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Activity in Ventrolateral and Mid-Dorsolateral Prefrontal Cortex during Nonspatial Visual Working Memory Processing: Evidence from Functional Magnetic Resonance Imaging

Chantal E. Stern,*,† Adrian M. Owen,‡ Irene Tracey,*,§ Rodney B. Look,*
Bruce R. Rosen,* and Michael Petrides¶

**Massachusetts General Hospital–NMR Center, Building 149, 13th Street, Charlestown, Massachusetts 02129; †Cognitive Neuroimaging Laboratory, Department of Psychology, Boston University, 64 Cummington Street, Boston, Massachusetts 02215; ‡MRC Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 2EF, United Kingdom; §Centre for Functional MRI of the Brain, Clinical Neurology Department, Oxford University, John Radcliffe Hospital, Headington OX3 9DU, United Kingdom; and ¶Cognitive Neuroscience Laboratory, Montreal Neurological Institute, McGill University, 3801, University Street, Montreal, Quebec H3A 2B4, Canada*

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Whole-brain functional magnetic resonance imaging was used to study five healthy human subjects while they performed two nonspatial visual working memory tasks and one control task. In the first memory task, the subjects were required to view a sequence of three pattern stimuli, randomly selected from a familiar set of four stimuli, and then identify which one of three simultaneously presented stimuli was the one that had not been presented in the previous array. In the other task, the subjects were required to observe an identical sequence of three randomly selected pattern stimuli and then to respond by selecting those same stimuli in the order presented. In comparison to a baseline control task, increases in signal intensity were observed, bilaterally, in the mid-dorsolateral frontal cortex and in the right ventrolateral frontal cortex in both memory tasks. When the two tasks were compared directly, however, the first memory task, which had the higher monitoring requirement, yielded significantly greater signal intensity changes in area 9/46 of the right mid-dorsolateral frontal cortex. These results provide further evidence for the precise functional contribution made by the mid-dorsolateral frontal cortex in visual working memory tasks and concur closely with findings in nonhuman primates.

INTRODUCTION

Several recent functional neuroimaging studies have provided evidence to support a two-stage model of working memory processing within the lateral frontal cortex (Owen *et al.*, 1996, 1998; Owen, 1997; Petrides *et al.*, 1993a,b, 1995). According to that model, the mid-dorsolateral frontal cortex (areas 46 and 9/46) will be recruited in both spatial and nonspatial working memory tasks, but only when active manipulation or monitoring of information is required (Petrides, 1994). In contrast, the ventrolateral frontal region is concerned principally with the selection of actions and the organization of responses based on active retrieval of information from posterior association systems. In earlier studies, it was demonstrated that either, or both, of these two lateral prefrontal regions can be activated in verbal (Petrides *et al.*, 1995) or in visual spatial (Owen *et al.*, 1996) memory tasks, depending on the precise executive processes that are called upon by the task that is being performed. In the present study, we used two memory tasks involving identical abstract visual patterns to show that, when nonspatial stimuli are used, activity in these two lateral frontal regions also depends on the precise executive processes that are called upon.

In the present experiment, we adapted a nonspatial visual working memory task that was shown to be extremely sensitive to the effects of lesions to the mid-dorsolateral part of the prefrontal cortex in the monkey (Petrides, 1995). On all trials of this task, a subset of stimuli drawn randomly from the same highly familiar set of a few stimuli is first presented. On the subsequent test phase of each trial, the subject is shown a display containing stimuli that had just been presented together with the one stimulus that had not been presented on that particular trial. Since, on each trial, the subset of stimuli presented and the one that is left out are randomly drawn from the same highly familiar set, correct performance depends critically on careful monitoring of the occurrence/nonoccurrence of stimuli from the known set. The experiments with monkeys have shown that this monitoring requirement, that is, the necessity to consider both the pre-

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sented and the nonpresented stimuli for success in a particular trial, is the critical variable giving rise to an impairment after mid-dorsolateral prefrontal lesions (Petrides, 1995). The same monkeys could perform normally in several other memory tasks which involved identical stimuli, but in which the correct response did not require the consideration of both presented and nonpresented stimuli for successful performance (Petrides, 1995).

