Activation of Human Prefrontal Cortex during Spatial and Nonspatial Working Memory Tasks Measured by Functional MRI

Separate working memory domains for spatial location, and for objects, faces, and patterns, have been identified in the prefrontal cortex (PFC) of nonhuman primates. We have used functional magnetic resonance imaging to examine whether spatial and nonspatial visual working memory processes are similarly dissociable in human PFC. Subjects performed tasks which required them to remember either the location or shape of successive visual stimuli. We found that the mnemonic component of the working memory tasks affected the hemispheric pattern of PFC activation. The spatial (LOCATION) working memory task preferentially activated the middle frontal gyrus (MFG) in the right hemisphere, while the nonspatial (SHAPE) working memory task activated the MFG in both hemispheres. Furthermore, the area of activation in the left hemisphere extended into the inferior frontal gyrus for the nonspatial SHAPE task. A perceptual target (DOT) detection task also activated the MFG bilaterally, but at a level approximately half that of the working memory tasks. The activation in the MFG occurred within 3–6 s of task onset and declined following task offset. Time-course analysis revealed a different pattern for the cingulate gyrus, in which activation occurred upon task completion. Cingulate activation was greatest following the SHAPE task and was greater in the left hemisphere. The present results support the prominent role of the PFC and, specifically, the MFG in working memory, and indicate that the mnemonic content of the task affects the relative weighting of hemispheric activation.

Introduction

Working memory is a system for the transient storage and processing of information (Baddeley, 1992). The functional anatomy of working memory has been investigated in physiological studies in nonhuman primates, and such studies have demonstrated that the dorsolateral prefrontal cortex (dPFC) is involved in short-term mnemonic coding (Fuster, 1973; Funahashi et al., 1989). Goldman-Rakic (1987) proposed an architecture for working memory in which different subregions of the dPFC maintain on-line representations of different informational domains (such as shape and object features) in memory through control over reciprocally interconnected brain regions or networks. This model of compartmentalized working memory systems has been supported by recent physiological data acquired from monkeys engaged in delayed response tasks requiring memory for location (Funahashi et al., 1989), features of objects, and faces (Wilson et al., 1993). Neurons in the PFC that are responsive during the performance of nonspatial working memory are located more ventrally than those responsive during the performance of spatial working memory tasks (Wilson et al., 1993).

The neural basis for working memory in humans has been investigated by neuroimaging studies using both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). A recent review of this literature (McCarthy, 1995) has identified consistent activation of the PFC among tasks in which short-term memory storage has been manipulated, although there have been inconsistencies with regard to the specific prefrontal regions activated and their hemispheric lateralization. For example, Petrides et al. (1993a) used PET to demonstrate activation of the right middle frontal gyrus in a task requiring memory for spatial patterns, and Cohen et al. (1994) used fMRI to demonstrate bilateral activation of dPFC in a letter-monitoring task. We have previously used fMRI to demonstrate activation of the right middle frontal gyrus in a task requiring short-term storage of spatial locations (McCarthy et al., 1994), and Smith et al. (1995) have also reported activation of the right MFG in a task which engaged memory for the location of visual forms. However, working memory for stimulus location has not invariably led to MFG activation (cf. Jonides et al., 1993; Courtney et al., 1995; Smith et al., 1995). In addition, the pattern of hemispheric activation of the PFC, and the extent of ventral activation has varied among studies (e.g., Jonides et al., 1993; Paulesu et al., 1993; Petrides et al., 1993b; Smith et al., 1995, 1996).

The degree to which differential activation of subregions of frontal cortex reflects the memory domain manipulated has important implications for the neural organization of cognitive processing in humans (Goldman-Rakic, 1987) and for the structure of working memory (Baddeley, 1992). Here we have employed fMRI to investigate activation of the PFC in subjects performing tasks requiring either the transient storage of the location or the shape of visual stimuli, as exemplars of spatial and nonspatial working memory, respectively. The pattern of activation, hemispheric symmetry, and temporal course of activation within subregions of the PFC was investigated.

Materials and Methods

Subjects

Ten neurologically normal, right-handed subjects (aged 23–42 years; seven males, three females) participated in the primary study and performed both spatial and nonspatial working memory tasks. All subjects had prior experience in fMRI studies. The experimental protocol was approved by the Human Investigation Committee of Yale University School of Medicine.

At the conclusion of the study, four additional right-handed subjects (aged 25–34 years; one male, three females) participated in a second study of either spatial or nonspatial working memory to test the stability of the group activation time-course (described below) and the influence of the image acquisition sequence upon activation. One subject was tested in both studies.

