Activity in Human Frontal Cortex Associated with Spatial Working Memory and Saccadic Behavior

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Abstract

■ We examined, with event-related fMRI, two hypotheses about the organization of human working memory function in frontal cortex: (1) that a region immediately anterior to the frontal eye fields (FEF) (superior frontal cortex, SFC) is specialized for spatial working memory (Courtney, et al., 1998); and (2) that dorsolateral prefrontal cortex (PFC) plays a privileged role in the manipulation of spatial stimuli held in working memory (Owen, et al., 1996; Petrides 1994). Our delayed-response task featured 2-D arrays of irregularly arranged squares that were highlighted serially in a random sequence. The Forward Memory condition required maintenance of the spatio-temporal sequence, the Manipulate Memory condition required reordering this sequence into a new spatially defined order, the Guided Saccade condition required saccades to highlighted squares in the array, but no memory, and the Free Saccade condition required self-paced, horizontal saccades. The comparison of fMRI signal intensity associated with 2-D saccade generation (Guided Saccades) versus fMRI signal intensity associated with the delay period of the working memorials condition revealed no evidence for greater working memory-related activity than saccade-related activity in SFC in any individual subject, nor at the level of the group, and greater 2-D saccade than delay-period activity in three of five subjects. These results fail to support the hypothesis that spatial working memory-related activity is represented preferentially in a region of SFC anterior to the FEF (Courtney, et al., 1998). The comparison of maintenance versus manipulation of spatio-temporal information in working memory revealed significantly greater activity associated with the latter in dorsolateral PFC, but not in ventrolateral PFC or in SFC. These results suggest that the delay-related function of SFC is limited to the maintenance of spatial information, and that this region does not support the nonmnemonic executive control functions supported by dorsolateral PFC. These results also indicate that the preferential recruitment of dorsolateral PFC for the manipulation of information held in working memory applies to tasks employing spatial stimuli, as well as to tasks employing verbal stimuli (D'Esposito, et al., 1999); Petrides et al., 1993; Postle et al., 1999). ■

INTRODUCTION

It is generally held that prefrontal cortex (PFC) is a critical substrate of many high level cognitive functions in primates, such as working memory, planning, and decision making. Working memory, which enables the short-term storage and manipulation of information that is not accessible for sensory analysis, arises from the coordinated recruitment of several mnemonic and executive control processes. Other frontal areas, too, demonstrate working memory-related activity, including premotor area 6 (e.g., Postle, Stern, Rosen, & Corkin, 2000; Awh et al., 1996; Baker, Frith, Frackowiak, & Dolan, 1996; Jonides et al., 1993) and superior frontal areas 6 and 8 (e.g., Postle & D'Esposito, 1999; Mellet et al., 1996; Smith, Jonides, & Koeppe, 1996; Sweeney et al., 1996). Particularly influential on systems and cognitive neuroscience models of the functional anatomical organization of working memory in primate PFC have been two classes of models: labeled-line models and processing models. Labeled-line models posit that the executive control functions of different regions of PFC mirror the primary function of the sensory processing areas that project to these discrete PFC regions in a segregated manner (Goldman-Rakic, 1987). Thus, dorsolateral PFC, an important

target of efferents from the dorsal visual processing stream, is viewed to be preferentially involved in visuospatial working memory, and ventrolateral PFC, an important target of efferents from the ventral visual processing stream, to be preferentially recruited for working memory for visual features of stimuli (Wilson, O'Scalaidhe, & Goldman-Rakic, 1993). Processing models, in contrast, emphasize PFC functional organization by cognitive process, rather than by stimulus type (Petrides, 1994). Thus, ventrolateral PFC is viewed as important for on-line storage of information held in working memory, with dorsolateral PFC preferentially recruited to facilitate the manipulation of this information (Owen, Evans, & Petrides, 1996; Owen et al., 1999; but see Postle & D'Esposito, 2000). In response to empirical challenges to labeled-line models of PFC (Postle, Stern, et al., 2000; D'Esposito, Aguirre, Zarahn, & Ballard, 1998; D'Esposito, Postle, Ballard, & Lease, 1999; Owen et al., 1998; Rao, Rainer, & Miller, 1997; Rushworth, Nixon, Eacott, & Passingham, 1997; Petrides, 1995), Courtney and colleagues have emphasized the importance of spatial working memory-related activity of a region superior and posterior to area 9/46 of the PFC: the cortex adjacent to the superior frontal sulcus (SFS) and immediately anterior to the frontal eye fields (FEF). Courtney, Ungerleider, Keil, and Haxby (1996), Courtney, Ungerleider, Keil and Haxby (1996), Courtney, Petit, Maisog, Ungerleider, and Haxby (1998) proposal of a specialized spatial working memory area within superior frontal cortex (SFC) is an important claim, because it represents the only published evidence consistent with the original labeled-line model of a dorsal/ventral segregation of spatial versus object working memory function in human frontal cortex.

An affirmative test of any hypothesis asserting functional specialization of an area must demonstrate that activity of this area is significantly greater for the function in question than for any other plausible functions. Thus, an affirmative test of the labeled-line hypothesis that a region of SFC is "specialized for spatial working memory" (Courtney et al., 1998, p. 1347) must demonstrate that voxels in this area evince spatial working memory-related activity that is significantly greater than saccade-related activity. Courtney et al. (1998) appreciated this logical necessity and claimed to have demonstrated that this area's activity was not motoric, and that this area was distinct from FEF.[1] We reasoned, however, that their results might have depended on the nature of saccadic behavior that was contrasted with spatial working memory behavior. In the monkey, more FEF neurons are active during target-acquiring, rewarded saccades than during spontaneous, unrewarded saccadic behavior (Schall, 1991; Bizzi & Schiller, 1970). In humans, positron emission tomography (PET) signal in FEF and/or SFC increases with increased rate of saccades (Paus, Marrett, Worsley, & Evans, 1995), with oculomotor delayed response and antisaccades as contrasted with reflexive saccades (Sweeney et al., 1996), and with execution of a prelearned sequence of saccades as contrasted with self-paced saccades (Petit et al., 1996). Courtney et al. (1998) contrasted activity elicited by visually guided horizontal saccades—i.e., saccades executed in one predictable dimension (1-D)—with activity elicited by memory for the location of face stimuli whose position varied unpredictably along two dimensions (2-D), horizontal and vertical. An alternative interpretation of their results, therefore, might posit that the more complex spatial processing requirements of the working memory task (i.e., unpredictable 2-D vs. repetitive 1-D spatial processing), rather than the presence of working memory demands, resulted in the greater anterior extent of working memory-related than saccade-related activity. A more demanding (i.e., unpredictable 2-D) saccade task, however, might be expected to produce a spatial extent of activation no different from a spatial working memory task. We tested this alternative hypothesis with an event-related fMRI experiment that featured spatial working memory, 2-D saccades to unpredictable locations, and repetitive 1-D saccades.

By varying the processing demands of our working memory task, we also assessed the relative sensitivity of different frontal regions, including SFC, to simple maintenance of spatial temporal information versus maintenance plus manipulation of this information. We have demonstrated previously that dorsolateral PFC (i.e., middle frontal gyrus, areas 9/46), but not ventrolateral PFC (i.e., inferior frontal gyrus, areas 44/45/47), is engaged to a greater extent by the requirement to manipulate memoranda in a verbal working memory task (D'Esposito et al., 1999; Postle, Berger, & D'Esposito, 1999). By varying the manipulation demands of working memory trials in the present study, we could assess whether ventrolateral PFC versus dorsolateral PFC versus SFC spatial working memory-related activity can also be dissociated by process.

RESULTS

Behavioral Performance

Group mean performance differed by working memory trial type neither in terms of accuracy (Forward Memory = 83.3% [*SE* = 3.7], Manipulate Memory = 77.5% [*SE* = 8.6], $t(4) = .95$) nor in terms of reaction time (Forward Memory = 1,655.2 msec [*SE* = 105.4], Manipulate Memory = 1,645.6 msec [*SE* = 126.1], $t(4) = .1$).