In the version of the above task adapted for use in the present functional neuroimaging study, referred to as Pattern Working Memory Task I, the subjects were first shown in sequence three stimuli that were drawn randomly from the same set of four familiar stimuli. During the subsequent test phase, the subjects saw simultaneously two of the three stimuli that had just been presented together with the one stimulus from the original set of four that had not been shown and had to choose the latter stimulus. It is important to point out that the stimuli were constantly drawn from the same set of four familiar stimuli. The decision to select, on the test phase of a given trial, the stimulus that had not been presented on the immediately preceding sequence demands careful monitoring of the occurrence/nonoccurrence of stimuli from the target set. In other words, the demands of the task would be the same whether a presented or a nonpresented stimulus was to be chosen by the subject. In the present study, the subject was required to select the stimulus not shown on the immediately preceding presentation sequence in order to keep the decision identical to that used in the monkey experiments.

In Pattern Working Memory Task II, the subjects were again shown three stimuli in sequence drawn randomly from the familiar set of four stimuli, and, during the subsequent test phase, the same three stimuli were presented simultaneously and the subject was required to select these designs in the remembered order. Both of these working memory tasks would be expected to recruit executive processes, such as active retrieval, assumed to depend on the ventrolateral prefrontal region, and monitoring, assumed to depend on the mid-dorsolateral frontal region, but to a different extent. As in the monkey task described above (Petrides, 1995), the fMRI Pattern Working Memory Task I required that the subject make a decision based on a careful monitoring of which stimuli from the familiar set had just been presented and which had not. In Pattern Working Memory Task II, which is essentially a span task, this monitoring requirement would be relatively reduced, because performance could be based, to a large extent, on the exact replay of the stored information.

The control task was selected to make minimal demands on the executive processes that are assumed to be subserved by both the mid-dorsolateral and the ventrolateral frontal regions. The subjects were shown the same stimulus three times and, during the test phase, three copies of this design were simultaneously presented. The subject was required to respond to the middle one. By comparing either of the memory tasks with the control task, we expected to observe activity in both the dorsolateral and the ventrolateral prefrontal regions, since relative to that task, they both involve the presumed executive functions of these regions. Furthermore, by comparing the two memory tasks directly we expected to observe greater activity in the dorsolateral frontal cortex in Pattern Working Memory Task I, which had greater monitoring requirements as described above.

METHODS

Scanning Methods and Data Analysis

Five young, normal subjects (three men, two women) were studied using fMRI (Kwong *et al.*, 1992; Ogawa *et al.*, 1992; Belliveau *et al.*, 1992). All studies were carried out at the MGH–NMR Center. MR imaging was performed using a high-speed 1.5-T scanner (General Electric Sigma scanner; Milwaukee, WI; modified by Advanced NMR, Wilmington, MA). Twenty 7-mm-thick contiguous slices were positioned with 3×3-mm in-plane resolution coronally from the frontal pole to the occipital lobe. A series of high-resolution, T1-weighted images was taken for anatomically defining the high-speed functional images. A receive-only radiofrequency quadrature head volume coil, an automatic shimming technique (Reese *et al.*, 1995), and an asymmetric spin-echo imaging sequence were used (TR = 2500, TE = 50). The data for each subject were concatenated to produce one continuous data set (comprising three separate runs). Task-induced changes in fMRI signal intensity were assessed using the Kolmogorov–Smirnov statistic (Stuart and Ord, 1991). This analysis was performed using the following procedure: All slices and time points were reconstructed using unfiltered Fourier transforms from complete *k*-space data to form a volumetric time series magnitude image data set. Each successive time point in the volumetric time series was registered to the first time point to compensate for slow motion of the subject's head that occurred during a scan (Jiang *et al.*, 1995). Every magnitude image in the time series was spatially filtered using a 2-D Hamming window resulting in a voxel size of $6.25 \times 6.25 \times 7.0$ mm (FWHM). Each voxel location was treated independently to estimate the empirical cumulative distribution functions during the control and the experimental states. The point(s) of maximal difference between the two estimated distribution functions, i.e., the Kolmogorov–Smirnov statistic, was computed for each voxel and the probability that this maximal difference could have occurred due to chance for each voxel was assembled into a volumetric proba-

