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Maintenance versus Manipulation of Information Held in Working Memory: An Event-Related fMRI Study

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One model of the functional organization of lateral prefrontal cortex (PFC) in primates posits that this region is organized in a dorsal/ventral fashion subserving spatial and object working memory, respectively. Alternatively, it has been proposed that a dorsal/ventral subdivision of lateral PFC instead reflects the type of processing performed upon information held in working memory. We tested this hypothesis using an event-related fMRI method that can discriminate among functional changes occurring during temporally separated behavioral subcomponents of a single trial. Subjects performed a delayed-response task with two types of trials in which they were required to: (1) retain a sequence of letters across the delay period (*maintenance*) or (2) reorder the sequence into alphabetical order across the delay period (*manipulation*). In each subject, activity during the delay period was found in both dorsolateral and ventrolateral PFC in both types of trials. However, dorsolateral PFC activity was greater in manipulation trials. These findings are consistent with the processing model of the functional organization of working memory in PFC.

Key Words: functional MRI; working memory; prefrontal cortex.

INTRODUCTION

Single-unit recordings in monkeys have revealed neurons in the lateral prefrontal cortex (PFC) that increase their firing during a delay between the presentation of information and its later use in behavior (Funahashi et al., 1989, Fuster & Alexander, 1971). The results of these studies have been taken as evidence that lateral PFC subserves working memory, a cognitive system that permits short-term, active maintenance and manipulation of in-

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formation when that information is not available in the environment (Baddeley, 1992; Baddeley et al., 1986). However, it remains unclear whether there are functional subdivisions within the PFC that are specialized for particular components of working memory. Goldman-Rakic and colleagues have proposed that lateral PFC in nonhuman primates is organized in a dorsal/ventral fashion subserving the temporary storage of ''where'' and ''what'' information, respectively (Wilson et al., 1993). That is, it is proposed that dorsolateral PFC (the principal sulcus in monkeys) is critical for maintaining an object's location in space, whereas ventrolateral PFC (the inferior convexity in monkeys) is critical for maintaining information about an object's color and shape. This hypothesis has the appeal of parsimony, as it represents a rostral extension of the dorsal/ventral organization of the visual system (Ungerleider & Haxby, 1994).

Several investigators have questioned whether a dorsal/ventral what/where functional organization of the lateral PFC of monkeys exists. These challenges are based on several lines of evidence: (1) other single-unit recording studies of dorsal and ventral regions within lateral PFC during delayed-response tasks have found a mixed population of neurons in both regions that are not clearly segregated by the type of information (i.e. spatial versus nonspatial) that is being stored (Fuster et al., 1982; Quintana et al., 1988; Rao et al., 1997; Rosenkilde et al., 1981), (2) cooling of a dorsal region of lateral PFC has been demonstrated to cause impairments on both spatial and nonspatial tasks (Bauer & Fuster, 1976; Fuster & Bauer, 1974; Quintana & Fuster, 1993), (3) lesions of a dorsal region of lateral PFC have been demonstrated to cause impairments on nonspatial working memory tasks (Mishkin et al., 1969; Petrides, 1995) and more ventral lesions in lateral PFC have caused spatial impairments (Butters et al., 1973; Iversen & Mishkin, 1970; Mishkin et al., 1969), and (4) 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).

Because injury to PFC in humans is rarely restricted to a single functional area, testing this divisional hypothesis with lesion studies in humans is difficult (Pierrot-Deseilligny et al., 1991; Ptito et al., 1995; Verin et al., 1993). However, many groups have employed functional neuroimaging techniques to address this question by assessing the pattern of PFC activity associated with performance of spatial and nonspatial working memory tasks. We have examined critically this literature for evidence for or against the what/where model of PFC organization. Derived from 24 studies that employed 40 different working memory paradigms, we plotted the locations of activations during performance of spatial and nonspatial working memory tasks on a standardized brain. This analysis revealed no evidence for a dorsal/ventral dissociation of spatial vs. object working memory function (D'Esposito et al., 1998a). Moreover, our own fMRI studies of the n-back working memory task with verbal and spatial (D'Esposito et al., 1998) or object and spatial

(Postle et al., 1997) stimuli did not reveal segregated regions of PFC activation.

Another possible axis along which human dorsolateral and ventrolateral PFC may be organized is the type of processing performed on information being held in working memory. Petrides and colleagues (Owen et al., 1996; Petrides, 1989) have proposed that ventrolateral PFC (Brodmann' areas 45/47) is the site where information is initially received from posterior association areas and held active to guide behavior. In contrast, dorsolateral PFC (areas 9/46) is recruited only when ''monitoring'' and ''manipulation'' of information held in working memory is required. In a preliminary assessment of this alternative hypothesis of prefrontal organization, we again analyzed the data from 24 previously reported functional neuroimaging studies of working memory. After dividing the working memory tasks according to the processing demands of the tasks, rather than the type of information being maintained, a dorsal/ventral dissociation emerged: Tasks that activated dorsolateral PFC were more likely to engage processes requiring computation on or transformation of memoranda in addition their maintenance in working memory (D'Esposito et al., 1998).

The purpose of the present study was to test directly this possible organization of PFC, by comparing a working memory condition that required retention of information (*maintenance*) during a delay with a condition that also required the transposition (*manipulation*) of information being held in working memory during the delay. We predicted that activation in dorsolateral PFC would be significantly greater during the delay period of the manipulation than the maintenance condition. To test this hypothesis, we implemented an event-related fMRI method that allowed us to isolate temporally the neural correlates of different component processes within a behavioral trial of a working memory task (Zarahn et al., 1997b). Our experiment would provide a more conclusive test of the processing-demands hypothesis than any previous neuroimaging study of working memory because our method did not require us to make the assumption of pure insertion, an assumption that is necessitated in block-design experiments that average neuroimaging signal across all components of several behavioral trials and that renders data from such experiments vulnerable to errors of inference (Zarahn et al., 1997b).

MATERIALS AND METHODS

Subjects. We studied seven right-handed male subjects (mean age 23.9 years, range 19–32 years old) who were recruited from the undergraduate and medical campuses of the University of Pennsylvania. Subjects were excluded if they had any medical, neurological, or psychiatric illness or if they were taking any type of prescription medication. All subjects gave informed consent.