Spatio-Temporal Working Memory and Saccades in Superior Frontal Cortex

Single-Subject Analyses

The results from the single-subject analyses are presented in Figure 1 and Table 1. The contrasts con-

tributing to these analyses each featured greater than 1300 effective degrees of freedom—sufficient power to find significant effects within each subject and to permit assessment of replication of (as well as variation in) effects across individual subjects. Bilateral SFC activity associated with the execution of Guided Saccades and with the delay period of working memory trials was observed in all five subjects. Bilateral FEF activity associated with the performance of free saccades was observed in all subjects but one (subject S; Figure 1, top three panels for each subject). Results from the two-tailed contrast of $[(\{0.5 \times \text{Delay}_{\text{Forward Memory}}\} + \{0.5 \times \text{Delay}_{\text{Manipulate Memory}}\}) - (1 \times \text{Stimulus Presentation}_{\text{Guided Saccade}})]$, which effected a test of the hypothesis that a region of SFC is specialized for spatial working memory function, indicated that, whereas none of the five subjects evinced spatial working memory activity in SFC that was greater than Guided Saccade activity, three of the five subjects evinced Guided Saccade activity that was greater than working memory activity (Figure 1, fourth panel for each subject; Table 1, first and second columns). The contrast of $[(\{0.5 \times \text{Delay}_{\text{Forward Memory}}\} + \{0.5 \times \text{Delay}_{\text{Manipulate Memory}}\}) - (1 \times \text{Stimulus Presentation}_{\text{Free Saccade}})]$, intended to approximate the analysis presented in Experiment 2 of Courtney et al. (1998) revealed evidence for greater working memory-related activity than Free Saccade-related activity in four of five subjects: Statistical maps in two subjects (W and K) revealed only greater working memory-related activity than Free Saccade-related activity; in one subject (H), only Free Saccade-related activity greater than working memory-related activity; and in the remaining two subjects (S and T), voxels showing each of these characteristics (Figure 1, fifth panel for each subject). In subjects S and T, the voxel(s) demonstrating greater working memory than Free Saccade activity were more anteriorly located than

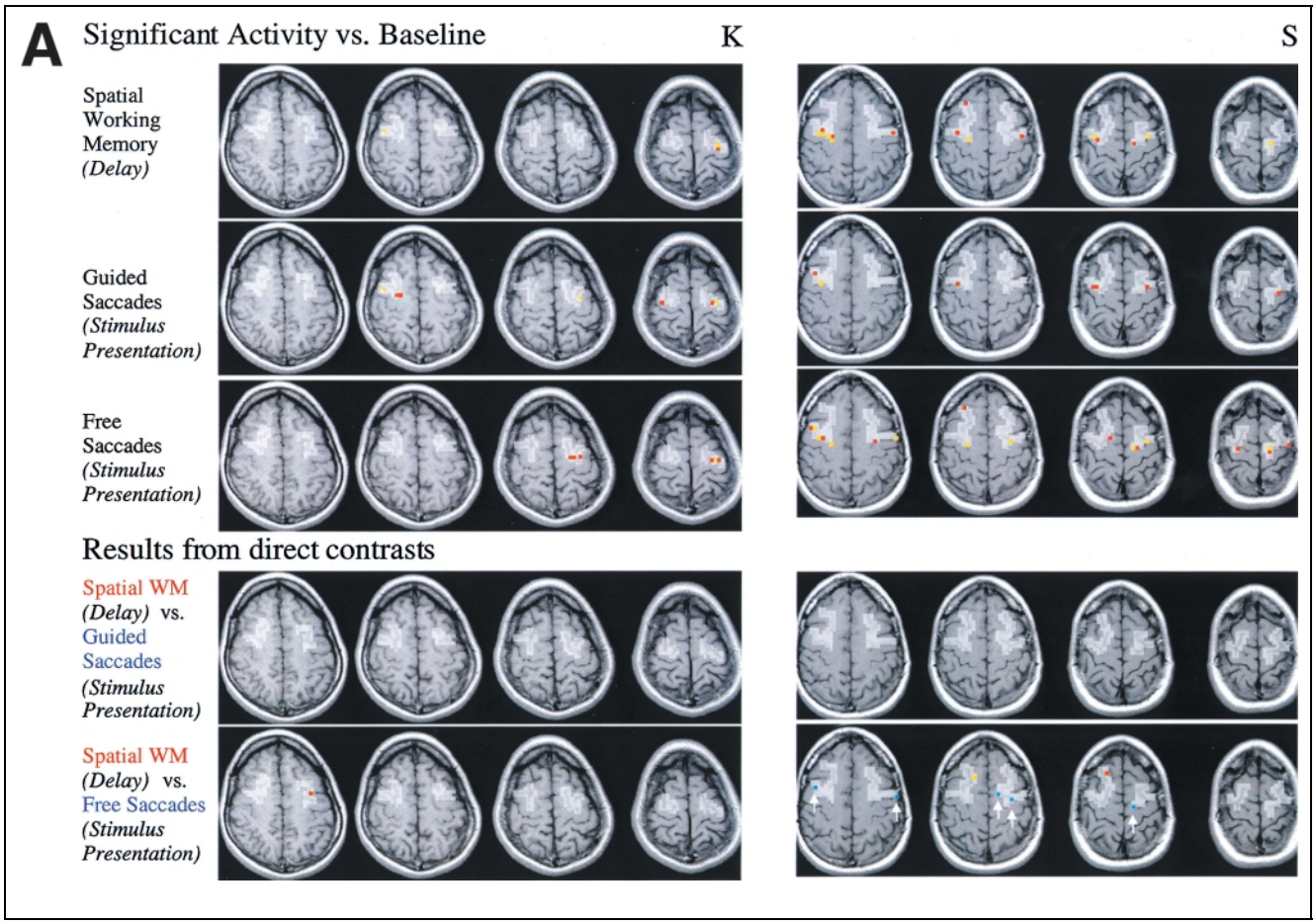

Figure 1. Results of individual-subject analyses from SFC ROI (translucent white overlay; see Methods for description of this ROI). These analyses were restricted to the SFC ROI because they related to the principal hypothesis tested in this study, which was restricted to this brain region. The top three panels of each subject's data present the results of one-tailed contrasts (task vs. baseline). The bottom two panels, presenting the results of two-tailed hypothesis testing contrasts, illustrate voxels evincing significantly greater working memory-related activity than saccade-related activity (presented in red and yellow), and voxels evincing significantly greater saccade-related activity than working memory-related activity (presented in blue). Arrows identify individual blue voxels for clarity of presentation.

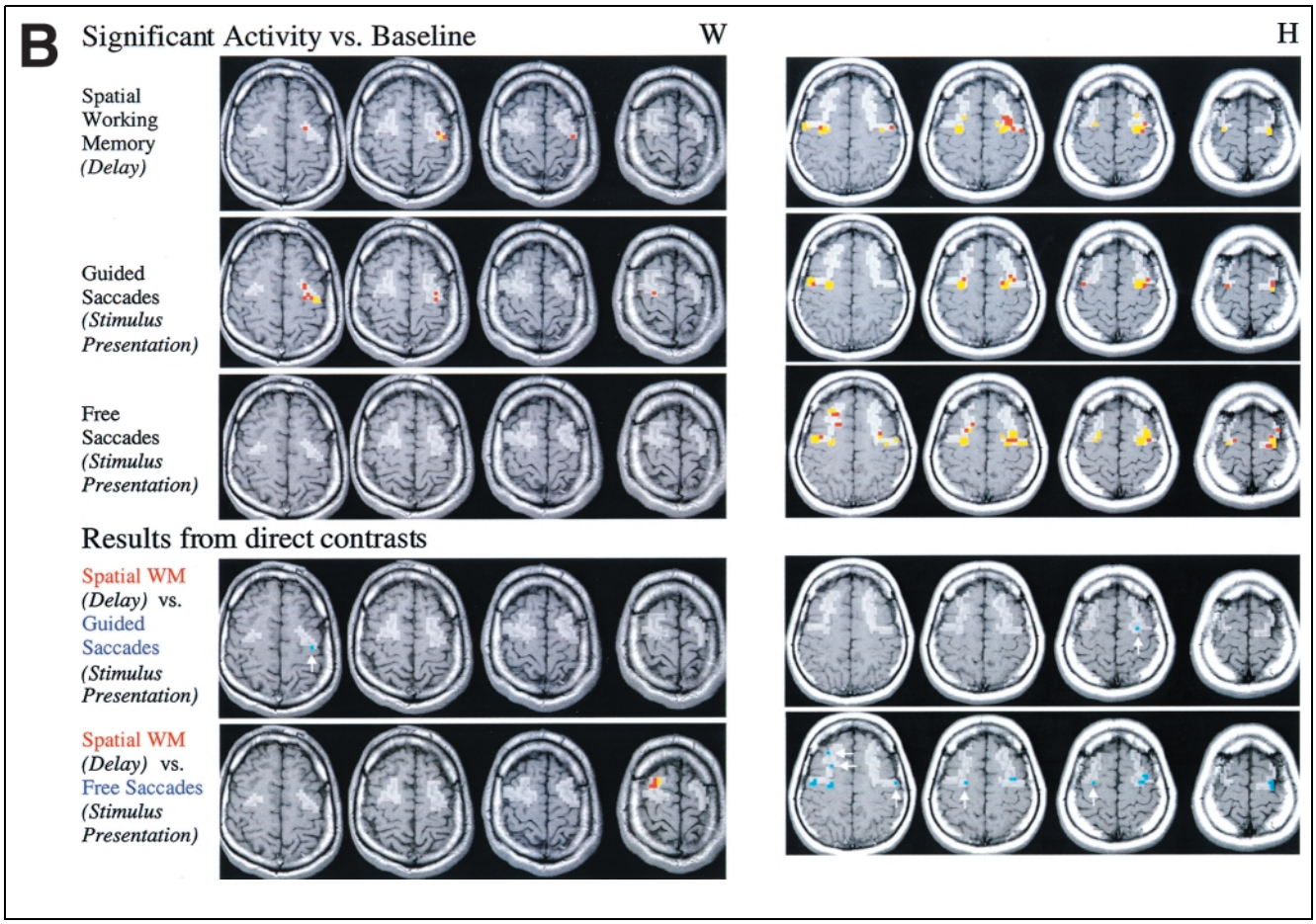

Figure 1. (continued)

those demonstrating the converse property. Finally, the contrast of [(1 × Stimulus Presentation$_{\text{Guided Saccade}}$) − (1 × Stimulus Presentation$_{\text{Free Saccade}}$)], comparing levels of activity associated with the two types of saccades in our experiment, revealed no differences in three subjects (W, K, and T), greater Guided Saccade-related activity than Free Saccade-related activity in one subject (S), and greater Free Saccade-related activity than Guided Saccade-related activity in two subjects (S and H; Table 1).