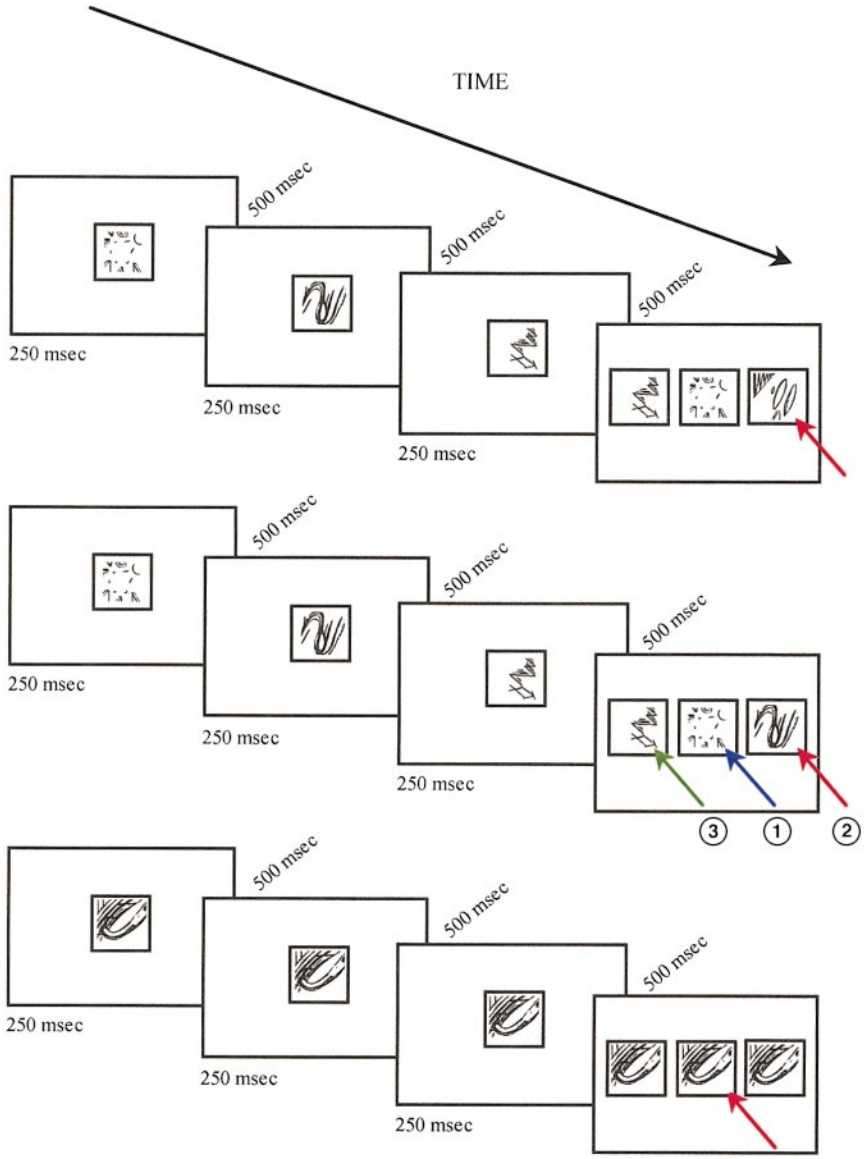