MRI technique. Imaging was carried out on a 1.5T SIGNA scanner (GE Medical Systems) equipped with a fast gradient system for echoplanar imaging. A standard radiofrequency (RF) head coil was used with foam padding to restrict head motion comfortably. High-resolution

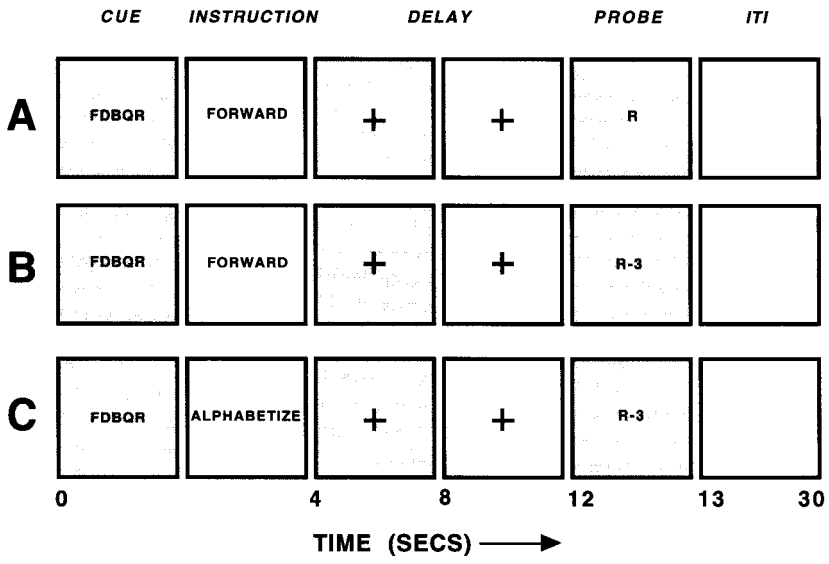

FIG. 1. Paradigms for delayed response task. A represents a trial in the *maintenance* condition of the *principal* experiment; B represents a trial in the *maintenance* condition of the *modified* experiment; and C represents a trial in the *manipulation* condition in both experiments. Covariates modeled each behavioral component identified at the top of the figure (see Fig. 2).

sagittal and axial T1-weighted images were obtained in every subject. A gradient echo, echoplanar sequence (TR = 2000 ms, TE = 50 ms) was used to acquire data sensitive to the BOLD signal (Kwong et al., 1992; Ogawa et al., 1992). Resolution was 3.75 × 3.75 mm in plane and 5 mm between planes (21 axial slices were acquired). Twenty seconds of gradient and RF pulses preceded the actual data acquisition to allow tissue to reach steady-state magnetization.

Experimental paradigms. The behavioral paradigm was a delayed-response task in which a set of five letters was presented simultaneously, in a randomly determined order, for 2.5 s, followed immediately by an instruction cue that was presented for 1.5 s (FORWARD or ALPHABETIZE) followed by an 8-s delay, during which only a fixation cross appeared on the screen, followed by a probe that was displayed for 1 s, during which the subject responded with a ''yes'' (right thumb) or ''no'' (left thumb) button press. Following these behavioral events there was a 17-s intertrial interval that allowed the fMRI signal to return to baseline. The total time from trial onset to trial onset was 30 s (Fig. 1).

Subjects were presented two types of trials in a pseudo-randomized order in which they were required to either (1) *maintain* a sequence of letters across a delay period or (2) *manipulate* this sequence during the delay in order to respond correctly to a probe. In the maintenance condition subjects were instructed to determine whether the letter presented at the probe was in the memory set that had been presented at the onset of the trial (Fig. 1A). This condition, therefore, simply required retention of the letters in the same format as presented at the beginning of the trial. In the manipulation condition the probe consisted of a letter and a number, and subjects were instructed to determine whether that letter would be in the ordinal position represented by the number if the items in the memory set were rearranged into alphabetical order (Fig. 1c). This condition, therefore, required subjects to transpose the order of the five

items presented at the beginning of the trial during the delay period. Five subjects performed this version of the task.

Two additional subjects performed a modified version of the task, during which the probe was changed for the maintenance trials. In this modified version, maintenance trials had the same type of probe (i.e., a letter–digit pair) as the manipulation trials (Fig. 1b). In this way, requirements to process order information were equivalent during both types of trials. This variation of the experiment was included to confirm that maintenance/manipulation differences that emerged from the first experiment were not due to discrepant requirements between the two conditions to retain order information.

Each experimental run in the scanner consisted of a block of 12 trials, 6 of each condition in a pseudo-random order, and each subject performed eight experimental runs, yielding a total of 96 trials. A total of 180 gradient-echo echoplanar images in time were obtained per slice in each 360-s run. Thus, a total of 1440 observations were obtained for each voxel in the brain for each subject.

Subjects viewed a backlit projection screen from within the magnet bore through a mirror mounted on the head coil. Stimulus presentation and response recording were handled by a Power Macintosh 7100/80 computer (Apple Computer, Cupertino, CA). These electronic devices have been demonstrated to add only white noise to echoplanar data collected at our site (Zarahn et al., 1997a).

Data analysis. Offline data processing was performed on SUN Ultra workstations using programs written in Interactive Data Language (Research Systems, Boulder, CO). After image reconstruction and prior to motion correction, the data were sinc interpolated in time to correct for the fMRI acquisition sequence. This step is of particular importance for our experiment because hemodynamic responses were to be compared across slices that were obtained at different points in the acquisition sequence (and therefore at different points in time). If left uncorrected, this would have introduced considerable variability and bias (a phase advance) into the hemodynamic responses. The data were then motion corrected a six parameter (three translational and three rotational), rigid-body, least squares realignment routine (part of the SPM96b package). The effect of this realignment procedure has been demonstrated (Friston et al., 1995a) to be very similar to that of another frequently employed registration technique, the Automated Image Registration (AIR) routine (Jiang et al., 1995; Woods et al., 1992). The ''spin-history'' correction advocated by Friston and colleagues (1996) was not applied (due to the long TR of 2 s, which attenuates T1 effects).

The details of the event-related fMRI analysis used in this study are presented elsewhere (Zarahn et al., 1997b). Briefly, the principle of the analysis was to model the fMRI signal changes occurring during particular temporal periods of the behavioral trials with covariates composed of shifted, BOLD impulse response functions (IRFs). An IRF is the fMRI response resulting from a brief pulse of neural activity (Boynton et al., 1996). Our method for deriving empirically an IRF is described below. This analysis technique allowed the testing of temporal relationships between BOLD fMRI signal and temporally separated behavioral subcomponents of trials (see Fig. 2).

