originally introduced (Petersen et al., 1988), it has become clear that it is a potentially flawed methodology which may lead to erroneous interpretation of imaging data.

The assumptions that must be relied upon for cognitive subtraction methodology can be faulty for at least two reasons. First, it involves the assumption of *additivity* (or *pure insertion*), the idea that a cognitive process can be added to a preexisting set of cognitive processes without affecting them (Sternberg, 1969). For example, the delayed-response paradigm typically used to study working memory (see figure 9.1) is comprised of a memory-requiring delay period between a "perceptual" process (the presentation of the item[s] to be stored) and a "choice" process (a required decision based upon the item[s] stored). It is proposed that the neural substrates of the memory process are revealed by a subtraction of the integrated (i.e., averaged, summed, or totaled) functional hemodynamic signal during a no-delay condition (i.e., a block of trials without a delay period) from the signal during a delay condition (i.e., a block of trials with a delay period). In this example, failure to meet the assumptions of cognitive subtraction will occur if the insertion of a delay period between the "perceptual" and "choice" processes interacts with the other behavioral processes in the task. For example, the nonmemory processes may be different in delay trials compared to no-delay trials.

A second reason that cognitive subtraction methodology can be faulty is that in neuroimaging, an additional requirement must be met in order for cognitive subtractive methodology to yield nonartifactual results: the transform between the neural signal and the neuroimaging signal must be linear. In two studies using functional MRI (fMRI), some nonlinearities have been observed in this system (Boynton et al., 1996; Vazquez & Noll, 1998). In our example of a delayed-response paradigm, failure will occur if the sum of the transform of neural activity to hemodynamic signal for the "perceptual" and "choice" processes differs when a delay is inserted as compared to when it is not present. In this example, artifacts of cognitive subtraction might lead to

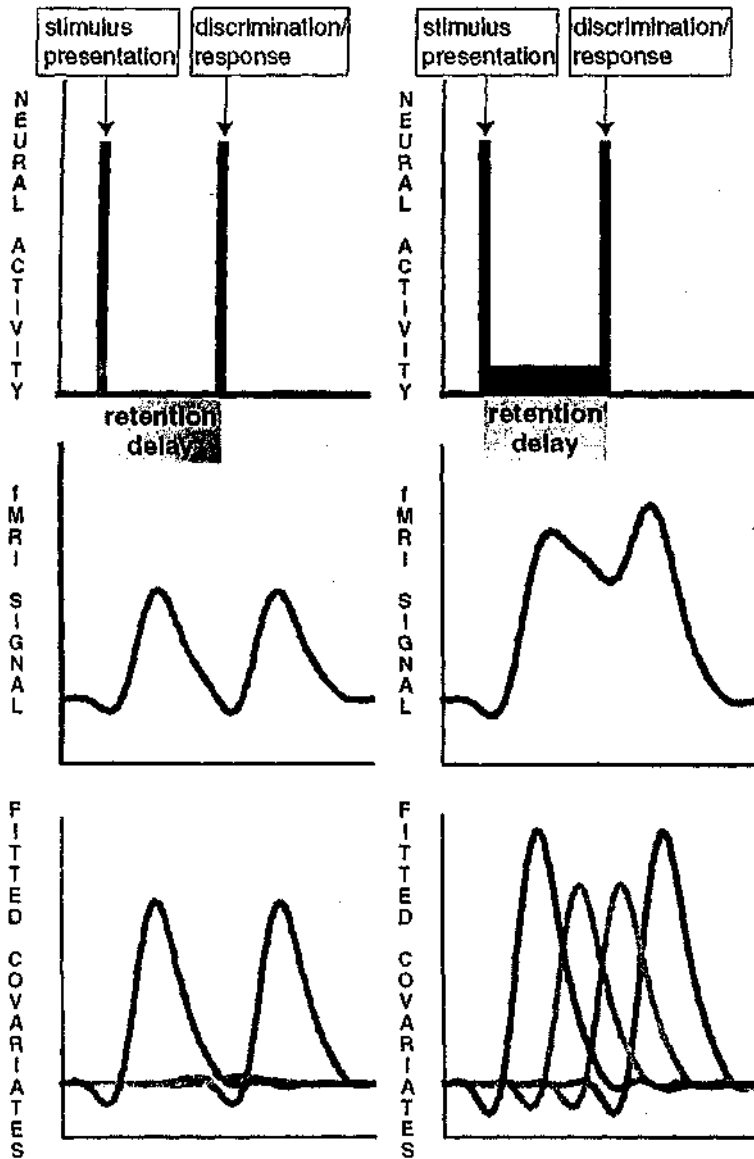
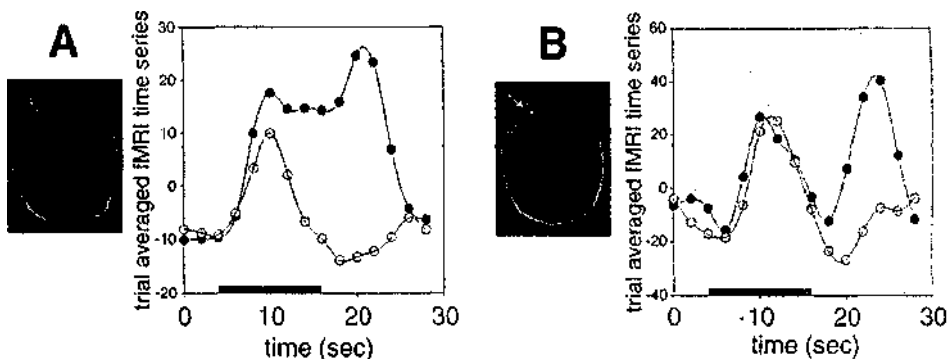


Figure 9.2

Two examples of how the fMRI data analysis model would respond to different neural responses during trials of a delayed-response paradigm. The left panel depicts a scenario in which there is only a brief period of neural activity (first row) associated with both the stimulus presentation and the discrimination/response periods of trials, with no increase above baseline during the bulk of the retention delay. Such neural activity change would lead to a particular profile of fMRI signal change (second row). The model covariates (hemodynamic responses shifted to sequential time points of the trial) scaled by their resulting least-squares coefficients are shown in the third row (gray lines, covariates modeling the retention delay; black lines, covariates modeling the stimulus presentation and the discrimination/response periods). The covariates modeling the retention delay would make only a small contribution to variance explanation. In contrast, the right panel depicts a situation in which there is some neural activity increase relative to baseline during the retention delay. In this case, the covariates modeling the retention delay would tend to explain a larger amount of variance in the fMRI signal than in the scenario in the left panel. In this way,



**Figure 9.3**

(A) An example of the time series of the fMRI signal averaged across trials for a PFC region that displayed delay-correlated activity (filled black circles represent activity for delay trials and open circles are trials without a delay). (B) An example of a time series where the integrated activity for the presentation of the cue and response during the delay trials (filled black circles) is greater than that observed during the combined presentation of the cue and response in the no-delay trials (open circles). The solid gray bar represents the duration of the delay period of the behavioral task (from Zarahn et al., 1999).

in temporary maintenance of spatial representations in humans. With this event-related fMRI design, we could be confident that activity observed was not due to differences in other components of the task (presentation of the cue or motor response) during the behavioral trials. Most important, these results do not rely on the assumptions of cognitive subtraction. An example of the time series of the fMRI signal averaged across trials for a PFC region that displays delay-correlated activity is shown in figure 9.3A.