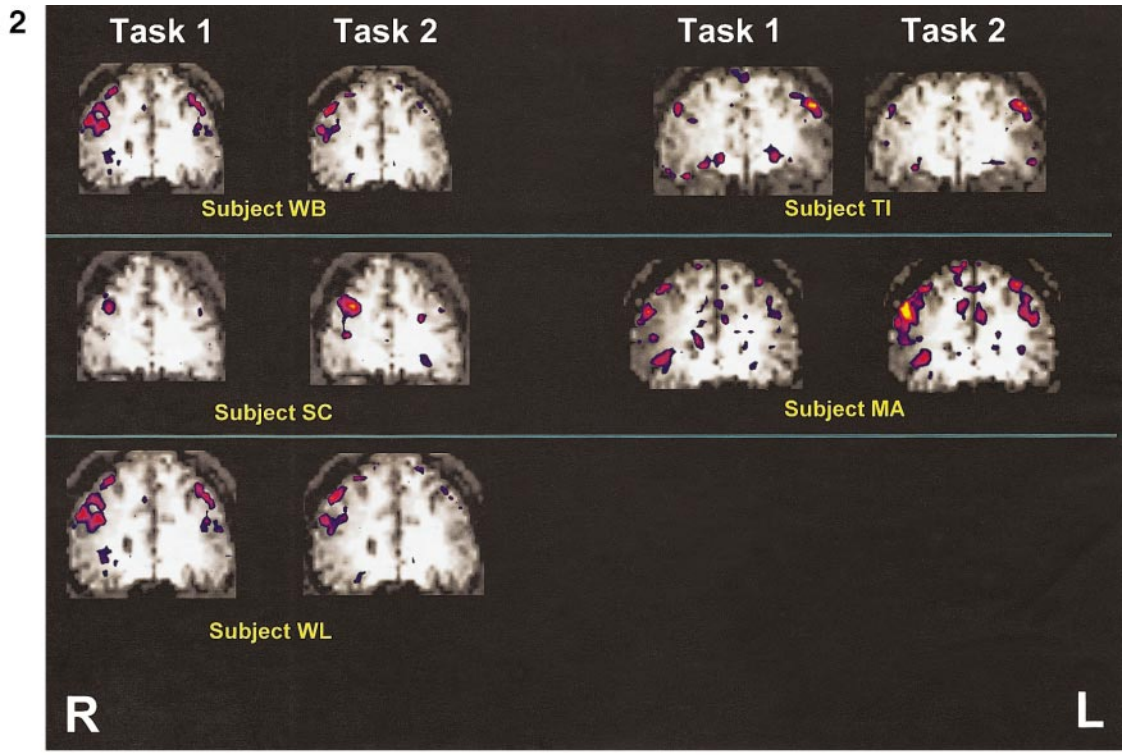