Of particular interest in this study were changes in BOLD signal associated with the delay periods of the behavioral tasks. Increases in fMRI signal across the delay were tested with a covariate that modeled the expected BOLD signal response in the event of an increase in neural activity (relative to the intertrial interval) occurring in the delay period (Fig. 2B). In addition to this delay-targeted covariate, there were also covariates modeling the other behavioral subcomponents of each trial. These covariates were included because the rationale of this design is to model fMRI signal changes during all components of the trial other than the delay, leaving only signal variance that is attributable to the delay to be modeled by the delay-targeted covariate. Specifically, these covariates were the stimulus presentation, the instruction presentation, and the probe components of the behavioral trials (Fig. 2). Thus, the combination of these other covariates with the delay-targeted covariate made the delay-targeted covariate highly specific for functional changes during the delay. The temporal specificity for the delay period afforded by our design allowed us to examine the neural substrates of working memory

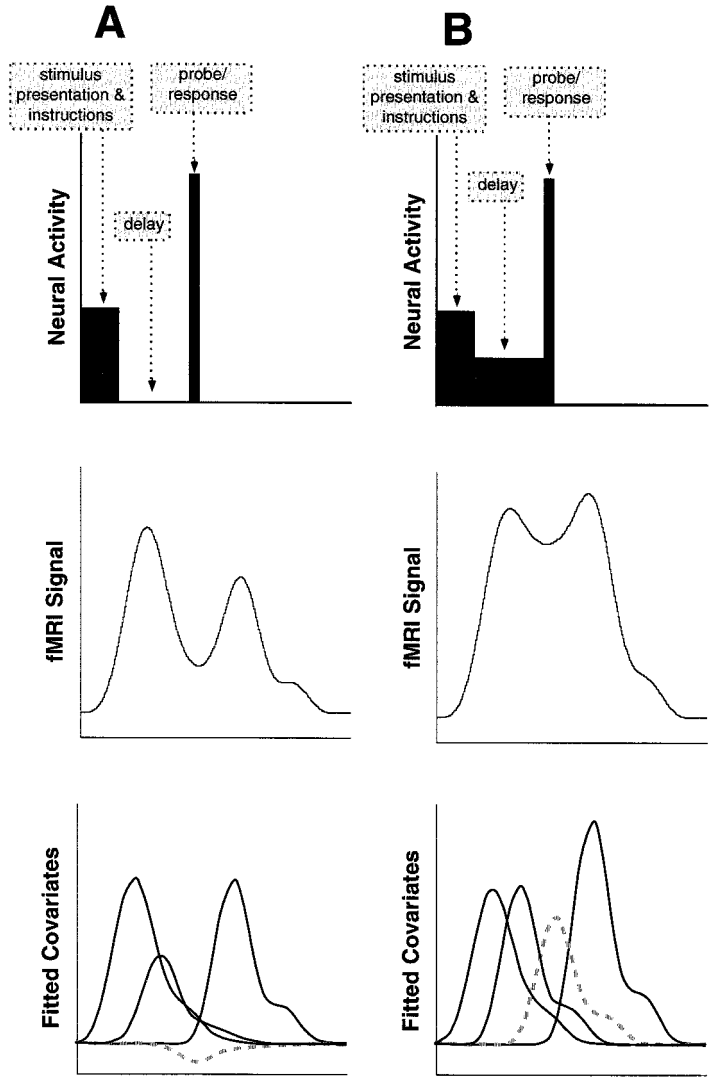

FIG. 2. Schematic illustration of the logic of the fMRI analysis. (A) A scenario in which there are only periods of neural activity (first row) associated with the stimulus presentation/ instruction and the probe/response periods of behavioral trials, with no increase above baseline during the bulk of the delay. Such neural activity change would lead to a particular profile of fMRI signal change (second row). Note that the peaks of fMRI signal are shifted in time with respect to the periods of neural activity they reflect as a result of the low pass filtering properties of the hemodynamic response. The model covariates (i.e., shifted impulse response functions), scaled by their resulting least squares coefficients, are shown in the third row (gray dotted line: covariates modeling the delay; black lines: covariates modeling the stimulus presentation, instructions, and the probe/response periods). It can be seen that the covariate modeling the delay would make no contribution to the explanation of variance in (A). In

without assuming pure insertion or linearity. For example, our interpretation of differences across conditions in delay-period activity could be made without regard for differences in neural activity between the two conditions in the cue, instruction, or probe periods of the trial, because the measure of fMRI signal during the delay period would be uncontaminated by fMRI signal changes resulting from these other portions of the trial (Zarahn et al., 1997b).

Because fMRI data are temporally autocorrelated under the null hypothesis (Aguirre et al., 1997; Zarahn et al., 1997a) the data analysis was conducted within the framework of the modified general linear model for serially correlated error terms proposed by Worsley and Friston (1995). Within the *K* matrix (Worsley and Friston, 1995) was placed a time-domain representation of the expected 1/f power structure (Zarahn et al., 1997a) and a filter that removes frequencies above 0.244 Hz. This filter was also applied to the fMRI time series and was intended to remove artifacts we observe in our data at and around the Nyquist frequency (0.25 Hz). It should be noted that the data were not smoothed temporally with a low pass filter, as advocated by Worsley and Friston (1995), because including a 1/f model adequately controls the false-positive rate (Zarahn et al., 1997a). Additionally, temporal smoothing would be undesirable with our technique because it would reduce the ability to detect signal changes during the delay.

Low frequency (sine and cosine) confounds up to 0.05 Hz (Friston et al., 1995b) and trial-effect covariates were included as covariates in our model, to account for frequency components and mean signal change, respectively, that were associated with each trial.

Relationships with the delay period were assessed by contrasts (yielding *t* statistics with 1135 *df*) involving the parameter estimates that corresponded to the independent variable that modeled the delay period (see Fig. 2). The mapwise corrected false-positive rate was controlled at $\alpha = 0.05$ by Bonferroni correction for the number of voxels per map (approximately 15,000 voxels; $t = 4.5$) or per region of interest (ROI; approximately 400 voxels; $t \sim 3.7$). For display purposes these thresholded maps and the T1 anatomical images were transformed to Talairach space by a 12-parameter affine transformation (Friston et al., 1995a), with nonlinear deformations (Ashburner & Friston, 1996).