Group Analyses

Perhaps there exists a specialized spatial working memory area whose activity is reliable across subjects, but too subtle to detect at the level of the individual subject. To test this possibility, group analyses were performed by first modifying the anatomical SFC ROI for each subject so that it only incorporated cortex anterior to the anteriormost extent of guided saccade-evoked activity (Figure 2a). This corresponds to the region hypothesized to be specialized for spatial working memory (Courtney et al., 1998). (As detailed in the Methods section, our group analysis method did not entail averaging data across subjects, or creating a group average image.) Second, for each subject, we pooled the fMRI signal from every voxel contained in this modified SFC ROI. Third, we applied the two-tailed contrast [({0.5 × Delay$_{\text{Forward Memory}}$} + {0.5 × Delay$_{\text{Manipulate Memory}}$}) − (1 × Stimulus Presentation$_{\text{Guided Saccade}}$)] to the pooled time series data from each subject. Finally, we calculated the group mean of the results of these contrasts (0.004; Figure 2b), and determined that this effect was not reliably different from 0 ($t(4) < .01$; *ns*).

Maintenance versus Manipulation of Spatio-Temporal Working Memory

The two-tailed contrast of (Delay$_{\text{Manipulate Memory}}$ − Delay$_{\text{Forward Memory}}$) yielded no suprathreshold voxels in any subject in any of the 3 ROIs that we tested (ventrolateral PFC, dorsolateral PFC, and SFC). Because an analogous contrast applied to (individual subject) verbal working memory data sets has produced robust suprathreshold results in dorsolateral PFC in two previous experiments (D'Esposito et al., 1999; Postle et al., 1999), and because the present study featured only half

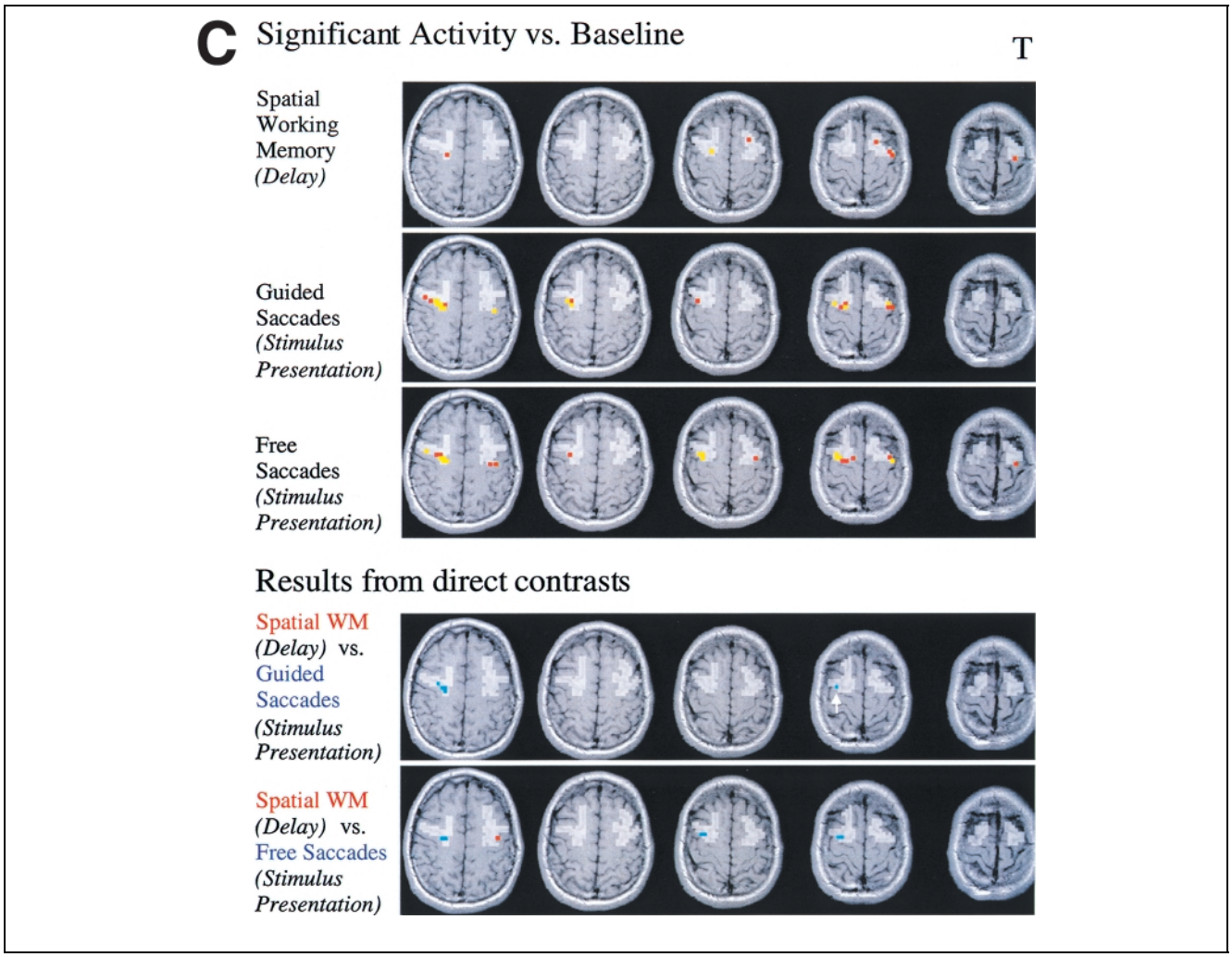

Figure 1. (continued)

the working memory trials of these previous studies, we reasoned that the individual-subject analyses in the present experiment may have lacked the sensitivity to detect a reliable but subtle effect. We therefore applied a group analysis to our data, employing the steps detailed in the Methods section. Our results, illustrated in Figure 3, indicated that there was no significant effect of $\text{Delay}_{\text{Manipulate Memory}}$ versus $\text{Delay}_{\text{Forward Memory}}$ in either direction, in ventrolateral PFC or in SFC. The group analysis did indicate, however, a significant effect of $\text{Delay}_{\text{Manipulate Memory}}$ greater than $\text{Delay}_{\text{Forward Memory}}$ in dorsolateral PFC ($t(4) = 4.8; p < .01$).