FIG. 1. Top: Pattern Working Memory Task I. The subject responds to the missing stimulus (arrow). Middle: Pattern Working Memory Task II. The subject responds to the stimuli in the order they were presented (first, second, and third responses are labeled 1, 2, and 3) Bottom: The visuomotor control task.

bility map. The probability map was then merged with anatomical images of the same location. For each subject, functional and anatomical images were then resampled into a standardized stereotaxic coordinate system (Talairach and Tournoux, 1988), and the coordinates of statistically significant mean fMRI signal changes throughout the brain volume were identified by an automatic peak detection algorithm.

Experimental Procedure

The study comprised two pattern working memory tasks and one control condition. The locations of the presented stimuli were randomized from trial to trial to ensure that performance could be based only on memory for the designs presented. During all scans, the visual stimuli were projected, via a computer and back-projection television system, to a screen viewed through an overhead mirror. Subjects were requested to fixate on a central marker which, by periodically changing from a − to a +, served to cue their responses during all of the tasks. Subjects responded by pressing one of three buttons which corresponded to the left, middle, and right locations. Prior to entering the scanner, all subjects received extensive training in this procedure.



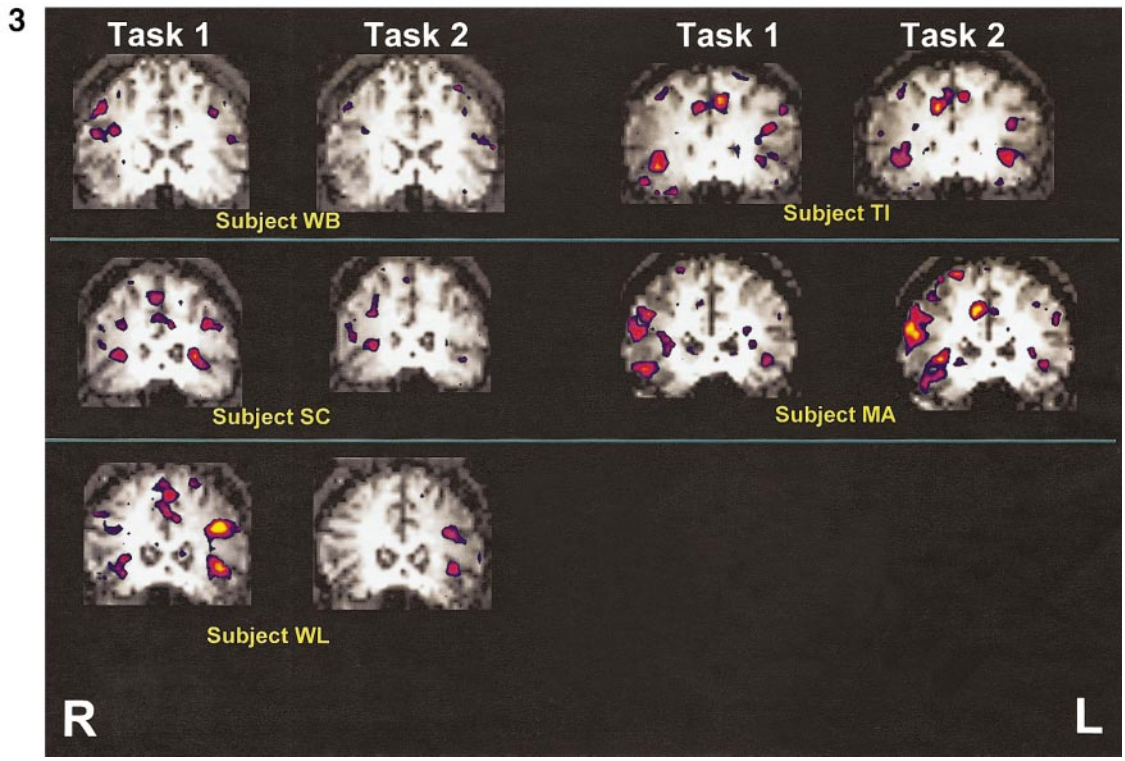


FIG. 2. fMRI signal increases in the mid-dorsolateral frontal cortex and midventrolateral frontal cortex for each of the five subjects during Pattern Working Memory Task I (Task 1) and Pattern Working Memory Task II (Task 2) compared with the visuomotor control task. Blue represents a significance level of $P < 0.01$ and yellow a level of $P < 2 \times 10^{-9}$. The left hemisphere appears on the right of each image. Regions showing statistically significant differences between conditions were localized anatomically by visually inspecting the functional and high-resolution anatomical images for each subject. In particular, the mid-dorsolateral frontal region was identified in each individual by locating the superior frontal sulcus and the inferior frontal sulcus.

FIG. 3. Images shown are posterior to the ones presented in Fig. 2. fMRI signal increases are shown for each of the five subjects during Pattern Working Memory Task I (Task 1) and Pattern Working Memory Task II (Task 2) compared with the visuomotor control task. Blue represents a significance level of $P < 0.01$ and yellow a level of $P < 2 \times 10^{-9}$. The left hemisphere appears on the right of each image.

TABLE 1

Stereotaxic Coordinates of Maximal Mean fMRI Signal Increases during Pattern Working Memory Task I (Monitor for the Missing Stimulus) Relative to the Visuomotor Control Task