Working Memory Tasks

Visual stimuli were delivered under computer control to an active matrix LCD panel whose images were back-projected onto a translucent Plexiglas screen mounted on the patient gurney of a whole-body MRI system. The subject viewed stimuli on the screen through a prism mirror mounted in the head coil. All stimuli were colored white and were presented against a dark background with a central fixation cross. All

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Gregory McCarthy, 1-3 Aina Puce, 1, 2 R. Todd Constable, 4
John H. Krystal, 5 John C. Gore 4 and Patricia Goldman-Rakic, 6
1Neuropsychology Laboratory, VA Medical Center, West Haven, CT 06516, and Departments of 2Surgery (Neurosurgery), 3Neurology, 4Diagnostic Radiology, 5Psychiatry, and 6Neurobiology, Yale University School of Medicine, New Haven, CT 06510, USA
behavioral responses were made with a fiber-optic response box on which subjects depressed a button with the index finger of their right hand.

Each experimental run lasted 96 s, during which functional images were acquired every 1.5 s (see below). Each run consisted of a pre-task baseline interval (27 s duration), a task interval in which subjects performed a working memory or control task (27 or 28.5 s), and a post-task interval (40.5 or 42 s). Subjects were instructed to maintain fixation and minimize blinking during the run.

The experimental design is illustrated in Figure 1. There were three experimental tasks: LOCATION, SHAPE, and DOT. The LOCATION and SHAPE tasks were memory-guided in that subjects were obliged to remember the location or shape, respectively, of each stimulus to perform the tasks accurately. In contrast, the DOT task was a perceptual target detection and vigilance task that did not require memory of previous stimuli. All three tasks, however, required subjects to fixate, to attend to visual stimuli, and to make two or three button presses per run. Subjects were practiced on all tasks prior to entering the magnet. The requirement for central eye fixation was stressed during these practice runs and throughout the imaging sessions.

In the LOCATION task, a single square appeared in a spatial location randomly chosen from among 20 possible locations. These locations were chosen to avoid obvious nameable patterns such as a clockface. After a 1.25 s exposure, the square disappeared for 0.25 s and was then replaced by another square at another randomly chosen location. The subject was instructed to respond with a button press whenever a square appeared in a location previously occupied during that run (a 'target'). A run consisted of 18 or 19 stimuli which included two or three targets. The exact number of targets and their position within the run were randomly determined. After the last stimulus was presented, the number of targets presented and the number of correct responses and reaction time were displayed at the center of the screen and remained visible during the post-task interval.

The SHAPE and DOT tasks used identical timing to the LOCATION task, and presented the subject with the same numbers of stimuli and targets. In the SHAPE task, a single irregular shape was randomly chosen from among 20 possible shapes and appeared at the center of the screen. After 1.25 s, the shape disappeared and was replaced by another randomly chosen shape 0.25 s later. The subject was instructed to respond with a button press whenever a shape appeared which had previously appeared during that run. The shapes were the same as those used by McCarthy et al. (1994) and were chosen not to resemble obvious objects such as circles or squares. The shapes were sized to fit within the bounding limits of the squares used in the LOCATION task.

In the DOT task, a single square appeared at the center of the screen. After 1.25 s, the square disappeared for 0.25 s and then reappeared, in the manner of the SHAPE task. During the appearance of two or three randomly chosen squares, a single pixel brightened for a 100 ms interval. The location of the pixel within the square, and the timing of its appearance were randomly determined. Subjects were instructed to press a button whenever they detected such a target event. Each square was identical in size to those used in the LOCATION task.

Each imaging session consisted of 12 experimental runs in which each of the three tasks was replicated four times. The experimental runs were blocked, but the task order was balanced across subjects. For the four subjects of the second study, only a single working memory task (SHAPE or LOCATION) was used and was replicated 16 times in a single imaging session.

MRI Studies
A 1.5 T MRI scanner (General Electric Signa, Milwaukee WI) with a quadrature head coil and echoplanar capability (Instascan, ANMR Systems Inc., Wilmington MA) was used. The subject's head was immobilized using a vacuum cushion and a Velcro forehead strap. Anatomical sagittal localizer scans were acquired (T₁-weighted: T₁ = 500, T₂ = 11, NEX = 1, FOV = 24 cm, slice thickness = 5 mm, skip = 2.5 mm, imaging matrix 256 × 192) to identify the anterior (AC) and posterior (PC) commissures. Four T₂-weighted coronal scans (T₁ = 500, T₂ = 11, NEX = 2, FOV = 40 cm, skip = 0 mm, slice thickness = 7 mm, imaging matrix 256 × 192) were then acquired centered 4 cm anterior to the AC (measured along the AC-PC line) to encompass the same prefrontal cortical regions previously shown active in working memory tasks (McCarthy et al., 1994) and to be used for co-registration with the functional images. Coronal magnetic resonance angiography (MRA) images were also obtained to identify the major venous vasculature in this region (T₁ = 45, T₂ = 7.7, α = 40°, NEX = 1, FOV = 24 cm, flow compensation, slice thickness 2 mm, imaging matrix 256 × 128).

Functional images were acquired using a gradient-echo echoplanar image acquisition sequence (T₁ = 1500, T₂ = 45, α = 60°, NEX = 1, FOV = 40 × 20 cm, slice thickness = 7 mm, skip factor = 0, imaging matrix 256 × 128). Images were acquired for each of the four anatomical coronal images described above. Each run consisted of the acquisition of 64 images for each of these four slices. Individual images were acquired in 67 ms and the interval between successive acquisitions of the same anatomical slice was 1.5 s (yielding a total imaging time of 96 s). Each run was preceded by four radiofrequency excitations to achieve steady-state transverse magnetization. In each 64-image acquisition, the task commenced at image 18.