Table 1. Summary of Contrasts (Numbers Correspond to the Number of Suprathreshold Voxels for Each Contrast)

Subject	*Working Memory Delay > Guided Saccades*	*Guided Saccades > Working Memory Delay*	*Working Memory Delay > Free Saccades*	*Free Saccades > Working Memory Delay*	*Guided Saccades > Free Saccades*	*Free Saccades > Guided Saccades*
W	0	1	6	0	0	0
H	0	1	0	22	0	3
K	0	0	1	0	0	0
S	0	0	2	5	5	1
T	0	5	1	6	0	0

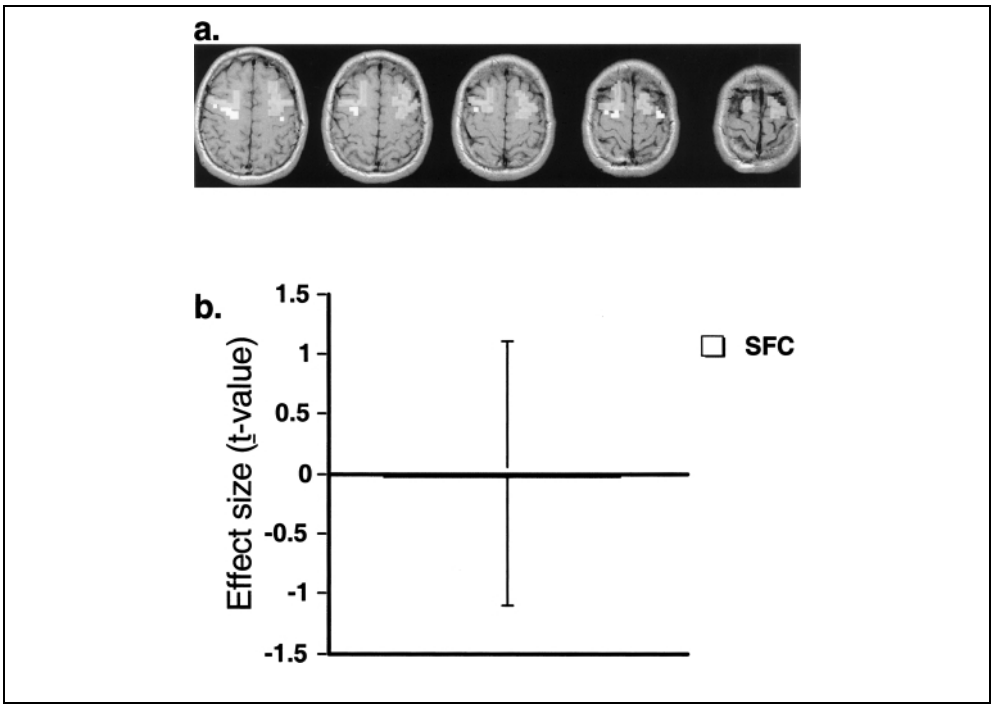

Figure 2. (a) Illustration from an individual representative subject (T) of the voxels evincing guided saccade-evoked activity (white squares, same as those illustrated in the second panel illustrating data from subject T in Figure 1), and the modified anatomical SFC ROI (translucent white overlay) from which fMRI data were pooled to perform the group test of the labeled-line hypothesis. Note that the modified ROI only incorporates cortex anterior to guided saccade-sensitive voxels. (b) Illustration of the results of the group analysis of the labeled-line hypothesis. The bar representing the group mean result of the (two-tailed) contrast $[(\{0.5 \times \text{Delay}_{\text{Forward Memory}}\} + \{0.5 \times \text{Delay}_{\text{Manipulate Memory}}\}) - (1 \times \text{Stimulus Presentation}_{\text{Guided Saccade}})]$ in the modified SFC ROI is too small to be visible in this figure; error bars represent the 95 percent confidence interval.

DISCUSSION

Spatio-Temporal Working Memory and Saccades in SFC

The comparison of fMRI signal intensity associated with 2-D saccade generation (Guided Saccades) versus fMRI signal intensity associated with the delay period of a spatio-temporal working memory task revealed no evidence for greater working memory than saccade-related activity in SFC in any individual subject, nor at the level of the group, and greater 2-D saccade than delay-period activity in three of five subjects. These results fail to support the hypothesis that spatial working memory-related activity is represented preferentially in a region of SFC anterior to the FEF (Courtney et al., 1998). When we compared fMRI signal intensity from behavioral conditions that we believe matched more closely the analyses described by Courtney et al. (1998), however, four of five subjects demonstrated a pattern of activity that replicated the results of that earlier study. We conclude, therefore, that the results suggesting that a region in SFC is specialized for spatial working memory presented in Courtney et al., 1998 are attributable to a methodological confound, rather than to fundamental physiological factors. Although it is incontestable that this region of SFC is activated in association with spatial working memory behavior (e.g., Postle & D'Esposito, 1999; Mellet et al., 1996; Smith et al., 1996; Sweeney et al., 1996), we have demonstrated in the present study that it is also activated, to an equivalent extent, in association with appropriately matched eye movement behavior that has no mnemonic component. Thus, we can reject the claim that there exists in SFC an area that is ''specialized for working memory'' (Courtney et al., 1998). The results of the present study are consistent with those of previous studies that have produced robust, and comparable, activation of SFC by both spatial and nonspatial working memory tasks (Postle & D'Esposito, 1999; Postle, Stern, et al., 2000; D'Esposito et al., 1998). The broader implication of these results is that they fail to find evidence consistent with labeled-line models of a dorsal/ventral organization of visual working memory function in human frontal cortex.

There were several methodological differences between our methods and those of Courtney et al. (1998). Among these: (1) the saccadic eye movement task of Courtney et al. (1998) featured visually presented targets, whereas our Free Saccade task did not; (2) the saccadic eye movement task of Courtney et al. (1998) was administered in blocks, whereas our Free Saccade trials were single trials, randomly interleaved with trials of other types; and (3) the spatial location working memory task of Courtney et al. (1998) did not require memory for temporal order in which memoranda were presented, in contrast to our working memory tasks. We do not believe, however, that these differences require a qualification of our conclusion that SFC is engaged to a comparable extent in the planning and execution of saccades as in the

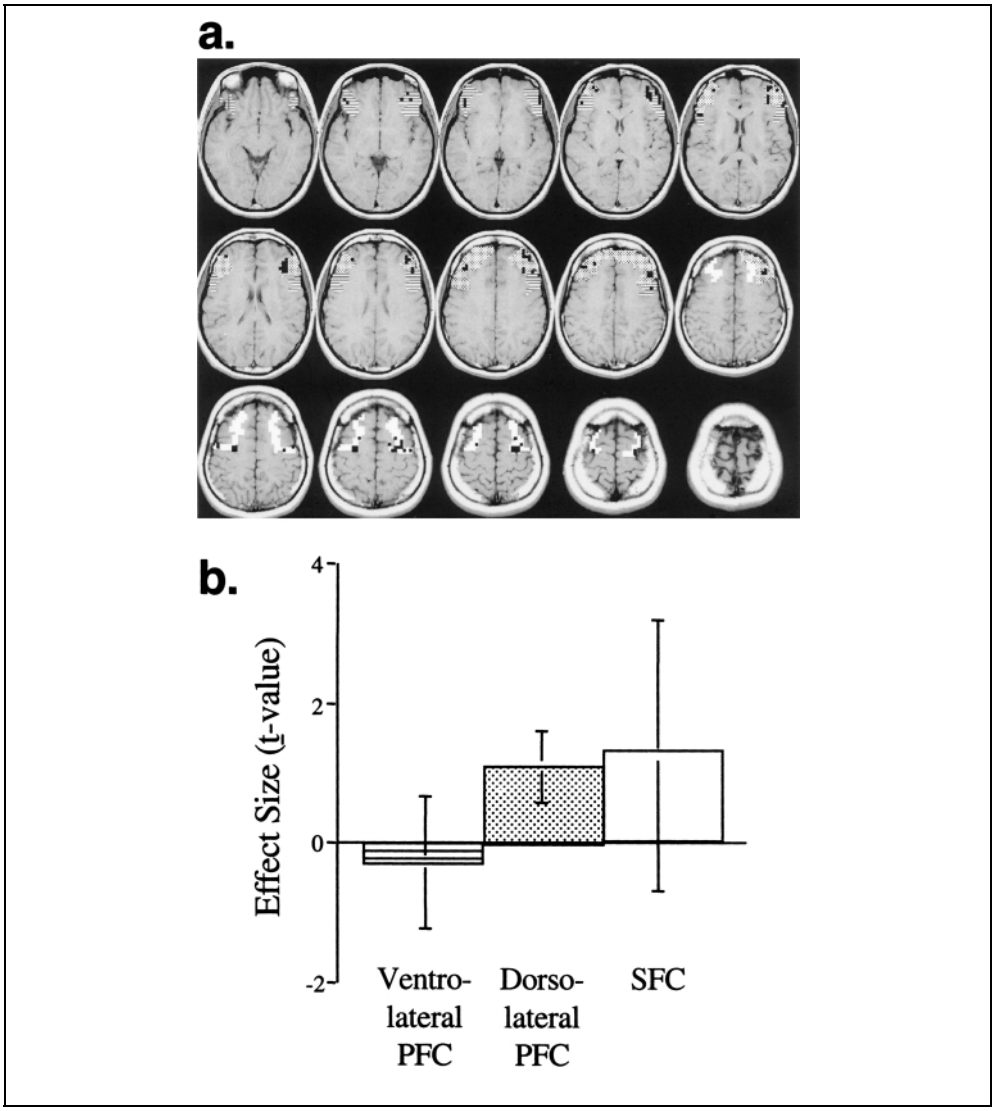

Figure 3. (a) Illustration of the voxels evincing significant delay-period activity (identified with the contrast [$Delay_{Manipulate\ Memory}$ + $Delay_{Forward\ Memory}$]; black squares) from a representative subject (H). The activity of these voxels, and of analogous voxels from the other subjects, was assessed in the group analysis of Forward Memory-related activity versus Manipulate Memory-related activity. The three ROIs in which these group analyses were performed are depicted in patterned overlays: horizontal bars = ventrolateral PFC; stippling = dorsolateral PFC; solid white = SFC. (b) Illustration of the results of the group analysis of the processing hypothesis, revealing reliably a greater Manipulate Memory than Forward Memory effect only in dorsolateral PFC. Each bar represents the group mean result of the (two-tailed) contrast ($Delay_{Manipulate\ Memory}$ − $Delay_{Forward\ Memory}$) in a particular ROI; error bars represent 95% confidence intervals.