x	*y*	*z*	*P*	Brodmann area
			Left hemisphere	
−34	48	21	0.0013	Mid-dorsolateral frontal cortex (area 46)
−43	27	31	0.00077	Mid-dorsolateral frontal cortex (area 9/46)
−3	9	50	0.00012	Supplementary motor area (medial area 6)
−21	−15	46	0.00026	Supplementary motor area (medial area 6)
−37	−39	−18	0.0025	Ventral occipitotemporal cortex (area 37)
−50	−45	−15	0.00012	Ventral occipitotemporal cortex (area 37)
−37	48	31	0.00033	Posterior parietal cortex (area 40)
			Right hemisphere	
40	51	15	0.00052	Mid-dorsolateral frontal cortex (area 46)
40	27	31	0.0017	Mid-dorsolateral frontal cortex (area 9/46)
37	30	9	0.0019	Ventrolateral frontal cortex (area 45)
43	12	15	0.00052	Ventrolateral frontal cortex (area 44)
40	15	46	0.00063	Premotor cortex (area 8)
37	6	25	0.00097	Premotor cortex (area 6)
37	0	43	0.00043	Premotor cortex (area 6)
15	0	65	0.00089	Premotor cortex (area 6)
28	−39	−21	0.00094	Ventral occipitotemporal cortex (area 37)
43	−45	−21	0.0013	Ventral occipitotemporal cortex (area 37)
37	−45	−12	0.0015	Ventral occipitotemporal cortex (area 37)
34	−45	43	0.00079	Posterior parietal cortex (area 40/7)
28	−63	40	0.00092	Posterior parietal cortex (area 7)

Note. The stereotaxic coordinates are expressed in millimeters and are based on the system used in the brain atlas of Talairach and Tournoux (1988). *x*, medial-to-lateral distance relative to the midline (positive = right hemisphere); *y*, anterior-to-posterior distance relative to the anterior commissure (positive = anterior); *z*, superior-to-inferior distance relative to the anterior commissure–posterior commissure line (positive = superior). Significance level (*P*) is given as uncorrected probability.

Pattern Working Memory Task I

In this task, three of a possible set of four abstract patterns that had been made familiar to the subject prior to scanning were presented in the center of the screen for 250 ms each and at 500-ms intervals (see Fig. 1). Thus, on each trial, three of four possible patterns were selected randomly and presented sequentially by the computer. Following a 500-ms delay, the three patterns were presented simultaneously on the screen, randomly positioned in three central boxes (Fig. 1). Of these three patterns, two were randomly selected from the sequence of three that had just been presented, while the third was the remaining (i.e., missing) pattern from the original set of four. Subjects responded by pressing the button corresponding to this missing pattern, that is, the one pattern that had not been presented earlier in that trial. Following a response, the next trial began with a new sequence of three randomly selected patterns from the same set of four. It should be noted that following each response, there was a variable intertrial interval which ensured that every trial was 4 s long. Therefore, in total there were 16 4-s trials in each epoch and the number of responses was kept constant across subjects and epochs.

TABLE 2

Stereotaxic Coordinates of Maximal Mean fMRI Signal Increases during Pattern Working Memory Task II (Respond to the Stimuli in Order) Relative to the Visuomotor Control Task

x	*y*	*z*	*P*	Brodmann area
			Left hemisphere	
−34	32	28	0.00036	Mid-dorsolateral frontal cortex (area 9/46)
−6	12	46	0.0014	Supplementary motor area (medial area 6)
−37	27	6	0.0081	Ventrolateral frontal cortex (area 45)
−34	9	34	0.0025	Ventrolateral frontal cortex (area 44)
−28	−3	56	0.00079	Premotor cortex (area 6)
−46	−27	−21	0.0016	Inferior temporal cortex (area 20/21)
−53	−45	−18	0.00031	Ventral occipitotemporal cortex (area 37)
−31	−36	59	0.0024	Posterior parietal cortex (area 7)
−40	−36	37	0.0024	Posterior parietal cortex (area 40/7)
			Right hemisphere	
46	27	31	0.00019	Mid-dorsolateral frontal cortex (area 9/46)
31	22	9	0.0011	Ventrolateral frontal cortex (area 45/47)
46	9	34	0.0014	Ventrolateral frontal cortex (area 44)
43	9	15	0.00078	Ventrolateral frontal cortex (area 44)
3	12	40	0.0017	Supplementary motor area (medial area 6)
31	6	56	0.00011	Premotor cortex (area 6)
21	−33	−31	0.0045	Inferior temporal cortex (area 20)
37	−45	−31	0.0062	Cerebellum
28	−51	40	0.00093	Posterior parietal cortex (area 7)

Note. See footnote to Table 1.