In this same study, we also found direct evidence for the failure of cognitive subtraction (see figure 9.3B). We found a region in PFC that did not display sustained activity during the delay (in an event-related analysis) yet showed greater activity in the delay trials as compared to the trials without a delay. In any blocked neuroimaging study, such as those reviewed above, that compares delay versus no-delay trials with subtraction, such a region would be detected and likely be assumed to be a "memory" region. Thus, this result provides empirical grounds for adopting a healthy doubt regarding the inferences drawn from imaging studies that have relied on cognitive subtraction.

Other studies using event-related designs have also investigated the temporal dynamics of neural activity, but during working memory tasks using nonspatial information. For example, Courtney and colleagues (1997) utilized a delayed response task that required the maintenance of faces. Ventral occipitotemporal regions exhib-

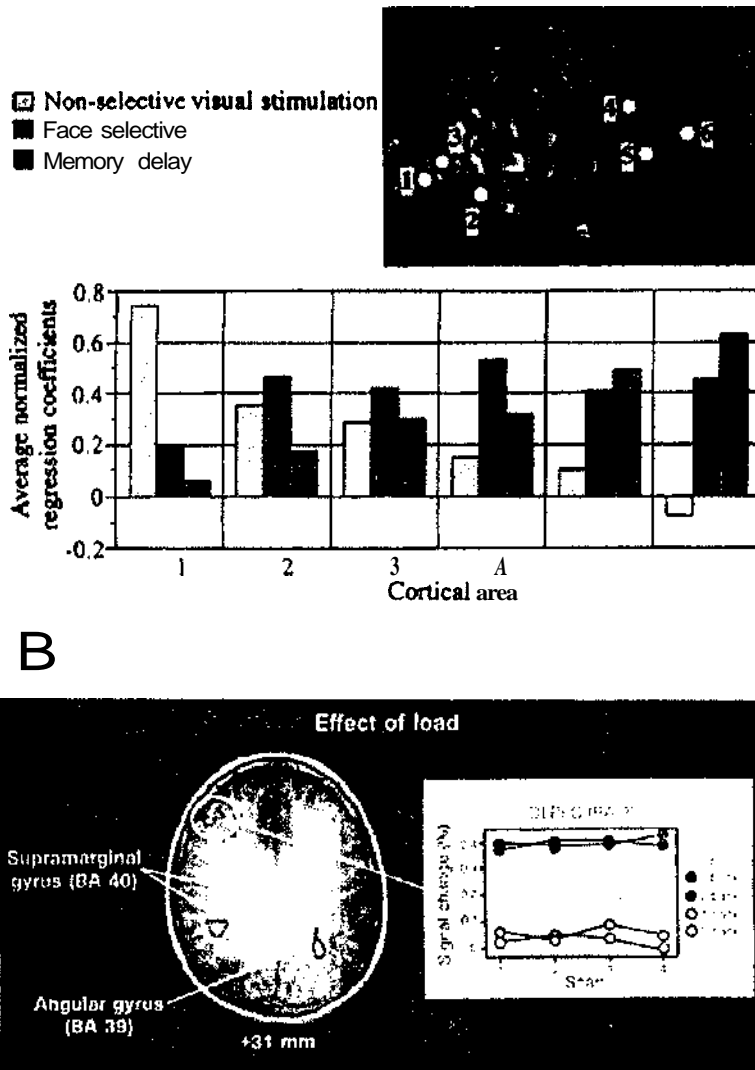


Figure 9.4

(A) Data from Courtney et al. (1997) study showing significant regions of activation in a face working-memory task. The graph illustrates the relative contribution of each component of the task (i.e., visual stimulation or memory delay period) to the signal in these regions. (B) Data from Cohen et al. (1997) study showing regions of activation that demonstrated a significant effect of load.

ceptual processing, whereas PFC demonstrated sustained activity over the memory delay, consistent with a role in active maintenance of face information. Figure 9.4A illustrates the gradual shift of the relative contribution of perceptual processing to memory processing from posterior to anterior cortical regions.

Cohen and colleagues (1997), in a different fashion than the Zarahn and Courtney studies, utilized a sequential letter n-back task, in which load was manipulated (from 0-back to 3-back) and the rate of stimulus presentation was slowed substantially (10 sec intertrial interval) in order to resolve temporal information. In the n-back task, letters are presented sequentially and the subject is required to respond to any letter that is identical to the one presented one, two, or three trials back. In the 0-back condition, subjects respond to a single prespecified target (such as X). The rationale of the experimental design was that sensory and motor processes would evoke transient increases in activation associated with stimulus presentation and response execution, and would not vary with memory load. Alternatively, areas involved in working memory would vary with memory load. A more refined prediction was made that load-sensitive areas would be dissociated into two types: those involved in active maintenance would exhibit sustained activation throughout the trial, and those involved in other working-memory processes (updating, temporal ordering) would exhibit transient activation but peak higher for increased memory loads. As expected, sensorimotor brain regions exhibited effects of time, but no effects of memory load. The PFC and posterior parietal cortex showed an effect of memory load. Dorsal and ventral regions of PFC (Brodmann's area 9/46 and 44) showed an effect of load but not an interaction with time that was consistent with a role of these regions in active maintenance processes (see figure 9.4B). Ventral PFC (area 44) also showed an effect of the interaction of time and memory load, suggesting a role in transient working-memory processes in addition to more sustained active maintenance processes.

Although PET imaging lacks the resolution to assess the temporal dynamics of neural activity in a manner similar to that in the fMRI studies described above, attempts at isolating maintenance processes with PET have been made. For example, several PET studies have been done with delayed-response tasks during which scanning was performed only during the retention interval (Baker et al., 1996; Fiez et al., 1996; Jonides et al., 1998). Obviously, the delay period must be much longer in these PET studies, in order to allow for adequate data to be obtained (around 30–40 sec), than is typically employed in a single trial (a few seconds) during an fMRI study. Nevertheless, various types of material have been used in these studies, including words and pseudo words (Fiez et al., 1996; Jonides et al., 1998), and objects and spatial information (Baker et al., 1996). These studies provide additional support for a role of PFC in active maintenance processes.

The studies described above have all presented stimuli using the visual modality. Two studies have examined activation patterns of working-memory tasks in other sensory modalities. For example, Klingberg et al. (1996) performed a PET study in which subjects were required to actively maintain auditory (pitch of tones), somatosensory (frequencies of a vibrating stimulus), or visual (luminance levels of a monochrome light) information across short delays (2-5 sec). An analysis of the effects of the task (working memory vs. detection) and modality (auditory vs. somatosensory vs. visual) did not reveal a task x modality interaction. The memory task, compared to a baseline detection task, activated a set of overlapping regions within lateral PFC across the different modality types, thus supporting a multimodal role for PFC. A similar conclusion was drawn by Schumacher et al. (1996), based on results of a PET study of subjects performing a verbal working-memory task (the 2-back task) with stimuli presented either visually or aurally. Again, comparison of the memory task to a control detection task revealed almost complete overlap in areas of activation within lateral PFC.