working memory maintenance and manipulation of spatial information. In response to the first point, the critical feature shared by the saccadic eye movement task of Courtney et al. (1998) and our Free Saccade task is the relative simplicity of the spatial demands of these tasks (i.e., they each entailed predictable kinematic computation in just one dimension) in contrast with the relatively more complex spatial demands of the memory tasks (which required unpredictable spatial computation in two dimensions). In response to the second point, the blocked nature of the saccadic eye movement task of Courtney et al. (1998) made direct statistical comparison of evoked fMRI signal intensity between it and a working memory task administered in single-trial format unfeasible (Aguirre & D'Esposito, 1999). Such a direct statistical comparison is required, however, to test conclusively the hypothesis promoted by Courtney et al. (1998). Our experimental design was constructed explicitly to permit this direct statistical comparison. And in response to the third point, we believe that the demands on a specialized spatial working memory area of the brain of a spatio-temporal order working memory task should be comparable to, if not greater than, those of a spatial location working memory task. Thus, our spatio-temporal working memory task would be expected to activate comparably, if not to a greater extent, an area specialized for spatial working memory in SFC than would the spatial location working memory task employed by Courtney et al. (1998). Also diminishing the importance of this third point of methodological difference are the results of previous experiments that required memory for the precise spatial location of memoranda (Postle & D'Esposito, 1999; Postle, Stern, et al., 2000; D'Esposito et al., 1998), and thus made demands on spatial working memory very similar to those made by the study of Courtney et al. (1998): These studies did not find

evidence for greater spatial than nonspatial working memory-related activity in SFC.

The fact that we did not find reliable evidence for significantly greater Guided Saccade-evoked activity than Free Saccade-evoked activity indicates that the differences between these two tasks, although substantial enough to elicit dramatic differences when contrasted with spatial working memory-related activity, were not great enough to survive direct statistical contrast. Courtney et al. (1998), too, reported little difference between spatial extent of activity evoked by their blocked horizontal saccades task and by ''transient'' activity associated with the serial presentation of three memoranda.

Maintenance versus Manipulation of Spatio-Temporal Working Memory

The comparison of maintenance versus manipulation of spatio-temporal information in working memory revealed significantly greater activity associated with the latter in dorsolateral PFC, but not in ventrolateral PFC or in SFC. These results suggest that the delay-related function of SFC is limited to the maintenance of spatial information, and that this region does not support the nonmnemonic executive control functions supported by dorsolateral PFC. These results also indicate that the preferential recruitment of dorsolateral PFC for the manipulation of information held in working memory applies to tasks employing spatial stimuli, as well as to tasks employing verbal stimuli (D'Esposito et al., 1999; Postle et al., 1999; Petrides, Alivasatos, Meyer, & Evans, 1993). We can thereby assert that processing models of the organization of working memory function in PFC generalize across different classes of stimuli. Note that our model of the neuroanatomical organization of working memory function in PFC is at variance with other processing models (e.g., Owen et al., 1999; Smith & Jonides, 1999) in that it does not posit that the maintenance of information in working memory is supported by ventral PFC more so than by dorsolateral PFC. In the present study, as in previous studies (D'Esposito et al., 1999; Postle et al., 1999), we found comparable levels of working memory maintenance-related activity in both PFC regions.

The present results also represent a replication and extension of earlier reports of greater dorsolateral than ventrolateral PFC activation for the active monitoring of spatial information in working memory than for its passive maintenance (Owen et al., 1996, 1999). This replication is important, because analysis of the earlier studies required a complicated set of ''cognitive subtractions'' (Posner, Petersen, Fox, & Raichle, 1988), the assumptions underlying that have subsequently been demonstrated to be vulnerable to failure (Zarahn, Aguirre, & D'Esposito, 1997b; Zarahn, Aguirre, & D'Esposito, 1999; Friston et al., 1996). The accumulating evidence for greater dorsolateral than ventrolateral PFC recruitment for the manipulation in working memory of many different types of information—spatial locations (Owen et al., 1996, 1999), letters (D'Esposito et al., 1999; Postle et al., 1999), and now, spatio-temporal order—is consistent with processing models of the organization of working memory function in PFC (D'Esposito et al., 1999; Petrides, 1994). Results from the present study suggest that SFC is not also preferentially recruited for the manipulation of information held in working memory.

METHODS

Subjects

We tested five healthy subjects (two males; mean age = 20.4) who were recruited from the undergraduate and medical campuses of the University of Pennsylvania. None reported a history of neurological or psychiatric illness, and all gave informed consent.

Behavioral Tasks

An fMRI experiment comprised a total of 96 behavioral trials, divided equally among Free Saccade, Guided Saccade, Forward Memory, and Manipulate Memory trial types. Trial order was randomized within each 12-trial block that corresponded to an fMRI scan (see fMRI Procedure). Each of the four trial types in our experiment followed the sequence of events illustrated in Figure 4a: Initial Instructions, ISI, Encoding/Saccades, Predelay Instructions, Delay, Probe. For the Free Saccade condition, subjects performed saccades from the offset of the ''Free Eye Movements'' instruction until the onset of the ''Fixate'' instruction, 6.5 sec later. Subjects had been pretrained to make horizontal saccades in time with a metronome clicking at a rate of 1 Hz. There was no metronome cue during scanning. Training did not specify the magnitude of these horizontal saccades. No task-related auditory cues were presented during scanning. No array of squares was presented to subjects on these trials until the Probe portion of the trial, and no square in the Probe array was labeled. For Guided Saccade, Forward Memory, and Manipulate Memory trials, any one of 96 irregular arrays of 10 squares, modeled after the Corsi blocks (Milner, 1971), was presented 1 sec after the onset of the Initial Instructions, and for the next 6 sec, one of six pseudorandomly determined blocks, in turn, turned black for 1 sec. A different, novel array of squares was presented on each of the 96 trials in this experiment. Each array was constructed with the constraint that each square in an array have a unique address in x- and y-coordinates on the computer screen. Selection of the six squares to be highlighted on a trial was made pseudorandomly, as was the sequence of locations highlighted, with the constraint that it not follow any of the four cardinal