TABLE 3

Stereotaxic Coordinates of Maximal Mean fMRI Signal Increases during Pattern Working Memory Task I Compared with Pattern Working Memory Task II

x	*y*	*z*	*P*	Brodmann area
			Left hemisphere	
−6	12	46	0.0024	Supplementary motor area (medial area 6)
−6	0	50	0.002	Supplementary motor area (medial area 6)
−12	−18	68	0.00068	Supplementary motor area (medial area 6)
			Right hemisphere	
46	30	31	0.00037	Mid-dorsolateral frontal cortex (area 9/46)
31	6	56	0.000075	Premotor cortex (area 6)

Note. See footnote to Table 1.

Pattern Working Memory Task II

In this task, the stimuli were the same as those employed in Pattern Working Memory Task I. On each trial, three of the possible set of four familiar patterns were presented in the center of the screen for 250 ms each and at 500-ms intervals (see Fig. 1). Following a 500-ms delay, the same three patterns were presented simultaneously on the screen, randomly positioned in the three central boxes (Fig. 1). The subject's task was to respond by pressing the three buttons corresponding to the order in which the three patterns had been presented, that is, to press the button corresponding to the pattern that had been presented first, followed by the second, and then by the third. After the third response, the next trial began with a new sequence of three randomly selected patterns from the set of four. A variable intertrial interval was employed so that each trial was 4 s long and the number of trials was kept constant.

Control Task

During the control task, a single familiar pattern was presented in the central box three times for 250 ms each and at 500-ms intervals (Fig. 1). After a 500-ms delay, the same pattern was presented simultaneously in the three boxes on the screen and the subject responded by pressing the middle button. As with the other two tasks, a variable intertrial interval was employed to ensure that each trial was 4 s long.

Scanning occurred over successive 4-min blocks which comprised 1 min of control task, two 1-min blocks of Pattern Working Memory Tasks I and II, in counterbalanced order, and a final 1 min of control task. Each scanning sequence was repeated three times in counterbalanced order for each one of the five subjects and fMRI images were acquired throughout the brain every 2.5 s.

RESULTS

The Pattern Working Memory Tasks I and II were well matched for level of accuracy, with subjects scoring 92 and 89% correct, respectively ($t(4) = 0.46$, $P > 0.05$). The responses were paced by the + and − cues, and there were no significant differences in the reaction times for the three tasks (Pattern Memory Task I 361 (SEM 20.4); Pattern Memory Task II 341 (SEM 42.4); control task 328 (SEM 23.72). The control task, which used stimuli similar to those used in the two experimental tasks and required similar responses, provided a baseline against which to examine the extent of activation within the lateral frontal cortex in the two experimental conditions. In addition, the two experimental conditions were compared directly to test the specific prediction that Pattern Working Memory Task I would yield significantly greater signal intensity changes in the mid-dorsolateral frontal region.

When activity in Pattern Working Memory Task I was compared with that in the control condition, significant and widespread increases in signal intensity were observed bilaterally in area 9/46 of the mid-dorsolateral frontal cortex (Table 1). In addition, significant increases were observed in areas 44 and 45 of the right ventrolateral frontal cortex. Bilateral changes were also observed in premotor cortex (areas 6 and 8), in ventral occipitotemporal cortex (area 37), and in regions of the posterior parietal cortex (areas 7 and 40).

When Pattern Working Memory Task II was compared with the control task (Table 2), focal changes were observed, bilaterally, in area 9/46 of the mid-dorsolateral frontal cortex and in areas 44 and 45 of the ventrolateral frontal region. Significant changes were also observed in premotor cortex (area 6), inferior temporal cortex (areas 20/21), and posterior parietal cortex (areas 7/40), bilaterally. In the left hemisphere, the ventral occipitotemporal cortex (area 37) was also activated, while in the right hemisphere a significant change was observed in the cerebellum.

Finally, when Pattern Working Memory Task I was compared with Pattern Working Memory Task II very few significant signal intensity changes were observed. There was a highly significant increase in signal in the right mid-dorsolateral frontal cortex (area 9/46) (Table 3) in Pattern Working Memory Task I. Significant changes were also observed bilaterally in premotor cortex (area 6) in Pattern Working Memory Task I. The fact that no significant differences were observed in posterior neocortex suggests that the two tasks were well matched in terms of basic visuoperceptual processing.