We tested our hypothesis about the functional organization of working memory in discrete regions of PFC by creating two ROIs, one encompassing dorsolateral PFC (areas 9 and 46) and one encompassing ventrolateral PFC (areas 44, 45, and 47). These ROIs were created on the ''canonical'' T1 axial images from SPM96b that conform to the Talairach system (Talairach & Tournoux, 1988) and then transformed using the 12-parameter normalization routine in SPM96b to the native space of each subject's high-resolution T1 images. By defining our anatomical ROIs objectively, on a normalized brain, we restricted our hypothesis testing to volumes defined in a standard anatomical space and eliminated bias for an anatomical dissociation.

Derivation of an impulse response function. Our rationale for deriving an IRF for each subject is based on our empirical observation that there is significant variability in the evoked hemodynamic response across subjects (Aguirre et al., 1998). An IRF was derived from primary sensorimotor cortex in each subject in the following manner. Prior to performing the experimental task described above, each subject performed a simple reaction time task. During this task, a white fixation cross was constantly illuminated in the center of a black background. Every 16 s the cross would change briefly (500 ms) to a white circle, which would cue the subjects to make a bilateral button press. A total of 20 such button press events were presented

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contrast to (A), (B) depicts a situation in which there is some neural activity increase relative to baseline during the delay. In this case, it can be seen that the covariate modeling the delay would tend to explain a larger amount of variance in the fMRI signal than in (A). See Zarahn, Aguirre and D'Esposito (1997) for more details regarding this analysis method.

during the 320-s scan (160 images). Other than the scan length, all scanning parameters were identical to those used for the working memory experiment.

These data were analyzed by first defining the central sulcus from each subject's T1 images. The central sulcus was identified as the first medial–lateral sulcus posterior to, and not in contact with, the posterior extent of the superior frontal sulcus on the superior-most slices. The search volume included both the sulcus and the surrounding gray matter, yielding a total (left and right combined) search volume of ~500 voxels per subject. Activated voxels in this region were detected using a shifted impulse analysis which is described in detail in another paper (Aguirre et al., 1998). In brief, this analysis created an impulse basis set for the mean evoked response versus a ''baseline'' intertrial interval. A t map was generated for each subject for the reaction time task using the summed effect of the evoked response at 4 and 6 s following the onset of the target stimulus. Each region was then thresholded at a critical t value corresponding to a Bonferroni corrected $\alpha = 0.05$. These critical t values ranged from 3.6 to 3.8. Finally, IRF estimates were extracted from the suprathreshold voxels by filtering the corresponding fMRI time series to remove high (> 0.244 Hz) frequencies, adjusting them to remove the effects of nuisance covariates (Friston et al., 1995b), and trial averaging them.

RESULTS

Principal Experiment

Behavioral performance. The mean accuracy of performance (maintenance: 93.3%, *SD* 2.7; manipulation: 87.2%, *SD* 5.4; ($t(4) = 3.1$; $p < .05$)) and mean reaction times (maintenance: 886.8 ms, *SD* 149.2; manipulation: 1255.9 ms, *SD* 239.5; ($t(4) = 5.6$; $p < .005$)) for the five subjects participating in the principal experiment confirmed our subjective impression that the manipulation condition was more difficult than the maintenance condition. In postexperiment debriefing, each of the subjects reported only alphabetizing stimuli during the manipulation trials in which this operation was required (i.e., no subjects performed the alphabetization procedure on stimuli during maintenance trials).

Imaging data. Analysis of voxels that were suprathreshold for a contrast comprising a sum of coefficients of the delay period covariates of the maintenance condition *and* the manipulation condition revealed activity across a number of brain regions. In all seven subjects, delay-correlated activity was found in dorsolateral PFC, ventrolateral PFC, lateral premotor area, supplementary motor area, superior and inferior posterior parietal areas, and superior temporal areas. A representative subject who illustrates this distributed pattern of activation is presented in Fig. 3.

Analysis of activity in voxels displaying a positive suprathreshold relationship with the delay-period covariate from either individual condition was performed within the dorsolateral and ventrolateral PFC ROIs. In all five subjects, activity during the delay period was found in both dorsolateral and ventrolateral PFC in both types of trials. Representative axial slices through these areas of activation in all of the subjects are presented in Fig. 4. By visual inspection, it can be seen that the extent of activation is consistently greater in the manipulation condition. In order to confirm this qualitative

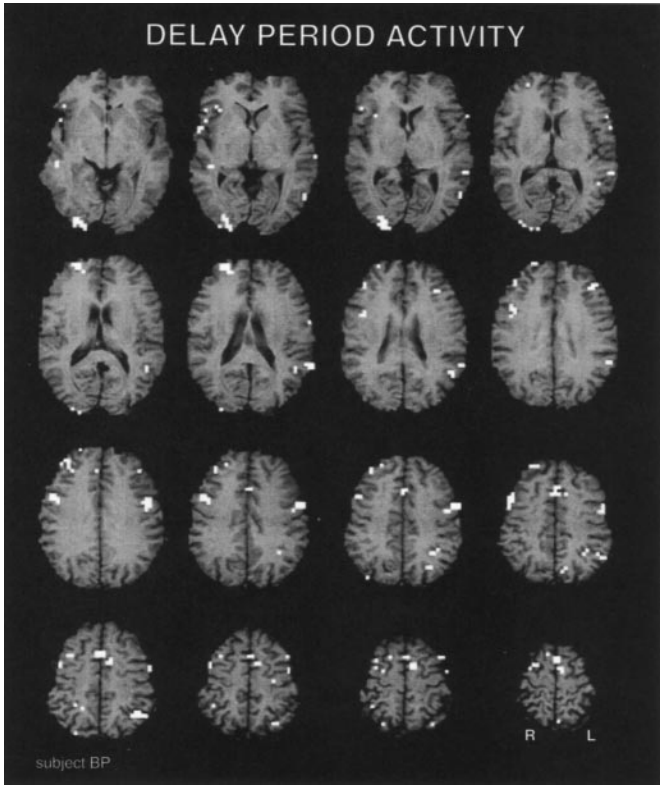

FIG. 3. Delay correlated activity, collapsed across maintenance and manipulation trials, across 16 axial brain slices in subject BP. The anatomical images presented in Figs. 3–5 display only the regions from which we obtained robust echoplanar signal. Our hypothesis testing was also restricted to these regions; thus, susceptibility artifact and signal dropout are not factors for consideration when assessing our data.