Studies of patients with lesions in PFC have shown impairments on delayed-response tasks (for review, see D'Esposito & Postle, 1999) that suggest the necessity of this cortical region in maintenance processes. However, these studies cannot rule out the possibility that other component processes necessary for successful performance of a delayed-response task, such as retrieval processes, rather than maintenance processes, are dependent on PFC integrity. However, several transcranial magnetic stimulation studies have shown that stimulation over lateral PFC during the delay period of a delayed-response task induces errors (Brandt et al., 1998; Muri et al., 1996; Pascual-Leone & Hallett, 1994). Taken together, imaging and lesion studies provide strong converging evidence for an association between active maintenance and PFC function.

### Executive Control Processes

The dual-task paradigm has been used as an effective behavioral tool for probing executive control processes. Sequential performance of two tasks, or parallel performance of two unrelated tasks that engage separate processing mechanisms, is thought to make minimal demands on executive control processes. However, two concurrently performed tasks that require similar processing structures will make greater demands on executive control and will lead to a decrement in performance (Baddeley, 1986). We have tested the idea that PFC is an important neural substrate of executive control by using fMRI to determine whether activation of PFC would be observed while normal human subjects performed a dual-task experiment (D'Esposito et al., 1995). During scanning, subjects concurrently performed a spatial

task (mental rotation of visual stimuli) and a verbal task (semantic judgments of auditory stimuli), cognitive challenges that were selected because they have been reported to activate predominantly posterior brain regions (i.e., not PFC regions). We reasoned that any activation in PFC regions would be due to the dual-task nature of the experiment and not to performance of either of the individual tasks per se. Our study did in fact demonstrate lateral PFC activation only during the dual-task condition, and not during either single-task condition.

Another study, utilizing PET, also explored the neural basis of executive control with a dual-task paradigm (Goldberg et al., 1998). Normal subjects were scanned while they performed two cognitive tasks, both individually and simultaneously. One task was the Wisconsin Card Sorting Test (WCST), a complex reasoning task, and the other was a rapidly paced auditory verbal shadowing task. A major difference between this dual-task study, and the one used by D'Esposito et al. (1995), is that one of the cognitive tasks, the WCST, activated PFC when performed individually. When the two tasks were performed simultaneously, there were significant decrements in performance compared with the individual task performance scores, as had been expected. There was less PFC activation under the dual-task condition, however, in contrast to when the WCST was performed separately. These results suggest that under circumstances in which the capacity of executive control is exceeded, cortical activity in PFC may be attenuated. Consideration of these results with those of D'Esposito et al. (1995) leads to a hypothesis that under dual-task conditions, PFC activity may increase to meet the processing demands, up to some level of asymptote, before attenuating. The Goldberg et al. study did not parametrically vary task demands during dual-task performance, however, and thus did not address this hypothesis.

Another PET study has also attempted to assess the neural correlates of deterioration of performance during concurrent performance of two tasks (Klingberg, 1998). In this study, subjects were scanned during performance of an auditory working-memory task, a visual working-memory task, during performance of both tasks, and during a control task. Unlike the D'Esposito et al. (1995) study but similar to the Goldberg et al. (1998) study, each of the single tasks, as compared to the control task, activated PFC. During the dual-task condition, there was no distinct region within PFC (or any other cortical regions) that was activated only in the dual task. Klingberg argued that these results are consistent with the hypothesis that concurrent tasks interfere with each other if they demand activation of the same part of cortex. This conclusion is supported by an earlier study by this group in which it was found that the larger the extent of overlap in the activation of two tasks when performed individually, the greater the decrement in behavioral performance when these two

tinnous performance task during which subjects were required to observe R sequence and respond to an x only when it was followed by an A. A factorial design used with two levels of memory (short versus long delay between cue PUB and two levels of difficulty) perceptually degraded versus nondegraded stimulus was ideal to test the issue of task difficulty because behavioral performance was equated between memory conditions (i.e., comparable performance spilloff delay PUB [one delay conditions] but was significantly worse in the conditions. Thus, task difficulty was increased independently of working-demands. The imaging results revealed a region with dorsolateral PFC that showed significantly greater activity in the long, SB compared to the short, delay condition, but did not show greater activity as a function of the difficulty manipulation. In contrast, anterior cingulate showed more activity on the more difficult task conditions, but did not show greater activation during the manipulation of the delay period. Thus, a double dissociation between regions responsive to working-memory demands versus task difficulty was demonstrated. Future studies, using designs, can address the issue of task difficulty more directly within by assessing the differential neural response to correct versus incorrect behavioral responses.

### dlPFC for

in monkeys during delayed-response tasks have also observed PFC neurons that are active during periods in addition to the delay period. For example, PFC neurons have been shown to respond during any combination of cue, delay, and response periods (Funahashi et al., 1989; Fuster et al., 1982). Although delay-specific neurons are most common, other types are frequently identified. Thus, the PFC appears to be involved in nonmnemonic processes that may include stimulus encoding, sustained attention to stimuli, preparation for a motor response, and the motor response itself. Most human functional imaging studies of working memory that use cognitive subtraction methodology have not emphasized the role of PFC in nonmnemonic cognitive processes, and sometimes suggest that is specific for working memory. Moreover, the interpretation of some functional imaging studies of other cognitive domains (language, visuosperception) have upon posthoc interpretations of observed PFC activation by their task as being due to the engagement of working-memory processes (Cohen et al., 1996; Cuenod et al., 1995). Such an interpretation tacitly assumes that PFC is specific for working memory. The demonstration that the same PFC region activated during tasks which engage working memory is also recruited during nonmnemonic processes would dispute this assumption. In light of the results of the monkey electrophysiological

tasks are performed concurrently outside the scanner (Klingberg & Roland, 1997). From the results of the 1998 study, Klingberg also argued that there was not a distinct PFC region which could be associated with any dual-task-specific cognitive process, such as task coordination or divided attention. This evidence does not, of course, rule out the possibility that the PFC supports cognitive operations unique to dual-task performance (e.g., task coordination and shifting attention) as well as working-memory operations, such as active maintenance and rehearsal. In fact, evidence that many different types of distinct operations may engage the PFC will be discussed below.

Studies of patients with frontal injury (McDowell, 1997; Baddeley, 1986) have demonstrated that despite performing comparably to healthy control subjects under single-task conditions, performance of the patients with PFC lesions was significantly inferior to control subject performance under dual-task conditions. Taken together, imaging and behavioral studies with patients provide converging evidence for an association between executive control and PFC function. These data cannot, however, support or refute the notion that a "system" or "controller module" lying within PFC mediates these executive processes. An important issue for future research will be to determine the neural basis of different executive control processes by using paradigms that can more precisely isolate such processes with less complex cognitive paradigms. Such studies will be reviewed in the "Current Issues" section, below.