The data were also examined to see whether the observed pattern of mean signal intensity changes

across the group was maintained at the level of individual subjects. Again, individual volumetric probability maps were assembled and converted to a logarithmic color scale and merged with anatomical images of the same location. Regions showing statistically significant differences between tasks were localized anatomically by visually inspecting the functional and high-resolution anatomical images for each subject. In particular, the mid-dorsolateral frontal region was identified in each individual by locating the superior frontal sulcus and the inferior frontal sulcus. The results confirmed the group analysis in that the most extensive changes in the mid-dorsolateral frontal cortex were observed in the task with the greater monitoring requirement (i.e., Pattern Working Memory Task I), whether the comparison was with the visuomotor control task or the Pattern Working Memory Task II.

DISCUSSION

Compared with the control task, both pattern working memory tasks yielded significant signal intensity changes, bilaterally, in the mid-dorsolateral frontal cortex and in the right ventrolateral frontal cortex. Thus, as predicted, during working memory processing of nonspatial visual material, both the ventrolateral and the mid-dorsolateral prefrontal regions were active since, relative to the control condition, the performance of both of these tasks required the executive processes subserved by these regions. In addition, compared with the control condition, Pattern Working Memory Task I, which could be performed successfully only by considering both the presented and the nonpresented stimuli (i.e., monitoring of the information within working memory), yielded several more significant peaks within mid-dorsolateral frontal cortex (area 9/46) than Pattern Working Memory Task II, in which monitoring was not critical for correct performance. Furthermore, when the two memory tasks were compared directly, significantly greater signal intensity changes were observed in area 9/46 of the right mid-dorsolateral frontal cortex during Pattern Working Memory Task I.

Pattern Working Memory Task II involved the active retrieval of the presented patterns, as well as a certain amount of monitoring during the test phase when the three patterns were selected in order. Thus, in comparison with the control task, fMRI signal intensity increases were observed in both the ventrolateral and the mid-dorsolateral prefrontal cortex in this task. However, the mid-dorsolateral frontal region was even more strongly recruited when the task absolutely required monitoring for successful performance as was the case in Pattern Working Memory Task I.

The observed mid-dorsolateral frontal cortex activity in Pattern Working Memory Task I is consistent with the results of previous studies in the monkey which have demonstrated that lesions of this region result in severe impairments when the animals are required to monitor the occurrence and nonoccurrence of nonspatial visual stimuli in working memory (Petrides, 1995). That monitoring is the critical variable giving rise to this impairment is clearly shown by the fact that the same monkeys can perform normally in other short-term memory tasks which involve identical stimuli. In addition, the results presented here extend the findings from a previous positron emission tomography study in which two different types of spatial memory task were used to activate either, or both, the ventrolateral and the mid-dorsolateral frontal regions (Owen *et al.*, 1996). In the Owen *et al.* PET study, the ventrolateral frontal region was activated during variants of a spatial span task which required subjects to retrieve sequences of locations. This task was designed to minimize the involvement of the mid-dorsolateral frontal cortex since no monitoring within spatial working memory was required. In two other tasks which required subjects to organize a search through a number of locations and to avoid returning to a subset of those locations, extensive monitoring was required, leading to significant increases in activity in a region of the right mid-dorsolateral frontal cortex similar to that observed in the current study.

The results of the current study provide further evidence that the engagement of the human mid-dorsolateral and ventrolateral frontal cortex during working memory processing depends on the type of processing required rather than simply the nature of the information being processed, which has been the prevailing view (Goldman-Rakic, 1987, 1994, 1995; McCarthy *et al.*, 1994, 1996; Wilson *et al.*, 1993). This conclusion is supported by recent electrophysiological data in nonhuman primates (Rao *et al.*, 1997), lesion work in nonhuman primates (Petrides, 1995), and a parallel fMRI study carried out in the same subjects, in which identical regions of the lateral prefrontal cortex were shown to be involved in both spatial and nonspatial working memory tasks when all factors unrelated to the type of stimulus material were appropriately controlled (Owen *et al.*, 1998).

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