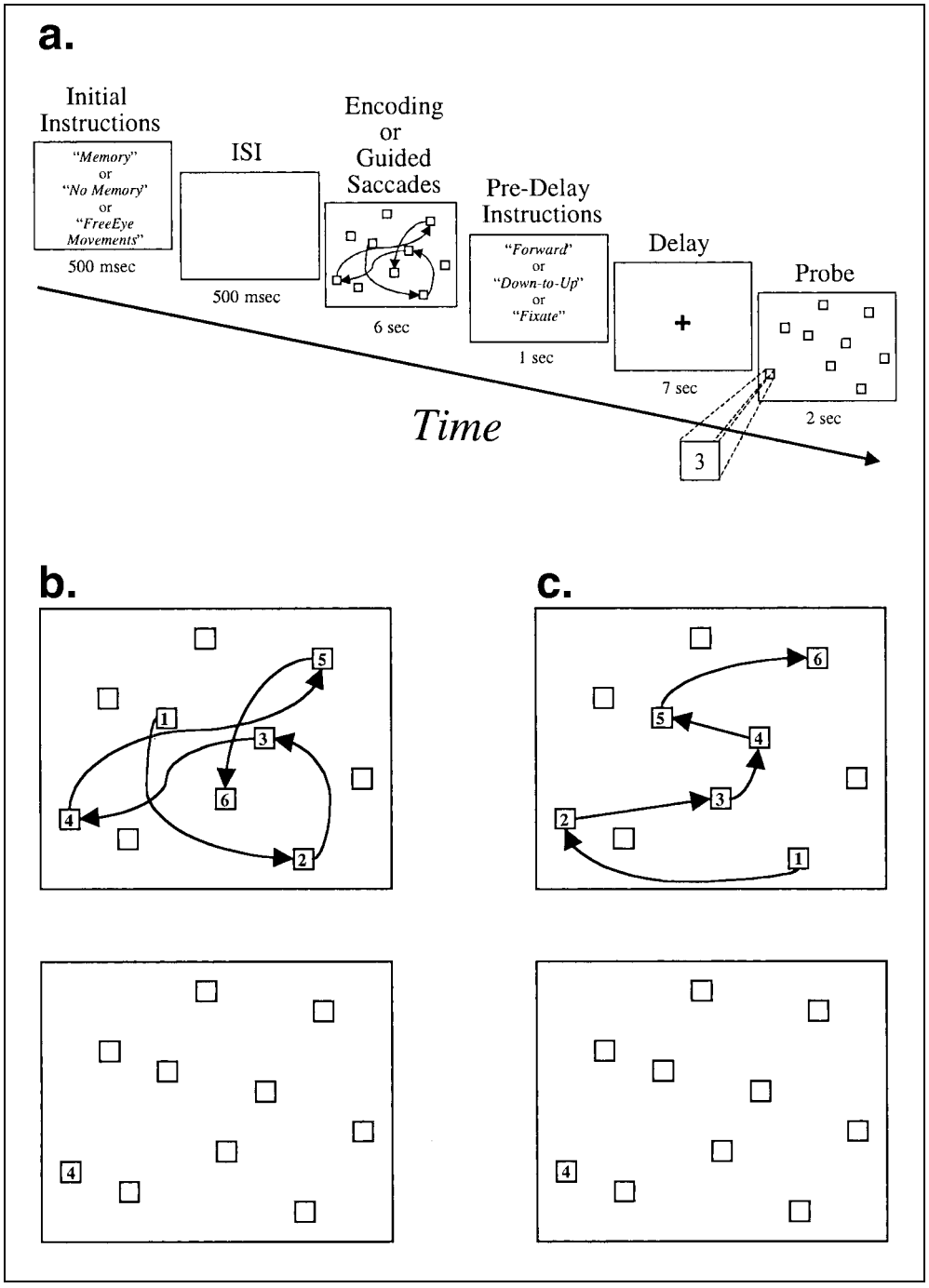

Figure 4. (a) Schematic timeline for each of the four trial-types in the experiment (see Methods for details). (b) Illustration of a Forward Memory trial. Digits and arrows in the top panel represent the order in which six blocks are highlighted in this hypothetical trial (neither digits nor arrows were presented during trials of the actual experiment). This spatio-temporal sequence must be retained during the Delay portion of the trial. The bottom panel illustrates an example of the display of the Probe if this were a "correct" trial. (c) Illustration of a Manipulate Memory trial. Digits and arrows represent a reordered spatio-temporal sequence (in this case, "down-to-up") into which subjects must reorder, during the Delay period, the sequence illustrated in panel (b). The bottom panel illustrates an example of the display of the Probe if this were an "incorrect" file.

reordering sequences that could be specified during Manipulate Memory trials (see below). Subjects had been trained to make a saccade to each square as it was highlighted. During Guided Saccade trials subjects had received the Initial Instruction of "No Memory," and thus knew not to encode the sequence of six locations in working memory. The subsequent Predelay Instruction during Guided Saccade trials was to "Fixate," and the array of squares reappeared 7.5 sec after the offset of the Predelay Instruction; no square in the Probe array was labeled. During Forward Memory trials and Manipulate Memory trials, whose identity was signaled to subjects by the "Memory" Initial Instruction, subjects encoded the position of each of the six highlighted squares and the order in which each had been selected. Only after the presentation of the six memoranda did subjects receive the Predelay Instructions to either (a) maintain the spatio-temporal information presented during the Encoding phase ("Forward") or (b) reorder this spatio-temporal information in one of

four ways: descending vertical order (''Up-to-Down''); ascending vertical order (''Down-to-Up''); ''Left-to-Right'' horizontal order; or ''Right-to-Left'' horizontal order. Maintain Memory and Manipulate Memory trials occurred in equal numbers within each 12-trial fMRI scan, and the four types of Manipulate Memory occurred in equal numbers across the 96 trials that comprised an experiment.

fMRI Procedure

Whole-brain T1-weighted images (21 axial slices, 0.9372 × 0.9375 mm in-plane, 5 mm thick) were obtained in every subject. A gradient echo, echoplanar sequence (TR = 2,000 msec, TE = 50 msec) was used to acquire whole-brain data sensitive to the BOLD signal (Kwong et al., 1992; Ogawa et al., 1992) within a 64 × 64 matrix (3.75 × 3.75 × 5 mm). Scans of the behavioral task were preceded by a scan in which we estimated the hemodynamic response function (HRF) for each subject. The HRF (interchangeably referred to as the impulse response function or ''IRF'') characterizes the fMRI response resulting from a brief pulse of neural activity (Boynton, Engel, Glover, & Heeger, 1996). The procedure for deriving an empirical estimate the HRF for each subject is detailed elsewhere (Aguirre, Zarahn, & D'Esposito, 1998). The empirical estimate of each subject's HRF was used in the analysis of that subject's fMRI data to smooth independent variables in the general linear model (GLM) that we used to analyze the results of the scans of our behavioral task.

fMRI Data Processing

We performed our analyses on spatially unsmoothed data sets in order to take maximal advantage of the spatial resolution of our fMRI scanning protocol. Unlike PET data, which features a high degree of spatial coherency, or smoothness (''global flow'') (Friston et al., 1990), fMRI data do not have inherently high spatial coherency (Zarahn, Aguirre, & D'Esposito, 1997a), and can thus be analyzed without imposing a higher degree of spatial smoothness on the data via exogenous smoothing. Our inferential statistics were derived using multiple regression. We modeled the BOLD signal changes occurring during each qualitatively distinct component of the behavioral trials (Initial Instructions, Stimulus Presentation, Predelay Instructions, Delay, Probe) with one series of covariates. Each covariate comprised an HRF positioned appropriately to represent neural activity associated with one of the task components (Postle, Zarahn, & D'Esposito, 2000; Zarahn et al., 1997b). The least-squares solution of the corresponding linear model of the dependent data (i.e., of the fMRI time series) was obtained with a GLM for autocorrelated observations (Worsley & Friston, 1995). (Note that, for consistency, we refer to a ''Stimulus Presentation'' covariate modeling eye movements during Free Saccade trials, even though no stimuli were presented during these trials.)

The least-squares solution of the modified GLM takes the form of parameter estimates (i.e., beta values) that are associated with each covariate of interest. These parameter estimates are interpreted as indices of the extent to which their corresponding covariates of interest explain the dependent data. Statistical maps were generated by computing t statistics associated with linear combinations of the parameter estimates associated with particular covariates of interest (Worsley & Friston, 1995). Thus, for example, we compared statistically the fMRI signal intensities associated with spatial working memory versus performance of Guided Saccades with the (two-tailed) contrast $[(\{0.5 \times \text{Delay}_{\text{Forward Memory}} - \text{baseline}\} + \{0.5 \times \text{Delay}_{\text{Manipulate Memory}} - \text{baseline}\}) - (1 \times \text{Stimulus Presentation}_{\text{Guided Saccade}} - \text{baseline})]$ (Figure 1). Spatial working memory was represented in this contrast as the mean of the appropriate Forward Memory and Manipulate Memory covariates because the Forward versus Manipulate distinction was only germane to our second hypothesis, testing the generalizability of the processing model of the functional organization of PFC. (For expository simplicity we have omitted the ''− baseline'' from subsequent descriptions of hypothesis-testing contrasts.)

A noteworthy feature of unsmoothed fMRI data sets is that the analyses can be performed in a ''massively parallel'' univariate manner, such that inferential statistical analyses of fMRI time series (in the case of the present report, with the modified GLM) are performed independently at each voxel in the data set. In this way, the activity of individual voxels can be assessed for statistical significance, and can be interpreted in the same was as would be a significant local maximum in a spatially smoothed data set. As is the case with many other types of data, one must take into account the number of statistical tests performed in the analysis in order to avoid inflation of the false positive rate of the resultant statistical map. One method for correcting for multiple statistical tests, the Bonferroni correction, has been demonstrated to control false-positive rates at the level of .05 when applied to unsmoothed data analyzed with the method described in this report (Zarahn et al., 1997a). Importantly, in this context, the Bonferroni correction cannot be viewed as ''too stringent'' (Postle, Zarahn, et al., 2000).