### The Issue of Task Difficulty, Mental Effort, and PFC Function

The issue of task difficulty often arises when interpreting the results of imaging studies of working memory. For example, in the dual-task studies described above, it can be argued that the dual-task condition will always be more difficult than either task condition performed alone. In fact, most tasks that are designed to engage working memory are more difficult and lead to poorer behavioral performance than the corresponding control tasks. Thus, in imaging studies of working memory it seems necessary to eliminate the possibility that PFC activation was simply due to a non-specific increase in mental effort. We addressed this issue in our dual-task study (D'Esposito, et al., 1995) by having subjects perform the spatial task alone, but at different levels of difficulty. Even during the more difficult condition, when performance was worse than that for the spatial task performed during the dual-task condition, we did not observe any PFC activation. This finding suggested that the PFC activation observed during the dual-task experiment was related specifically to the executive control process required to organize and execute two tasks simultaneously.

Barch and colleagues (1997) have directly addressed this issue and have been able to dissociate working memory from task difficulty in PFC. This study utilized a con-

studies cited above, it seems that this pattern of PFC activation would be observed in humans as well. In fact, there are several lines of evidence to support the claim that the PFC is not specific for working memory.

Functional neuroimaging studies of working memory that utilize blocked designs are typically conducted by comparing the signal during a task proposed to engage working memory to a "control" task which does not engage this construct. Since these control tasks are designed not to require working memory, the control task compared to a resting baseline would be a logical candidate for testing the hypothesis that PFC regions which demonstrate activation associated with working memory also display activation in association with nonmnemonic processes. In one such study (D'Esposito, Ballard, et al., 1998), during fMRI scanning, subjects performed a three-condition experiment (working-memory task, non-working-memory task, rest). In the working-memory task, subjects observed serially presented stimuli and determined if each stimulus was the same as that presented two stimuli back (the 2-back task). The non-working-memory task in one experiment required subjects to identify a single predetermined stimulus; in another experiment, subjects were required to make a button press to every stimulus. In all subjects in both experiments, the working-memory task exhibited greater PFC cortical activity compared to the non-working-memory task. In these *same* PFC regions, significantly greater activation was also observed during both non-working-memory tasks compared to rest. This idea is consistent with the idea that human lateral PFC supports processes in addition to working memory. Thus, in this study, the reverse inference of the form "if prefrontal cortex is active, working memory is engaged" was not supported.

McCarthy and colleagues (1994, 1996) have studied similar detection tasks, along with working-memory tasks. Lateral PFC was activated in a spatial working-memory task, as well as during two control tasks (detection of a dot in an object or detection of a red object) relative to a resting baseline. The strength of activation during these detection tasks was noted to be approximately half (and sometimes approaching) the magnitude observed in the working-memory task.

Finally, if we revisit the spatial working-memory experiment performed with an event-related design described above (Zarahn et al., 1999), it can be seen clearly (figure 9.3 left panel, showing fMRI signal) that there is significant activity above baseline in a region of the PFC that displayed activity above baseline even during trials without a delay period. Data from Courtney et al. (1997) demonstrate this point as well. In two of the PFC activated regions (areas labeled 4 and 5) there is some contribution by the nonselective visual stimulation task component (figure 9.4A) in addition to the contribution made by the memory task component. Thus, each of the studies described does not support models that posit neural substrates subserving

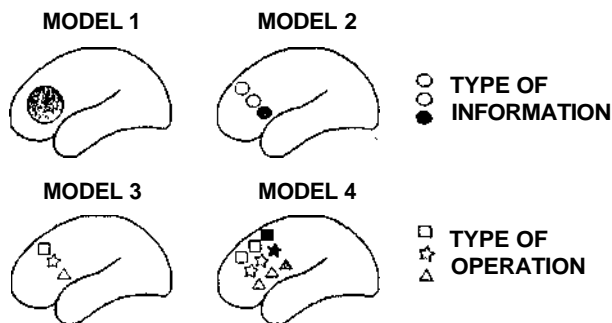
memory-specific processing, but rather is supportive of models which posit that memory is a property of neural networks which also mediate perceptuomotor processes (Fuster, 1995).

## ISSUES

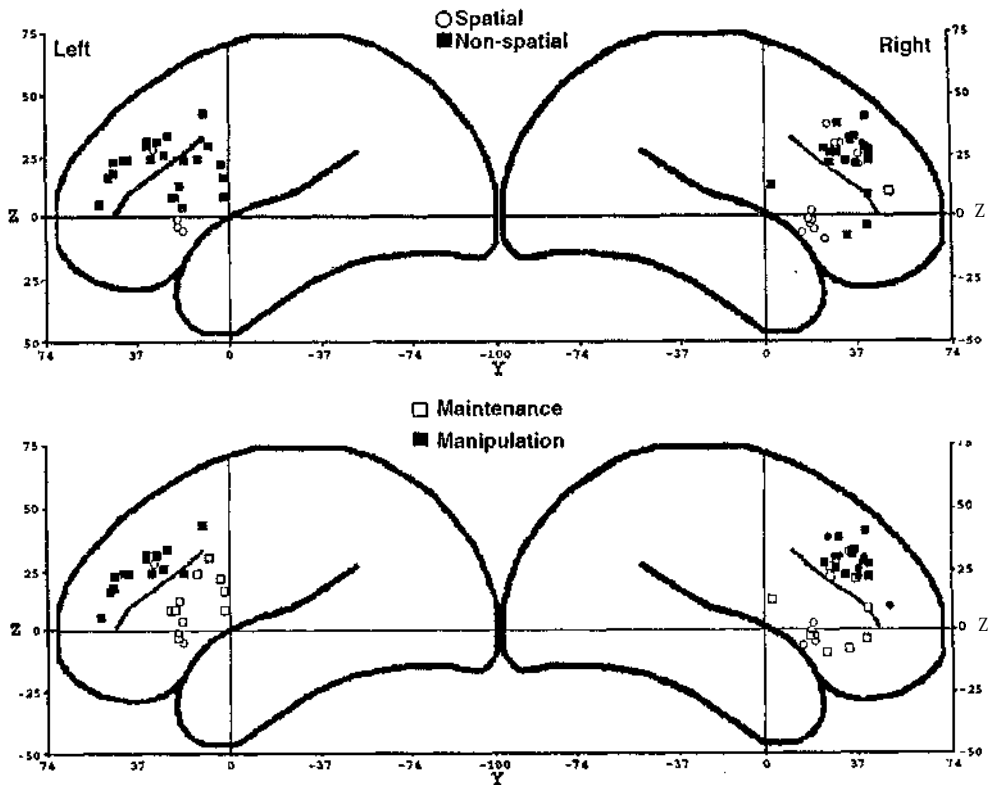
### Does Human Prefrontal Cortex Have Functional Subdivisions?