assessment, we performed a direct contrast of delay-period activity of the two conditions in each subject, and these analyses confirmed that there was greater dorsolateral PFC activity in manipulation trials: The direct contrasts of delay-period activity in the manipulation vs. the maintenance conditions yielded suprathreshold voxels in dorsolateral PFC in each of the five subjects, with three subjects revealing suprathreshold voxels in dorsolateral PFC alone. The single suprathreshold cluster in one of the remaining two subjects spanned the border of areas 46 and 45 (subject RS, Fig. 4). In the direct contrast, dorsolateral PFC was activated bilaterally in three of the subjects (subjects AK, WK, BP), unilaterally in the left hemisphere in one subject (subject RS), and unilaterally in the right hemisphere in the remaining subject (subject AW). Across the five subjects there were a total of 20 suprathreshold voxels identified in the direct contrast in the left hemisphere of

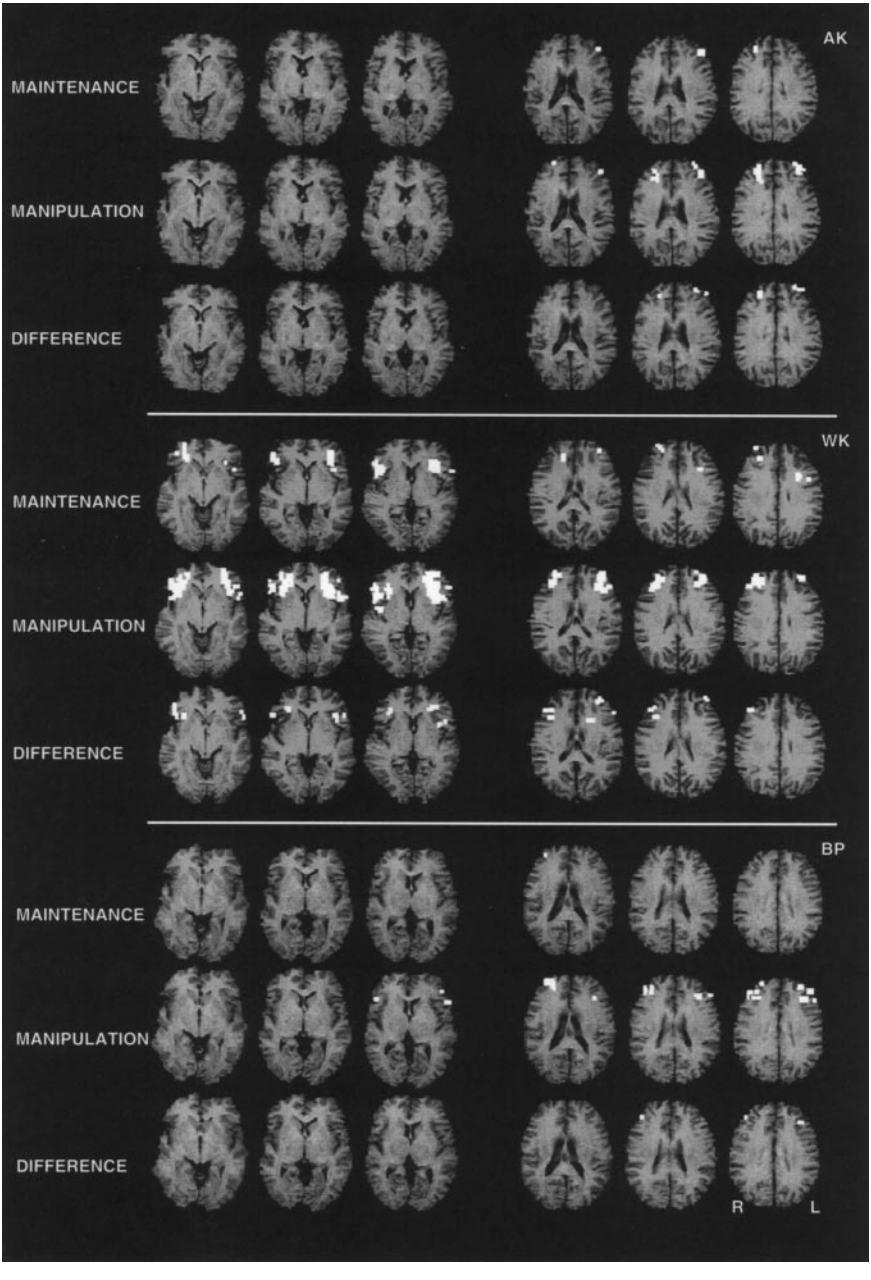

FIG. 4. Delay-correlated activity from three axial slices from the dorsolateral and the ventrolateral PFC ROIs in six subjects. The top row for each subject represents delay-period activity in *maintenance* trials compared to baseline; the middle row represents delay-period activity in *manipulation* trials compared to baseline; and the bottom row represents voxels in which delay-period activity was greater in the manipulation than the maintenance trials.