Regions of Interest

In view of the need to correct each statistical map for the number of voxels represented in that map (i.e., for the number of independent statistical comparisons), use of an a priori defined Region of Interest (ROI)

increases one's sensitivity to detect hypothesized effects within that region. This is because the critical *t* value for a contrast performed within a several hundred-voxel ROI (e.g., a *t* value of 3.7 for the 257 voxels in the SFC ROI of subject K) would be lower than the critical *t* value for the same contrast performed across the several thousand-voxel volume of the entire brain (e.g., a *t* value of 4.7 for the 16,595 voxels in the whole-brain data set of subject K). SFC ROIs were created for each subject by incorporating the 6 mm of cortex surrounding SFS, starting from its caudal terminus and extending rostrally and ventrally to the junction of Brodmann's areas 8 and 9, and the 6 mm of gray matter surrounding the precentral sulcus (PCS), beginning with its superiormost extent and extending ventrally and laterally to the superiormost level at which the insular cortex was visible. This ROI incorporated fully and exceeded, along both sulci, the widely accepted localization of the FEF in the vicinity of the junction of the PCS and the SFS (Kimmig, Greenlee, Huethe, & Mergner, 1999; Luna et al., 1998; Paus, 1996; Petit et al., 1996; Petit, Clark, Ingelholm, & Haxby, 1997; Sweeney et al., 1996). ROIs for dorsolateral and ventrolateral PFC were created by first defining them on the ''canonical'' representation of a brain in Talairach space that is provided in SPM96b, using the atlas of Talairach and Tournoux (1988) to confirm our identification of anatomical landmarks. The dorsolateral PFC ROIs corresponded by Brodmann's areas 9 and 46, the ventrolateral PFC ROIs corresponded to Brodmann's areas 44, 45, and 47. Next, we transformed these ROIs from Talairach space into the native space in which each subject's data had been acquired by applying the 12 parameter affine transformation (Friston et al., 1995) with nonlinear deformations (Ashburner & Friston, 1996), routine in SPM96b (effectively, a ''reverse normalization''). Because some individual anatomical variability is not accounted for in the reverse normalization process, we adjusted the ROIs after transformation to better correspond to the anatomical images of each subject so that they would cover perfectly the intended brain regions.

Hypothesis Testing

Hypothesis testing proceeded in two steps: single-subject analyses and group analyses. Single-subject analyses permitted us to maintain the high spatial resolution afforded by fMRI, and to detect intersubject variability. Such information is lost in analysis approaches that combine data from all subjects at an early stage of analysis, and are thus restricted to testing for activation patterns that are consistent enough across subjects in a standard space to be detected after group-averaging. Our single-subject analyses, in contrast, treated each subject as a case study, and permitted us to assess replication of (as well as variation in) effects across individual cases. In essence, data from five subjects performing the same task represented a single result with four replications, analogous to the treatment of data from monkey electrophysiological studies. Single-subject analyses with methods comparable to those described here (and, importantly, with a large number of observations per subject, as in the present study) have been demonstrated to feature ample sensitivity to detect signal intensity changes of interest (Postle & D'Esposito, 1999; Zarahn et al., 1999). One-tailed contrasts were performed to assess activity isolated to a particular task component. The results of such one-tailed contrasts are illustrated in the top three panels corresponding to each subject's data in Figure 1. Tests of hypotheses requiring the direct statistical comparison of two conditions were performed as two-tailed contrasts. All contrasts performed with single subject data in the present study had in excess of 1,300 effective degrees of freedom.

Group analyses were performed as random effects models, an approach that permits generalization of results obtained from a sample to the population represented by that sample. This inferential step cannot be made with the fixed effects group analyses that have been employed by the majority of fMRI experimentalists to date (Friston, Holmes, & Worsley, 1999; Woods, 1996). Importantly, random effects analyses are invulnerable to spurious results that can arise if a disproportionately large effect size in a single subject ''drives'' the mean effect size for the group, as can happen with fixed effects analyses. Our group analysis method entailed neither averaging data across subjects nor creating a group average image. Rather, we employed objective, data-driven methods to define analogous groups of voxels within each subject, applied the contrast of theoretical interest to each subject voxels, and assessed the reliability of the results across subjects with a two-tailed *t* test.

The group analysis of the labeled line hypothesis in SFC proceeded in four steps. First, we defined anatomical ROIs for each subject as the cortex within the SFC ROI anterior to the anteriormost extent of guided saccade-evoked activity (Figure 2a). Second, for each subject, we pooled the fMRI signal from every voxel contained in this modified SFC ROI. Third, we applied the two-tailed contrast $[(\{0.5 \times \text{Delay}_{\text{Forward Memory}}\} + \{0.5 \times \text{Delay}_{\text{Manipulate Memory}}\}) - (1 \times \text{Stimulus Presentation}_{\text{Guided Saccade}})]$ to the pooled time series data from each subject. The resultant *t* values indexed, for each subject, the extent to which delay-period activity was greater than or less than guided-saccade activity. The final step was to enter the *t* value for each subject into a paired *t* test (with degrees of freedom equaling the number of subjects minus 1).[2]

The processing hypothesis was tested in three ROIs, and also proceeded in four steps. First, we defined

functionally the voxels from ventrolateral PFC, dorsolateral PFC, and SFC from each subject to be interrogated for the analysis. For example, for the group test of Manipulation Memory versus Forward Memory in dorsolateral PFC, we identified for each subject the voxels active during the delay-periods of these two trial types with the one-tailed contrast ($Delay_{Manipulate\ Memory} + Delay_{Forward\ Memory}$). Second, we extracted from the delay-active voxels for each subject the corresponding pooled time series. Third, we applied to these spatially averaged time series the orthogonal two-tailed contrasts of ($Delay_{Manipulate\ Memory} - Delay_{Forward\ Memory}$). Fourth, we assessed the reliability of results across subjects by calculating the group mean and computing a *t* statistic. Steps 2, 3, and 4 were repeated for the ventrolateral PFC and the SFC ROIs. Although such a group analysis can effectively test for the presence of an effect that is too subtle to be detected in single-subject analyses, it features markedly lower spatial resolution. In the analysis illustrated in this paragraph, for example, inferences arising from the results of this group analysis could only be applied to the whole of dorsolateral PFC, because no constraints were placed upon the location within dorsolateral PFC from which delay-active voxels could be identified.

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The data reported in this experiment have been deposited in National fMRI Data Center (http://www.fmridc.org). The accession number is 2-2000-1112R.

Notes

1. The experimental design employed by Courtney et al. (1998) precluded meaningful direct statistical comparison of relative evoked fMRI signal intensities, however, because it measured spatial working memory-related activity from randomized single trials and saccade-related activity from ''on–off'' blocks. These two experimental design types are expected to feature markedly different task-related power, independent of the behavioral content of the tasks themselves (Aguirre & D'Esposito, 1999).
2. The *t* values are normalized indices of effect size that can be compared across subjects, because the residual error term that makes up the denominator of the *t* value is positively, linearly related to the same scaling factor (or ''gain effect'') that characterizes differences in overall BOLD signal intensity across scanning sessions (Postle, Zarahn, et al., 2000; Zarahn, in preparation).

REFERENCES

Aguirre, G. K., & D'Esposito, M. (1999). Experimental design for brain fMRI. In C. T. W. Moonen & P. A. Bandettini (Eds.), *Functional MRI* (pp. 369–380). Berlin: Springer-Verlag.

Aguirre, G. K., Zarahn, E., & D'Esposito, M. (1998). The variability of human, BOLD hemodynamic responses. *Neuroimage, 8,* 360–369.

Ashburner, J., & Friston, K. (1996). Fully three-dimensional nonlinear spatial normalization: A new approach. *Neuroimage, 3,* S111.

Awh, E., Jonides, J., Smith, E. E., Schumacher, E. H., Koeppe, R. A., & Katz, S. (1996). Dissociation of storage and rehearsal in verbal working memory: Evidence from positron emission tomography. *Psychological Science, 7,* 25–31.

Baker, S. C., Frith, C. D., Frackowiak, R. S. J., & Dolan, R. J. (1996). Active representation of shape and spatial location in man. *Cerebral Cortex, 6,* 612–619.

Bizzi, E., & Schiller, P. H. (1970). Single unit activity in the frontal eye fields of unanesthetized monkeys during eye and head movement. *Experimental Brain Research, 10,* 150–158.

Boynton, G. M., Engel, S. A., Glover, G. H., & Heeger, D. J. (1996). Linear systems analysis of functional magnetic resonance imaging in human V1. *Journal of Neuroscience, 16,* 4207–4221.

Courtney, S. M., Petit, L., Maisog, J. M., Ungerleider, L. G., & Haxby, J. V. (1998). An area specialized for spatial working memory in human frontal cortex. *Science, 279,* 1347–1351.

Courtney, S. M., Ungerleider, L. G., Keil, K., & Haxby, J. (1996). Object and spatial visual working memory activate separate neural systems in human cortex. *Cerebral Cortex, 6,* 39–49.

Courtney, S. M., Ungerleider, L. G., Keil, K., & Haxby, J. V. (1997). Transient and sustained activity in a distributed neural system for human working memory. *Nature, 386,* 608–611.

D'Esposito, Aguirre, G. K., Zarahn, E., & Ballard, D. (1998). Functional MRI studies of spatial and non-spatial working memory. *Cognitive Brain Research, 7,* 1–13.

D'Esposito, M., Postle, B. R., Ballard, D., & Lease, J. (1999). Maintenance versus manipulation of information held in working memory: An event-related fMRI study. *Brain and Cognition, 41,* 66–86.