While the evidence presented above suggests that the PFC appears to be critical for the processing of temporarily stored information, it is unclear whether there are functional subdivisions within the PFC which are specialized for particular aspects of working memory. The frontal lobes comprise a large proportion of the cerebral cortex, and PFC represents the largest portion of the frontal lobes. Each of the studies highlighted above has demonstrated activation in lateral PFC. Within lateral PFC activation has been seen in dorsal portions (Brodmann's areas 9 and 46) as well as ventral portions (Brodmann's areas 44, 45, 47). Medial aspects of the PFC as well as the orbitofrontal cortex have not been consistently activated in working-memory tasks.

There are at least four ways to conceptualize how the operations subserved by the PFC might be organized neuroanatomically (see figure 9.5). First, the PFC as a whole may be involved in *all* working-memory processes (e.g., simple maintenance operations such as rehearsal, and more complex operations such as retrieval, reordering, performing spatial transformations, etc.) that can be directed at distributed representations in posterior brain regions (model 1). Second, there may be different PFC regions for the temporary maintenance of different types of representations (e.g.



**Figure 9.5**  
Models of prefrontal cortical organization.



**Figure 9.6**

Meta-analysis of published functional neuroimaging studies of working memory. Each square represents a significant activation reported in a standardized atlas (Talairach & Tournoux, 1988). Top panel shows activations from either spatial or nonspatial studies; bottom panel reports activations from the same studies reclassified as requiring maintenance or manipulation processes.

this review, we found no evidence for a clear dorsal/ventral dissociation of activation based on the type of information being held in working memory. As illustrated in figure 9.6, there are numerous spatial working-memory studies that have demonstrated activation within ventral PFC and, likewise, nonspatial working-memory studies that have demonstrated activation within dorsal PFC.

In nearly every study reviewed in the above analysis, either spatial or nonspatial working memory was examined within each subject, but not both types of working memory. In an empirical study, we have tested subjects during two different working-memory tasks with different sets of stimuli during fMRI. In the memory condition, subjects attended to serially presented stimuli and determined if a letter or location of

spatial, object), regardless of operation (model 2). Third, there may be different PFC regions required for different operations (e.g., maintenance, manipulation), regardless of the type of representation (model 3). Finally, there may be different PFC regions required for either the type of operation or the type of representation (model 4).

***Organization by Content?*** Goldman-Rakic and colleagues have proposed that the different regions of the PFC are critical for the temporary maintenance of different types of information. Specifically, they have provided evidence that monkey PFC is segregated into one region that retains information about an object's color and shape (ventrolateral PFC) and a second region that retains the object's location in space (dorsolateral PFC) (Wilson et al., 1993). This view is derived from evidence from recording of neurons within a more ventral region, the inferior prefrontal convexity, while monkeys performed spatial-delayed or pattern-delayed response tasks, and from finding that a greater number of neurons in this region responded selectively during the delay period to pattern rather than to location information. Also, lesions comprising the dorsal PFC have been shown to impair spatial working memory (Funahashi et al., 1993; Gross, 1963), whereas other studies reveal impaired nonspatial working memory following more ventral lesions (Mishkin & Manning, 1978; Passingham, 1975).

These findings have led to the hypothesis that lateral PFC is organized in a dorsal/ventral fashion subserving the temporary storage of "what" and "where" information. This hypothesis has the appeal of parsimony, because a similar organization has been identified in the visual system (Ungerleider & Haxby, 1994). Also, anatomical studies in monkeys have demonstrated that parietal cortex (spatial vision regions) projects predominantly to a dorsal region of lateral PFC (Cavada & Goldman-Rakic, 1989; Petrides & Pandya, 1984), whereas temporal cortex (object vision regions) projects more ventrally within lateral PFC (Barbas, 1988).

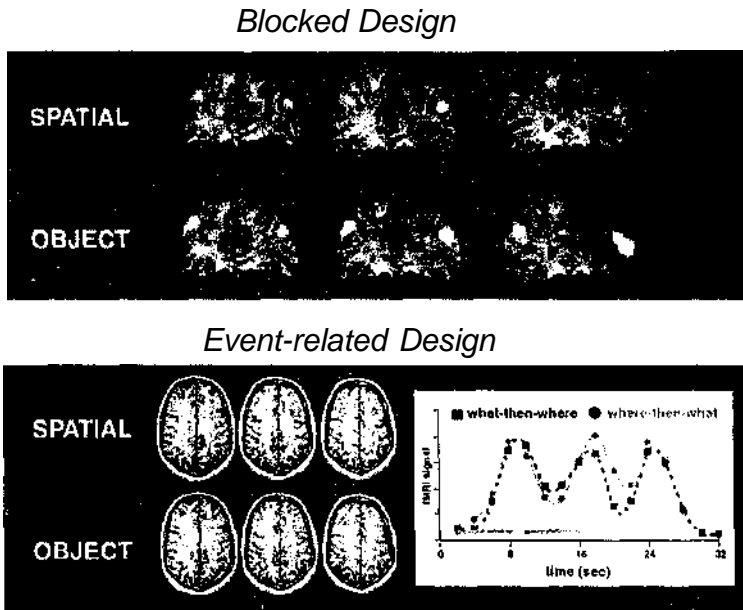
Functional neuroimaging studies have been able to address this question in humans by determining the pattern of PFC activity during spatial and nonspatial working-memory tasks. Because many such studies have been conducted, we critically examined this literature for evidence for or against the "what" versus "where" model of PFC organization (D'Esposito, Aguirre, et al., 1998). In our review, we plotted the locations of activations from all reported functional neuroimaging studies of spatial and nonspatial working memory on a standardized brain. Based on the animal literature, it is proposed that the human homologue of the principal sulcal region of lateral PFC, the middle frontal gyrus (Brodmann's area 9/46) would subserve spatial working memory, whereas nonspatial working memory would be subserved by a more ventral region, the inferior frontal gyrus (Brodmann's areas 47, 44, 45). In

a square was the same as that presented two stimuli back. In the control condition, subjects were asked to identify a single predetermined letter or location. Group and individual subject analyses revealed activation in right middle frontal gyrus that did not differ between spatial and nonspatial working memory conditions. Again, these data do not support a dorsal/ventral organization of PFC based on the type of information held in working memory.

Other investigators using virtually identical n-back tasks have found similar results (Owen et al., 1998; Postle et al., 2000). In the Owen study, the spatial 2-back task used required memory for one of three locations that were highlighted by filling in a white box. To equate for difficulty, the nonspatial memory task was performed as a 1-back task and used abstract patterns for stimuli. In the Postle et al. study, the nonspatial 2-back task used Attneave shapes as stimuli that each look distinctive (Attneave & Arnoult, 1956) and were difficult to verbalize (Vanderplas & Garvin, 1959). The spatial 2-back task used identical black circles or Attneave shapes as stimuli in nine different spatial locations on the screen. The results of this study are presented in figure 9.7 (top panel; see also color plate 19). Using a task similar to the 2-back task but with less frequent targets, McCarthy et al. (1996) found that both the spatial (a single square stimulus in 20 different locations) and nonspatial (irregular shapes) conditions activated dorsal PFC, with a ventral extension of the activation in the left hemisphere in the nonspatial task. Since these tasks were not directly compared statistically, it is unclear if an actual difference in the spatial extent of activation between conditions exists.