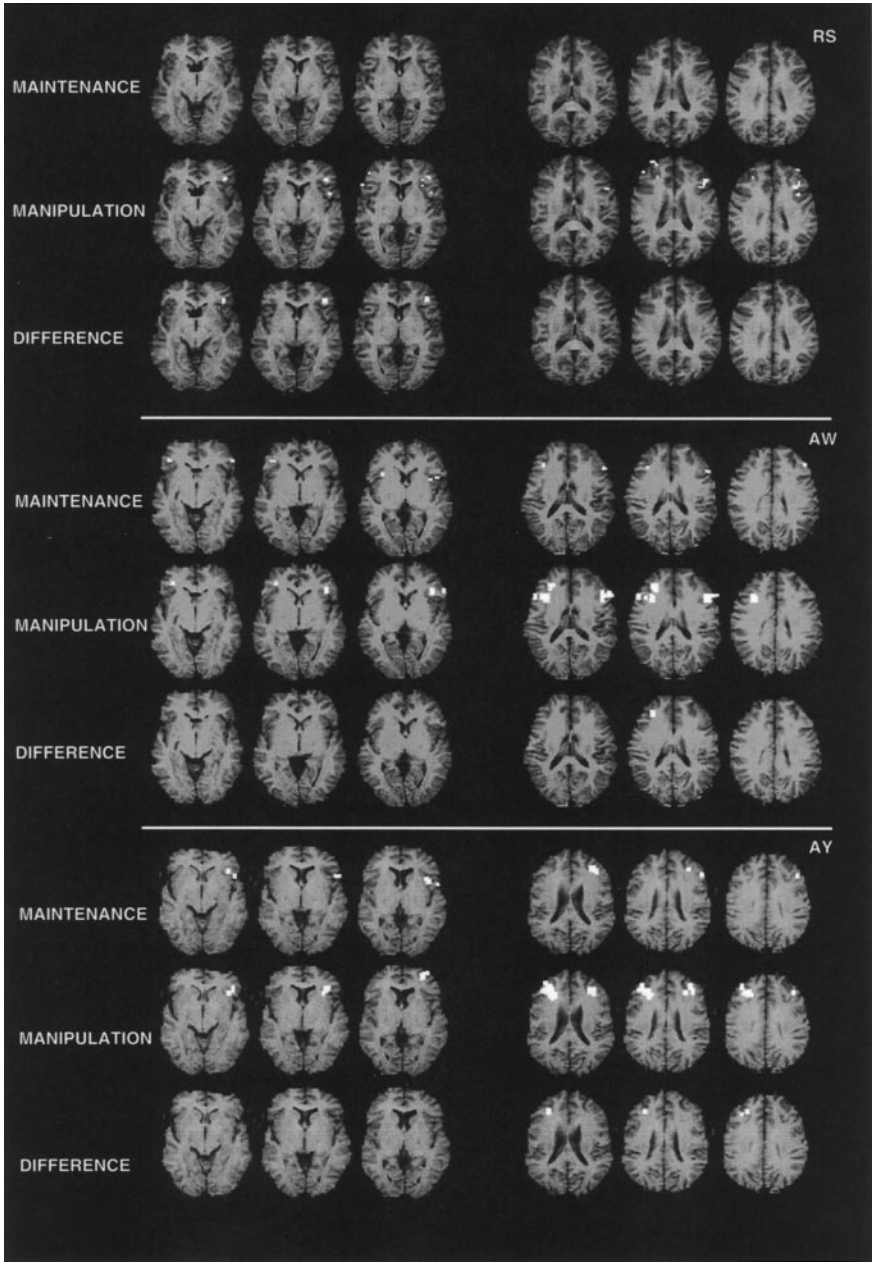

FIG. 4—*Continued*

TABLE 1
Suprathreshold Dorsolateral PFC Voxels from the Manipulation vs. Maintenance Contrast

Subject	Talairach coordinates			No. voxels/cluster	No. voxels		Mean *t*	
	x	*y*	*z*		Left	Right	Left	Right
Principal experiment								
AK	−50	35	15	4	10	3	4.15	4.15
	−56	49	15	1				
	23	44	28	3				
	−39	53	28	3				
	−30	56	27	2				
WK	36	27	21	1	1	9	4.13	4.23
	41	38	24	8				
	−38	38	34	1				
BP	19	49	18	2	5	4	4.74	4.02
	41	38	28	2				
	−40	30	32	3				
	−56	30	38	2				
RS[a]	−43	34	4	2	2	0	4.11	
AW	−40	53	10	2	2	2	3.73	3.79
	30	36	25	2				
Modified experiment								
DK	−41	41	35	1	0	1		3.78
AY	30	30	30	5	5	0	3.84	

[a] The *z* coordinate of the dorsal-most extension of this cluster is 10.

dorsolateral PFC (mean *t* value = 4.18) and 18 suprathreshold voxels in the right hemisphere of dorsolateral PFC (mean *t* value = 4.05). No PFC voxels demonstrated significantly greater activity in maintenance vs. manipulation delay-period activity. The Talairach coordinates of these suprathreshold voxels for each subject are presented in Table 1. The mean Talairach coordinates across subjects for the left PFC ROI were −45, 40, and 19 and for the right PFC ROI were 30, 39, and 25. Both of these mean loci of activation fall within the ''conservative'' boundary of Brodmann's area 46 as defined by Rajkowska and Goldman-Rakic (Rajkowska and Goldman-Rakic, 1995).

Examples of trial-averaged signal from voxels in dorsolateral PFC that demonstrated significantly greater activation in the maintenance condition are shown in Fig. 5. In both trial types, there was an fMRI signal greater than baseline throughout the period of time corresponding to the delay period (taking into account the delay and dispersion of the fMRI signal (Aguirre et al., 1998)). However, during the manipulation trials there was greater delay-period activity than during the maintenance trials. This delay-period behavior was observed in all voxels that were detected in the direct contrast

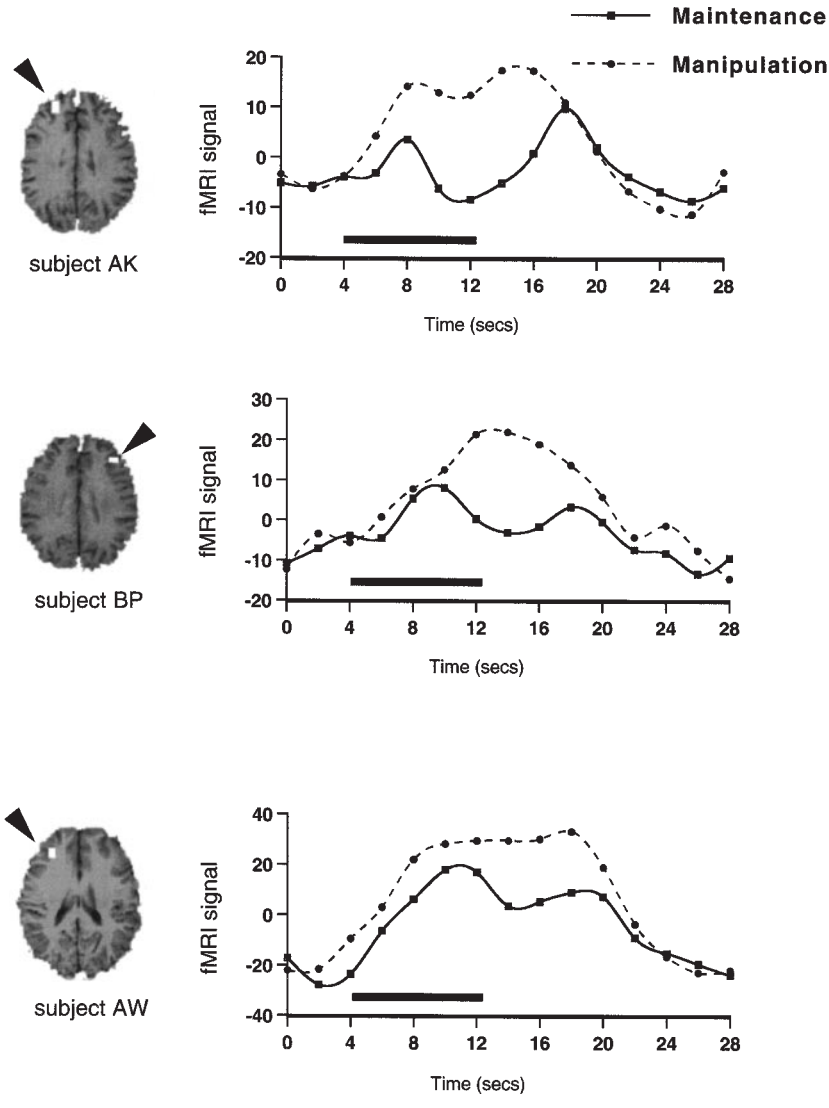

FIG. 5. Trial averaged time series from voxels that were significant in the manipulation–maintenance direct contrast in three representative subjects. In each subject note the two peaks in the maintenance condition corresponding to the stimulus presentation and the probe periods of the trial. In the manipulation condition, in contrast, the voxel displayed maintained a high level of activity throughout the delay period. The solid bar represents the duration of the delay period.