Friston, K. J., Ashburner, J., Frith, C. D., Poline, J.-B., Heather, J. D., & Frackowiak, R. S. J. (1995). Spatial registration and normalization of images. *Human Brain Mapping, 2,* 165–189.

Friston, K. J., Frith, C. D., Liddle, P. F., Dolan, R. J., Lammertsma, A. A., & Frackowiak, R. S. (1990). The relationship between global and local changes in PET scans. *Journal of Cerebral Blood Flow and Metabolism, 10,* 458–466.

Friston, K. J., Holmes, A. P., & Worsley, K. J. (1999). How many subjects constitute a study? *Neuroimage, 10,* 1–5.

Friston, K. J., Price, C. J., Fletcher, P., Moore, C., Frackowiak, R. S. J., & Dolan, R. J. (1996). The trouble with cognitive subtraction. *Neuroimage, 4,* 97–104.

Goldman-Rakic, P. S. (1987). Circuitry of the prefrontal cortex and the regulation of behavior by representational memory. In V. B. Mountcastle, F. Plum, & S. R. Geiger (Eds.), *Handbook of Neurobiology* (pp. 373–417). Bethesda, MD: American Physiological Society.

Jonides, J., Smith, E., Koeppe, R., Awh, E., Minoshima, S., & Mintum, M. (1993). Spatial working memory in humans as revealed by PET. *Nature, 363,* 623–625.

Kimmig, H., Greenlee, M. W., Huethe, F., & Mergner, T. (1999). MR-Eyetracker: A new method for eye movement recording in functional magnetic resonance imaging (fMRI). *Experimental Brain Research, 126,* 443–449.

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., Kennedy, D. N., Hoppel, B. E., Cohen, M. S., Turner, R., Cheng, H. M., Brady, T. J., & Rosen, B. R. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences, U.S.A., 89,* 5675–5679.

Luna, B., Thulborn, K. R., Strojwas, M. H., McCurtain, B. J., German, R., Genovese, C. R., & Sweeney, J. A. (1998). Dorsal cortical regions subserving visually guided saccades in humans: An fMRI study. *Cerebral Cortex, 8,* 40–47.

Mellet, E., Tzourio, N., Crivello, F., Joliot, M., Denis, M., & Mazoyer, B. (1996). Functional anatomy of spatial mental imagery generated from verbal instructions. *Journal of Neuroscience, 16,* 6504–6512.

Milner, B. (1971). Interhemispheric differences in the localization of psychological processes in man. *British Medical Bulletin, 27,* 272–277.

Ogawa, S., Tank, D. W., Menon, R., Ellermann, J. M., Kim, S. G., Merkle, H., & Ugurbil, K. (1992). Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping using MRI. *Proceedings of the National Academy of Sciences, U.S.A., 89,* 5951–5955.

Owen, A. M., Evans, A. C., & Petrides, M. (1996). Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: A positron emission tomography study. *Cerebral Cortex, 6,* 31–38.

Owen, A. M., Herrod, N. J., Menon, D. K., Clark, J. C., Downey, S. P. M. J., Carpenter, T. A., Minhas, P. S., Turkheimer, F. E., Williams, E. J., Robbins, T. W., Sahakian, B. J., Petrides, M., & Pickard, J. D. (1999). Redefining the functional organization of working memory processes within human lateral prefrontal cortex. *European Journal of Neuroscience, 11,* 567–574.

Owen, A. M., Stern, C. E., Look, R. B., Tracey, I., Rosen, B. R., & Petrides, M. (1998). Functional organization of spatial and nonspatial working memory processing within the human lateral frontal cortex. *Proceedings of the National Academy of Sciences, U.S.A., 95,* 7721–7726.

Paus, T. (1996). Location and function of the human frontal eye-field: A selective review. *Neuropsychologia, 34,* 475–483.

Paus, T., Marrett, S., Worsley, K. J., & Evans, A. C. (1995). Extraretinal modulation of cerebral blood flow in the human visual cortex: Implications for saccadic suppression. *Journal of Neurophysiology, 74,* 2179–2183.

Petit, L., Clark, V., Ingeholm, J., & Haxby, J. (1997). Dissociation of saccade-related and pursuit-related activation in human frontal eye fields as revealed by fMRI. *Journal of Neurophysiology, 77,* 3386–3390.

Petit, L., Orssaud, C., Tzourio, N., Crivello, F., Berthoz, A., & Mazoyer, B. (1996). Functional anatomy of a prelearned sequence of horizontal saccades in humans. *Journal of Neuroscience, 16,* 3714–3726.

Petrides, M. (1994). Frontal lobes and working memory: Evidence from investigations of the effects of cortical excisions in nonhuman primates. In F. Boller & J. Grafman (Eds.), *Handbook of neuropsychology* (pp. 59–82). Amsterdam: Elsevier.

Petrides, M. (1995). Impairments on nonspatial self-ordered and externally ordered working memory tasks after lesions of the mid-dorsolateral part of the lateral frontal cortex in the monkey. *Journal of Neuroscience, 15,* 359–375.

Petrides, M., Alivisatos, B., Meyer, E., & Evans, A. C. (1993). Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proceedings of the National Academy of Sciences, U.S.A., 90,* 878–882.

Posner, M. I., Petersen, S. E., Fox, P. T., & Raichle, M. E. (1988). Localization of cognitive operations in the human brain. *Science, 240,* 1627–1632.

Postle, B. R., Berger, J. S., & D'Esposito, M. (1999). Functional neuroanatomical double dissociation of mnemonic and executive control processes contributing to working memory performance. *Proceedings of the National Academy of Sciences, U.S.A., 96,* 12959–12964.

Postle, B. R., & D'Esposito, M. (1999). "What"—then—"where" in visual working memory: An event-related fMRI study. *Journal of Cognitive Neuroscience, 11,* 585–597.

Postle, B. R., & D'Esposito, M. (2000). Evaluating models of the topographical organization of working memory function in frontal cortex with event-related fMRI. *Psychobiology, 28*, 132–145.

Postle, B. R., Stern, C. E., Rosen, B. R., & Corkin, S. (2000). An fMRI investigation of cortical contributions to spatial and nonspatial visual working memory. *Neuroimage, 11,* 409–423.

Postle, B. R., Zarahn, E., & D'Esposito, M. (2000). Using event-related fMRI to assess delay-period activity during performance of spatial and nonspatial working memory tasks. *Brain Research Protocols, 5,* 57–66.

Rao, S. C., Rainer, G., & Miller, E. K. (1997). Integration of what and where in the primate prefrontal cortex. *Science, 276,* 821–824.

Rushworth, M. F. S., Nixon, P. D., Eacott, M. J., & Passingham, R. E. (1997). Ventral prefrontal cortex is not essential for working memory. *Journal of Neuroscience, 17,* 4829–4838.

Schall, J. D. (1991). Neuronal activity related to visually guided saccades in the frontal eye fields of rhesus monkeys: Comparison with supplementary eye fields. *Journal of Neurophysiology, 66,* 559–579.

Smith, E. E., & Jonides, J. (1999). Storage and executive processes of the frontal lobes. *Science, 283,* 1657–1661.

Smith, E. E., Jonides, J., & Koeppe, R. A. (1996). Dissociating verbal and spatial working memory using PET. *Cerebral Cortex, 6,* 11–20.

Sweeney, J. A., Mintun, M. A., Kwee, S., Wiseman, M. B., Brown, D. L., Rosenberg, D. R., & Carl, J. R. (1996). Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. *Journal of Neurophysiology, 75,* 454–468.

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain*. New York: Thieme.

Ungerleider, L. G., Courtney, S. M., & Haxby, J. V. (1998). A neural system for visual working memory. *Proceedings of the National Academy of Sciences, U.S.A., 95,* 883–890.

Wilson, F. A. W., O'Scalaidhe, S. P., & Goldman-Rakic, P. S. (1993). Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science, 260,* 1955–1958.

Woods, R. P. (1996). Modeling for intergroup comparisons of imaging data. *Neuroimage, 4,* S84–S94.

Worsley, K. J., & Friston, K. J. (1995). Analysis of fMRI time-series revisited—again. *Neuroimage, 2,* 173–182.

Zarahn, E. (in preparation). Scaling noise in BOLD fMRI data.

Zarahn, E., Aguirre, G. K., & D'Esposito, M. (1997a). Empirical analyses of BOLD fMRI statistics: I. Spatially unsmoothed data collected under null-hypothesis conditions. *Neuroimage, 5,* 179–197.

Zarahn, E., Aguirre, G. K., & D'Esposito, M. (1997b). A trial-based experimental design for fMRI. *Neuroimage, 6,* 122–138.

Zarahn, E., Aguirre, G. K., & D'Esposito, M. (1999). Temporal isolation of the neural correlates of spatial mnemonic processing with functional MRI. *Cognitive Brain Research, 7,* 255–268.