Four other studies compared spatial and nonspatial working memory tasks; none of these studies found a dorsal/ventral distinction of activation within PFC (Baker et al., 1996; Belger et al., 1998; Smith et al., 1995, 1996). However, in each of these studies there was a suggestion of a hemispheric dissociation between spatial and nonspatial working memory (i.e., greater right PFC activation in spatial paradigms and greater left PFC activation in nonspatial paradigms). These hemispheric differences were found during performance of delayed-response tasks comparing spatial stimuli to nonspatial stimuli—letters (Smith et al., 1996) and objects (Baker et al., 1996; Belger et al., 1998; Smith et al., 1995)—as well as during spatial and nonspatial n-back tasks (Smith et al., 1996). It is important to note that the lateralization of PFC during the n-back task found by Smith and Jonides has not been found in other laboratories (D'Esposito, Aguirre, et al., 1998; Owen et al., 1998; Postle et al., 2000).

Data from one laboratory stand out as an exception to the group of studies presented above in which a dorsal/ventral organization based on the type of information being held in working memory was found (Courtney et al., 1996, 1998). In an initial blocked-design PET study of delayed-response tasks using faces and locations of faces



**Figure 9.7**

(*Top*) Data from a blocked design fMRI experiment by Postle et al. (2000) showing nearly identical bilateral PFC activation associated with spatial and object working memory in an individual subject. (*Bottom*) Data from an event-related fMRI experiment from Postle, D'Esposito et al. (1999) study showing activation maps displaying suprathreshold activity in spatial and object delay periods in dorsolateral PFC in a single subject, illustrating the marked degree of overlap in PFC activity in the two conditions. The graph to the right shows the trial-averaged time series extracted from dorsolateral PFC voxels with object delay-period activity. Again, note the similarity of fMRI signal intensity changes in spatial and object delay periods. (See color plate 19.)

as stimuli (Courtney et al., 1996), it was found that a direct comparison of the two memory conditions revealed that the spatial working-memory task resulted in greater activation within left superior frontal sulcus (Brodmann's areas 8/6), and the face working-memory task resulted in greater activation of right ventral PFC (areas 9/45/46). A confusing finding of this study was that the spatial working-memory task did not produce PFC activation relative to a control task. In a follow-up study using an event-related fMRI design (Courtney et al., 1998), a double dissociation was found between face and spatial working memory. It was observed that within superior frontal sulcus in both hemispheres, there was significantly more sustained activity during spatial than during face working-memory delays. By contrast, left inferior frontal cortex showed significantly more sustained activity during face than during spatial working-memory delays. A particular strength of this study is that a subset of subjects performed a visually guided saccade task, and it was demonstrated that the

systems, one dorsal and the other ventral, within lateral PFC (Petrides, 1994). It is proposed that ventral PFC (Brodmann's areas 45/47) is the site where information is initially received from posterior association areas and where active comparisons of information held in working memory are made. In contrast, dorsal PFC (areas 9/46) is recruited only when active manipulation/monitoring within working memory is required.

To test this alternative hypothesis of PFC organization, we again analyzed the data derived from previously reported working-memory functional neuroimaging studies. We divided all working-memory tasks according to the conditions under which information is being temporarily maintained, rather than according to the type of information being maintained. For example, delayed-response tasks require a subject to maintain information across a *nondistracted* delay period. To achieve accurate performance on this type of task, no additional processing of the stored information is necessary except for its maintenance across a delay period that has no distracting stimuli. Thus, a delayed-response task, engaging "maintenance" processes, should recruit ventral PFC, according to Petrides's model. Alternatively, all other working-memory tasks reported in the literature require either (1) reshuffling of the information being temporarily maintained and/or (2) processing of intervening stimuli during the maintenance of stored information. For example, in self-ordered tasks, subjects must update in working memory each stimulus that they choose, in order to pick a new stimulus correctly (Petrides et al., 1993). The continuous nature of the n-back tasks requires constant reshuffling of the contents held in working memory because different stimuli are simultaneously being stored, inhibited, and dropped from memory (Cohen et al., 1994). Finally, other tasks, such as one in which subjects must compare the first and last notes of an eight-note melody (Zattore et al., 1994), simply require the maintenance of information across a distracted delay. Thus, these types of tasks, engaging "manipulation" processes as well as "maintenance" processes, should additionally recruit dorsal PFC, according to Petrides's model. We thus made an operational distinction between two general types of working-memory tasks used in neuroimaging studies: *maintenance* and *manipulation* tasks.

When all locations of lateral PFC activation reported in the literature are plotted onto a standardized brain according to this classification of tasks as either *maintenance* or *manipulation*, a dorsal/ventral dissociation becomes evident (see bottom panel of figure 9.6), supporting the Petrides model. This model derived initial support from an empirical PET study performed by Owen and colleagues (1996), in which they found dorsal PFC activation during three spatial working memory tasks thought to require greater manipulation/monitoring of remembered information than two other memory tasks, which activated only ventral PFC. Several other functional neuroimaging studies also appear to support Petrides's hypothesis. In a PET study, a

region which was active during the spatial working-memory delay period was anterior and superior (by approximately 8.5 mm) to the frontal eye fields active during the saccade task. Interestingly, this is the only study of working memory for different types of information in which the nonspatial stimuli used was faces, which may be an important determinant contributing to the dissociation that was found.

We have performed a study using event-related fMRI that examined the neural correlates of the maintenance of spatial versus nonspatial information. Our study differed from Courtney et al. (1998) in that our nonspatial stimuli were objects (Attneave shapes) and we employed a task with a "what-then-where" design, with an object and a spatial delay period incorporated in each trial (see figure 9.7, bottom panel). This task was adapted from a monkey electrophysiology study by Miller and colleagues which provided evidence that there was extensive overlap in "what" and "where" neurons within lateral PFC without a clear segregation (Rao et al., 1997). Similar to this monkey study, even when we modeled only the delay period (similar to Zarahn et al., 1999, discussed above), identical regions of PFC were activated when subjects remembered spatial or object information. Reliable spatial/object differences in the delay period were observed, in contrast, in posterior cortical regions (Postle & D'Esposito, 1999). In fact, these data are consistent with earlier single-unit recording studies of dorsal and ventral regions within lateral PFC during delayed-response tasks that found a mixed population of neurons in both regions which are not clearly segregated by the type of information (i.e., spatial versus nonspatial) being stored (Fuster et al., 1982; Quintana et al., 1988; Rao et al., 1997; Rosenkilde et al., 1981). Other evidence that does not support a dorsal/ventral what/where organization of PFC is that cooling (Bauer & Fuster, 1976; Fuster & Bauer, 1974; Quintana & Fuster, 1993) and lesions of a dorsal region of lateral PFC cause impairments on nonspatial working-memory tasks (Mishkin et al., 1969; Petrides, 1995), and ventral lesions in lateral PFC cause spatial impairments (Butters et al., 1973; Iversen & Mishkin, 1970; Mishkin et al., 1969). Finally, a paper has found that ventral PFC lesions in monkeys did not cause delay-dependent defects on a visual pattern association task and a color-matching task (Rushworth et al., 1997). A critical review of these issues can be found in a paper by Rushworth and Owen (1998). Clearly, further work will be necessary to reconcile the different findings from animal and human studies to determine if the active maintenance of different types of information is subserved by distinct regions of the lateral PFC.