of maintenance vs. manipulation delay-period activity. The trial-averaged signal of many of the voxels detected in the maintenance vs. manipulation contrast indicated that many of these dorsolateral PFC voxels also demonstrated responses associated with the presentation of the cue/instructions and with the motor response that accompanied the probe (Fig. 5).

Modified Experiment

Because the manipulation condition in the principal experiment explicitly required subjects to compute and store order information during the delay period, but there was no comparable component in the maintenance condition, it was possible that the difference in delay-period activation that we observed in this experiment arose from the differential demands of the two conditions on maintaining the order of items held in working memory, rather than on the difference in processing demands, as articulated in our hypothesis. For this reason we tested two additional subjects on the modification of this task in which a necessity to retain serial order of stimuli was added to the maintenance condition, but the two conditions still differed in the amount of manipulation required by each.

Behavioral performance. The performance of the two subjects who performed the modified version of the experiment, as assessed by mean accuracy (maintenance: 90.6%, *SD* 7.3; manipulation: 80.3%, *SD* 16.2) and mean reaction time (maintenance: 1211.0 ms, *SD* 226.3; manipulation: 1207.3 ms, *SD* 176.4) was similar to that of the subjects who performed the principal experiment, with the exception that RTs were slower in the modified forward condition. In postexperiment debriefing, both of the subjects reported only alphabetizing stimuli during the manipulation trials in which this operation was required.

Imaging data. As in the principal experiment, analysis of delay-period activity combined across both conditions revealed activity distributed across frontal, parietal, and temporal cortex; similarly, the data revealed voxels demonstrating a suprathreshold relationship with the delay-period covariates from either individual condition within both the dorsolateral and the ventrolateral PFC ROIs. Representative axial slices through these areas of activation in one of the two subjects (subject AY) are presented in Fig. 4. Also, consistent with the results of the principal experiment, direct contrasts of delay-period activity of the two conditions indicated that there was greater dorsolateral PFC activity in manipulation trials: The contrasts revealed maintenance $>$ manipulation suprathreshold voxels in dorsolateral PFC in both subjects and in ventrolateral PFC in one subject (Table 1). Importantly, no PFC voxels demonstrated significantly greater activation during maintenance delays than during manipulation delays. This result was consistent with the processing hypothesis and inconsistent with the alternative ''order'' hypothesis that we tested with the modified experiment. The dorsolateral PFC activation identified by the manipulation vs. maintenance contrasts was located

unilaterally in the left hemisphere in one subject and unilaterally in the right hemisphere in the other. The Talairach coordinates of these suprathreshold voxels are presented in Table 1.

DISCUSSION

We have previously presented two lines of evidence that are inconsistent with the hypothesis that human PFC is organized into functionally distinct dorsal and ventral regions corresponding to the type of stimulus material held in working memory. First, an analysis of the locations of activation within PFC of all previously reported functional neuroimaging studies of spatial and nonspatial working memory did not reveal this pattern (D'Esposito et al., 1998). Second, empirical fMRI studies of performance of spatial and nonspatial working memory tasks by the same subjects revealed activation in similar regions within PFC in the two conditions (D'Esposito et al., 1998; Postle & D'Esposito, in press). The purpose of the present study was to test directly another organizational principle that may better characterize the functional anatomy of human lateral PFC. Specifically, we tested whether a dorsal/ventral PFC organization exists according to the type of processing performed upon information being held in working memory.

In every subject, increased activity during the delay period of the delayed-response task was found in both dorsolateral (Brodmann's areas 9, 46) and ventrolateral (areas 44, 45, 47) regions of PFC on trials that simply required retention of information across a delay interval (maintenance trials), as well as on trials that also required transposition of information held in working memory (manipulation trials). Further, and consistent with our hypothesis, dorsolateral PFC exhibited significantly greater activity in the manipulation condition in each of the seven subjects participating in this experiment, whereas only three subjects exhibited greater ventrolateral PFC activity. There were no voxels identified in any subject that demonstrated greater delay-period activity in the maintenance versus the manipulation condition. These findings suggest that dorsolateral PFC may exhibit greater recruitment during behavioral conditions that require transformation of the information held in working memory. Thus, we propose that dorsolateral PFC may subserve an additional and distinctly different function than ventrolateral PFC. This interpretation of our data is consistent with the model of the organization of memory function supported by PFC proposed by Petrides (1989).

In five subjects, the probe of the maintenance trials was a single letter, and subjects judged whether the probe was from the target set. In the manipulation trials, the probe was a single letter *and* a number, and subjects judged whether the letter was in the ordinal position of the number, after the items in the memory set had been alphabetized. Even though subjects were instructed to rehearse the forward order of the letters in the maintenance trials, the possibility exists that this difference in response requirements may have created differences in the type of information that was maintained across the

delay period in addition to the type of processing performed on the information. That is, our design may have confounded the storage of order information, necessary on the ''alphabetize'' trials, but not on the ''forward'' trials, with manipulation demands. To test this alternative hypothesis, two additional subjects were studied with a modified version of our task in which the maintenance and manipulation trials were probed in an identical fashion. Even under these conditions, subjects exhibited greater dorsolateral PFC activation during the manipulation condition. This finding further strengthens our interpretation of our data, that dorsolateral PFC is recruited to a greater extent under conditions that require transformations of maintained information.