*Organization by Process?* Another possible axis along which human lateral PFC may be organized is according to the type of operations performed upon information being stored in working memory rather than the type of information being temporarily stored. Petrides has proposed a two-stage model in which there are two processing

running memory task, thought to require updating of the contents in working memory, was compared to a letter span task that did not require such a process (Salmon et al., 1996). When compared directly, greater activation in the running memory task was found in right dorsal PFC (area 9), and to a lesser extent in left dorsal PFC. The letter span task activated only ventral PFC. In another PET study that compared a simple delayed matching task (match a color or pattern) versus a more complex delayed matching task (alternate between matching colors and patterns), only the latter task activated the right dorsal PFC but both tasks activated ventral PFC (Klingberg et al., 1997).

We have tested this process-specific organization of PFC using event-related fMRI (D'Esposito et al., 1999). In our study, subjects were presented two types of trials in random order, in which they were required to either (1) *maintain* a sequence of letters across a delay period or (2) *manipulate* (alphabetize) this sequence during the delay in order to respond correctly to a probe. Similar to the spatial working-memory study described above, we identified brain activity related to the three periods of our task: stimulus presentation, delay, and response. In each subject, activity during the delay period was found in both dorsal and ventral PFC in both types of trials. However, dorsal PFC activity was greater in trials during which information held in working memory was manipulated (figure 9.8). These findings suggest that dorsal PFC may exhibit greater recruitment during conditions where additional processing of information held in working memory is required, and support a process-specific organization of PFC.

A challenge for the further development of the hypothesis that human lateral PFC is organized by processing requirements is determining the psychological constructs

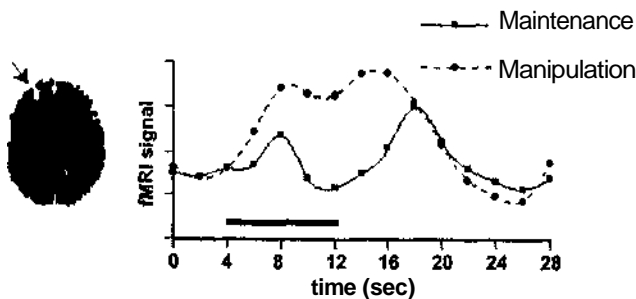


Figure 9.8

Trial averaged time series from voxels within PFC that were significant in the manipulation-maintenance direct contrast. Note the two peaks in the *maintenance* condition corresponding to the stimulus presentation and the probe periods of the trial, whereas in the *manipulation* condition the voxel maintained a high level of activity throughout the delay period. The solid black bar represents the duration of the delay period of the behavioral task.

which differ between tasks that activate dorsal versus ventral PFC. Certainly, there are many possible component processes that may be necessary in tasks which activate dorsal PFC. The component processes that we have labeled "manipulation" will need to be determined. Also, if lateral PFC is functionally subdivided, it will also be important to determine if it is organized hierarchically, with information passing from ventral to dorsal PFC. If a hierarchical organization does exist, it is expected that those tasks which we classified as *manipulation* tasks would activate ventral as well as dorsal PFC.

Two studies have shown that dorsal PFC is recruited during performance of tasks with no overt requirements to manipulate information held in working memory but under increased load conditions (Manoach et al., 1997; Rypma, Prabhakaran, et al., 1999). For example, Rypma et al. observed activation in dorsal 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 sec. When subjects were required to maintain three letters in working memory, relative to one letter, activation in frontal regions was limited to left ventral PFC (BA 44). However, when subjects were required to maintain six letters, relative to one letter, additional activation of dorsal PFC was observed, similar to studies in which successful performance required the manipulation of information held in working memory (e.g., D'Esposito et al., 1999; Owen et al., 1996). Two possibilities exist to explain these findings. First, dorsal and ventral PFC may be involved in active maintenance processes, but only dorsal PFC is involved during the manipulation of information. This idea is consistent with the findings by D'Esposito et al.: that the maintenance and manipulation of information during an alphabetization task was directly examined. Alternatively, under conditions during which subjects must actively maintain loads of information that approach or exceed their capacity, dorsal PFC is additionally recruited for the mediation of strategic processes necessary for the maintenance of a high load of information.

Delayed-response tasks like the ones employed by Rypma et al. (1999) and Manoach et al. (1997) involve several component processes for the encoding, retention, and retrieval of information. Since these were blocked designs, it is possible that the recruitment of dorsal PFC observed under conditions of high memory load may have been due to differential recruitment (compared to the low memory load condition) of processes engaged during any or all of these task periods. Thus, we subsequently performed a study using event-related fMRI that allowed us to examine brain activity which correlated with individual components of the task (*encoding, delay, and response*) in dorsal and ventral PFC while subjects maintained either two or six *items* in working memory across an unfilled delay period (Rypma & D'Esposito, 1999).

parietal cortex in storage processes in contrast to maintenance/rehearsal processes thought to be subserved by the PFC. In a study of verbal working memory by Awh et al. (1996), an n-back task was designed to separate the brain regions underlying storage and rehearsal. As previously described, the memory condition requires subjects to determine whether or not a letter presented is identical to one presented two letters previously in a sequence. In a "search" control condition, subjects are required to identify a predetermined stimulus (the letter M). In a "rehearsal" control condition, subjects engage in silent rehearsal by repeating each letter silently to themselves until the next letter appears. In this blocked, cognitive subtraction paradigm, it was reasoned that subtraction of the search control condition from the memory condition would reveal activation in brain regions involved in both phonological storage and rehearsal, whereas subtraction of the rehearsal control condition from the memory condition would reveal regions involved only in phonological storage. Finally, by inference, in comparison to the first subtraction, regions involved in rehearsal could be identified as well. These series of subtractions suggested that left ventral PFC (Brodmann's area 44, Broca's area) and premotor areas are involved in subvocal rehearsal (since they did not appear in the [memory-rehearsal] comparison), and posterior parietal cortex participates in phonological storage (since it remained in the [memory-rehearsal] comparison and was also present in the [memory-search] comparison). A similar conclusion was drawn from an earlier PET study of verbal working memory in which subjects performed a delayed response task with letters as stimuli (Paulcsu et al., 1993).

A study by Fiez et al. (1996) appeared to contradict the above findings because they failed to find parietal activation when scanning with PET during the retention interval of a task that required the encoding of five words or nonwords and retrieval after scanning of the 40 sec retention interval. These results considered the possibility that parietal activation was actually due to encoding or retrieval processes rather than to storage processes. Jonides and colleagues (1998) subsequently addressed this question directly. These investigators provided behavioral evidence that Fiez et al. (1996) may not have found evidence for parietal activation because their imaging data were heavily influenced by storage of semantic, rather than phonological, representations. Based on empirical PET data using a delayed-response task with only nonwords as stimuli (thus decreasing the likelihood of storing this information in a semantic code), they demonstrated posterior parietal activation during the storage condition. These investigators proposed that left posterior parietal cortex, which is active in most verbal working-memory tasks, is specific to phonological coding and storage. An important finding consistent with this proposal is that patients with verbal working-memory deficits which are abnormal when storing phonological codes are normal

Effects of increased memory load, lateralized to right hemisphere, were observed only in dorsal PFC in the *encoding* period. This result suggests that dorsal PFC plays a greater role in initial encoding of information for subsequent retrieval and not necessarily during the maintenance of such information. 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) similar to those required in the more complex tasks discussed above.

In summary, the studies reviewed suggest that PFC has functional subdivisions which may be organized by the type of information held in working memory as well as by the type of operation performed on this information. Regarding organization by content, one research group found a dorsal PFC (spatial) vs. ventral PFC (faces) difference in the pattern of activation, whereas other groups have found a hemispheric effect (left PFC, objects; right PFC, spatial). Working-memory tasks that engage "manipulation" processes have consistently found greater activation in dorsal PFC, relative to ventral PFC, regardless of the type of information being maintained and manipulated. Although more work is clearly necessary, these findings represent a significant step toward understanding the functional organization of PFC.

### The Role of **Non-PFC** Regions in Working Memory

This chapter has extensively reviewed the role of the PFC in working memory, and possible ways in which the PFC may be functionally subdivided to support working memory. However, working memory is clearly a complex cognitive system that relies on posterior, as well as anterior, cortical regions. It is likely that subcortical structures such as the basal ganglia and thalamus also play critical roles in this network. Methods have been developed to allow for the study of the interactions among several brain regions within a functional network subserving a cognitive system such as working memory (McIntosh et al., 1996). Such studies, reviewed in another chapter in this volume, will provide a means for extending the knowledge obtained from the activation studies reviewed in this chapter. Finally, in a review of a large number of working-memory studies mentioned above (D'Esposito, Aguirre, et al., 1998), two other cortical regions are consistently activated during tasks that require working memory: lateral and medial premotor areas (Brodmann's area 6 and area 8) and posterior parietal cortex (Brodmann's area 40/7).

*Posterior Parietal Cortex* Like PFC, posterior parietal cortex is an area of multi-modal association cortex (Mesulam, 1985), that is, it receives from, and projects to, other primary and unimodal association areas all modalities of information (somatosensory, auditory, visual). Smith and Jonides (1998) have emphasized the role of

when storing semantic and visual codes (Saffran & Marian, 1975; Warrington et al., 1971).

We have recently provided additional evidence that posterior cerebral regions are critical for memory storage by employing an event-related fMRI design (Postle et al., 1999). We used an item-recognition experiment that required memory for the identity and position in the display of either of two letters or five letters (to identify load-sensitive regions), or memory for the identity and position in the alphabet of any of five letters (to identify manipulation-sensitive regions). In each subject, voxels in the left perisylvian cortex showed load, but not manipulation, sensitivity; and regions of PFC in all subjects showed the opposite pattern. This double dissociation provides additional evidence for a role of posterior perisylvian regions in storage processes and also highlights the differential role of this region from PFC. More work is clearly necessary to investigate the functional heterogeneity of posterior parietal cortex, which has evolved as a region as important for working memory function as the PFC.

*Premotor Areas* Lateral premotor cortex is consistently activated in working-memory tasks. The location of activation is typically within the precentral sulcus (see D'Esposito, Aguirre, et al., 1998, for review) and likely lies within the frontal eye fields (FEF). Penfield and Boldrey (1937), using electrical stimulation, defined the FEF as the cortex lying around the precentral sulcus at the level of the middle frontal gyrus. Humans with lesions in this region have impaired visually guided (Rivaud et al., 1994) and memory-guided saccades (Pierrot-Deseilligny et al., 1991). Moreover, several PET studies have observed activation in the region around precentral sulcus during voluntary saccades (Anderson et al., 1994; Fox et al., 1985; Sweeney et al., 1996). In the Courtney et al. (1998) study, reviewed earlier, evidence was provided that there are actually two distinct regions within this area surrounding the precentral sulcus: one region that correlates with the retention delay of the memory task and one region that correlates with saccades. Although there may be a distinct region anterior to the FEF involved in temporary maintenance of spatial information, it is possible that the spatial information coded in the FEF is involved in some aspect of memory as well. Some FEF neurons display sustained activity during the delay of memory-guided saccade tasks in nonhuman primates (Bruce & Goldberg, 1985). Also, lesions within the FEF in monkeys (Deng et al., 1986) and humans (Pierrot-Deseilligny et al., 1991) have been shown to impair memory-guided saccades. Finally, increased FEF activity in PET studies of memory-guided saccades occurs even during a comparison with a visually guided saccade control task (Sweeney et al., 1996).

The role of medial premotor areas in working memory has been extensively reviewed by Petit and colleagues (1998). In this study, two regions of interest were

examined: dorsomedial PFC that comprises supplementary motor area (SMA) and anterior cingulate cortex (ACC). In an earlier review of the function of these regions, Picard and Strick (1996) proposed that the SMA can be subdivided into the SMA proper, which subserves basic spatial and temporal organization of movement, and a more anterior region, pre-SMA, which subserves additional cognitive demands, such as selection of and preparation for a motor response. Likewise, ACC can be subdivided into a caudal cingulate area that subserves simple motor functions, and a more anterior cingulate area that subserves more complex motor functions. By first identifying the SMA proper and the cingulate motor area by simple motor movements, Petit et al. were able to demonstrate that the location of sustained activity over working memory delays during both spatial and face working-memory tasks was within two distinct areas, pre-SMA and the anterior portion of the ACC. Since these areas were identified by a contrast between sustained activity during working-memory delays as compared with sustained activity during control delays in which subjects were waiting for a cue to make a simple manual motor response, it suggests that the activation of these regions does not reflect simple motor preparation, but rather a state of preparedness for selecting a motor response based on the information held on-line.

### **Summary**

Elucidation of the cognitive and neural architectures underlying human working memory was an important focus of cognitive neuroscience for much of the 1990s. One conclusion that arises from this research is that working memory, a faculty which enables temporary storage and manipulation of information in the service of behavioral goals, can be viewed as neither a unitary nor a dedicated system. Data from numerous imaging studies have been reviewed and have demonstrated that the PFC is critical for several component processes of working memory, such as executive control and active maintenance. Moreover, it appears that the PFC has functional subdivisions which are organized by both the type of information being temporarily maintained and the type of operations performed on this information. In addition to the PFC, other brain regions, such as premotor areas and posterior parietal association cortex, comprise a functional network that may subserves other component processes of working memory function, such as selecting motor responses based on information held-on-line, and on storage processes. Numerous questions remain regarding the neural basis of this complex cognitive system, but imaging studies such as those reviewed in this chapter should continue to provide converging evidence for such questions.

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