Another possible confound in our interpretation of these data is that the manipulation condition was more difficult than the maintenance condition. Thus, the increase in activation in dorsolateral PFC that we observed during manipulation trials may have simply reflected an increase in difficulty (i.e., mental effort) of the task, rather than a functionally specific change in neural activity associated with the changed information processing demands of the task. We believe that we can discount this alternative explanation of our results for several reasons. First, our data do not demonstrate a consistent, general, nonspecific increase in activity in response to increased difficulty, because consistent increases in ventrolateral PFC were not observed in the manipulation condition. Second, data from a subsequent study that serves as a replication of the results presented here indicate that the maintenance effect manifests itself in dorsolateral PFC even when performance indicates that the subject found the maintenance condition more difficult than the manipulation condition (D'Esposito & Postle, 1998). Finally, data from another laboratory found that activity in dorsolateral PFC (i.e., middle frontal gyrus), although sensitive to manipulation of working memory demands, is not sensitive to manipulations of task difficulty (Barch et al., 1997), suggesting that dorsolateral PFC is not a brain region that responds selectively to nonspecific mental effort.

Several other functional neuroimaging studies have presented data consistent with our empirical findings. Owen, Petrides, and colleagues found, in a PET study, dorsolateral PFC activation during three spatial working memory tasks thought to require greater monitoring of remembered information than two other memory tasks, which activated only ventrolateral PFC (Owen et al., 1996). A recent PET study by another group (Salmon et al., 1996) compared a running memory task, thought to require updating of the contents in working memory, versus a letter span task which did not require such a process. When these tasks were compared directly, greater activation in the running memory task was found in right dorsolateral PFC (area 9) and to a lesser extent in left dorsolateral PFC. The letter span task activated only ventrolateral PFC. Another recent PET study (Klingberg et al., 1997) that compared a simple delayed matching to sample task to a more complex ''alternating'' delayed matching to sample task (that imposed more contingen-

cies and featured more complex instructions) found that only the latter task activated the right dorsolateral PFC but that both tasks activated ventrolateral PFC. In a preliminary PET study (Berman et al., 1996) that varied the amount of material remembered versus the number of manipulations performed on the material, only the latter condition correlated with increased blood flow in dorsolateral PFC. Taken together, these studies provide strong support for the processing model of a distinction between working memory function of dorsolateral and ventrolateral PFC in humans.

Each of the PET studies reviewed in the preceding paragraph used a cognitive subtraction methodology. An important contribution of our study was the use of an event-related fMRI method. This allowed us to examine neural activity during the task component of interest, the delay period, uncontaminated by other components such as the presentation of the cue, instructions, or the preparation for and execution of the motor response. Our data indicate that many PFC voxels also showed significantly increased activity during nondelay components of the task (not reported). This observation is entirely consistent with single-unit recording studies in monkeys performing delayed response tasks that have also observed PFC neurons that are active during nondelay portions of the task. For example, although Funahashi and colleagues (1989) identified delay-specific neurons as the most commonly observed in PFC (28%), other types were identified frequently (e.g., 24% of PFC neurons responded only to the motor response). Therefore, in attempting to determine regional differences in PFC activation, averaging fMRI signal across all components of the task (the conventional method in blocked, averaged neuroimaging studies) could have created confounds that may have interfered with our interpretation of the results.

Given our proposal that dorsolateral PFC is critical for manipulating information held in working memory, an explanation as to why we observed dorsolateral PFC activation in the maintenance trials should be offered. We have observed in several different types of delayed-response tasks that delay-period activity is widely distributed throughout the brain, as well as within dorsolateral PFC (e.g., Ballard et al., 1998; D'Esposito et al., 1999; Postle & D'Esposito, in press; Rypma & D'Esposito, 1999; Zarahn et al., 1999). One explanation is that dorsolateral PFC is recruited during both maintenance and manipulation processes, whereas ventrolateral PFC is engaged only during maintenance processes. Alternatively, it is possible that during behavioral conditions in which the demands of maintenance processes exceed the capacity of short-term memory (which may be the case in our task), manipulation processes may be engaged. Behavioral evidence exists that additional processes may be engaged when short-term memory capacity is exceeded. For example, there is no decrement in performance on the comprehension of prose passages during the simultaneous holding of three letters in memory but a decrement is found while holding six letters (Baddeley & Hitch, 1974). Recent studies in our laboratory do not support this view, however, because

they fail to find delay-period load effects in dorsolateral PFC (D'Esposito & Postle, 1998; Rypma & D'Esposito, 1999).

A common finding across the studies mentioned above, and present in our review of the literature (D'Esposito et al., 1998), is that activation within dorsolateral PFC during tasks requiring manipulation tends to be bilateral or lateralized to the right hemisphere regardless of whether spatial or nonspatial stimuli were used. Our present study did not find a strong right hemisphere lateralization during the manipulation condition. Our literature review (D' Esposito et al., 1998) also suggested that activation within ventrolateral PFC during tasks that required only maintenance of different types of information (i.e., spatial versus nonspatial) across a delay tended to be lateralized. We observed that when ventrolateral PFC is activated, there was greater activation in the right hemisphere during spatial tasks and greater left hemisphere activation during nonspatial tasks. If this finding holds after empirical testing, coupled with the findings of the present study, it would suggest that *working memory* in human PFC is organized by processing requirements in a dorsal/ventral fashion and organized by information type in a hemispheric fashion. If working memory in lateral PFC is organized as we propose, it will also be important to determine if it is organized hierarchically, with information passing from ventrolateral to dorsolateral PFC, as proposed by Petrides and colleagues (Owen et al., 1996; Petrides, 1996). If a hierarchical organization does exist, we would expect those tasks that require manipulation to recruit circuits in ventrolateral as well as dorsolateral PFC. This was the finding in our study.

A challenge for the further development of the hypothesis that human lateral PFC is organized by processing requirements of working memory tasks is specifying with more precision the psychological processes that differ between tasks that activate dorsolateral versus ventrolateral PFC. Certainly, there are many possible component processes that were present during our manipulation trials that may have contributed to dorsolateral PFC activation. For example, alphabetizing a string of letters may include component processes such as (i) activation of long-term memory representations (i.e., the order of the alphabet), (ii) strategic reordering of the currently active representations, (iii) maintenance of temporal order information, and (iv) inhibition of the original order of the letter string. The simultaneous recruitment of each of the processes that may comprise what we have called ''manipulation'' may bear resemblance to processes that have been called ''executive'' processes (reviewed in Kimberg et al., 1998). Further research will be necessary to determine if these behaviorally dissociable processes are also subserved by distinct regions of the PFC. On a gross level, our data support the idea that working memory is not a unitary system, as proposed by Baddeley (1992). However, our data cannot determine whether an ''executive'' exists within PFC. We have simply found that one type of process preferentially engages a different region of PFC than another.

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