In addition to the gradient-echo echoplanar image described above, the four subjects of the secondary study were also studied using spin-echo (T₁ = 1500, T₂ = 120 or 100, NEX = 1, FOV = 40 × 20 cm, slice thickness = 7 mm, skip factor = 0, imaging matrix 256 × 128) echoplanar image acquisition. Eight experimental runs were performed with each imaging sequence.

Analysis of MRI Data
The images comprising each experimental run were examined for head movement and acquisition artifacts by plotting the center of mass of each image in each run and by animating the image time series. Individual images that showed obvious acquisition artifacts were eliminated from further analysis.

Two primary methods of analysis were used to emphasize individual and group effects. Data from individuals were analyzed by computing t-tests for each voxel's signal intensity comparing pre-task and task intervals. The t-tests were computed separately for each of the four replications of each task. Images 3–20 comprised the pre-task baseline analysis period, while images 23–45 comprised the task analysis interval. These analysis periods were offset from the start and end of the task period to accommodate the ~6 s rise time and somewhat slower fall time of the task-related MR signal changes as observed previously (McCarthy et al., 1994). The resulting t-images of the first and second, and third and fourth task replicates were then averaged. These two average t-images were then subjected to a logical 'and' procedure ('split t-test') such that only voxels which exceeded a t-value of 1.5 (or were less than a t-value of -1.5) in both t-images were retained (Schneider et al., 1993; Puce et al., 1994).

Figure 1. Schematic illustration of the SHAPE, LOCATION, and DOT tasks (see text for details). Each run consisted of 18 or 19 stimuli presented at a rate of one every 1.5 s and containing two or three randomly distributed targets. The stimuli in the SHAPE and DOT tasks were presented in the center of the screen, while the stimuli in the LOCATION task appeared at randomly chosen locations. For convenience, target stimuli for each task are shown as the fourth stimulus in each sequence.
Figure 2. Activated voxels (color overlay) from the LOCATION (a,b), SHAPE (c,d), and DOT (e,f) tasks in an individual subject identified by the split-f procedure described in Materials and Methods. Each pixel indicates a significant increase in activation (t > 2) during the task interval relative to the pre-task baseline. For these pixels, activation decreased by at least 50% by the conclusion of the post-task interval. Activation data are overlaid over their corresponding anatomical T1-weighted images. The two adjacent slices shown were those which contributed to the spatially normalized group average shown in Figure 3. In this and all subsequent figures, the right hemisphere is shown on the left side of the images.

As a further test, the group mean time-series for each task were interrogated by drawing anatomical regions of interest (ROI) over the superior frontal gyrus (SFG), middle frontal gyrus (MFG), inferior frontal gyrus (IFG), cingulate gyrus (Cing), and white matter control regions, and integrating the MR signal intensity. The mean signal intensity and standard deviation were calculated for the pre-task analysis interval across the three tasks for each anatomical ROI. The integrated intensity for each ROI in each image in the series was then converted to a z-score deviation from this common pre-task value so that the task effects would be in comparable units expressing statistical distance in standard deviations from common baseline "noise".

The mean activation time-courses produced by the group analysis were then used in a second study to test further the reliability of the findings. In this analysis, the group mean activation time-course obtained from the anatomical region of interest analysis described above was convolved with the time-series for each voxel from the data acquired in a series of four new subjects. This technique identified voxels which had a similar time-course to the group activation time-course.

Results

Performance Data

The mean reaction time (RT) and standard error for the three tasks were as follows: LOCATION, 673 ± 38 ms; SHAPE, 709 ± 15 ms; and DOT, 452 ± 13 ms. An analysis of variance (ANOVA) showed a significant main effect of task (F = 32.7, P < 0.01) for RT. Post-hoc analysis using Tukey's HSD revealed that both working memory tasks had significantly longer RTs than the...
DOT task ($P < 0.05$), but the working memory tasks did not differ significantly from each other. The percentage of correct responses was $56 \pm 4\%$ for the LOCATION task, $74 \pm 8\%$ for the SHAPE task, and $78 \pm 13\%$ for the DOT task. While there was a trend for lower percentage correct responses for the LOCATION task, the differences in accuracy between the tasks were not statistically significant ($F = 2.8$, $P = 0.08$).

$t$-Test Analyses of fMRI Images

Individual Subject Images

Across subjects, the working memory tasks most consistently activated the MFG where clusters of significantly activated voxels were observed in 9 of the 10 subjects. The activated regions typically included the inferior frontal sulcus which separates the MFG from the IFG. Representative data for an individual subject are presented in Figure 2a-f in which the significantly activated voxels (as described in Materials and Methods) are represented as color overlays displayed upon anatomically consecutive T1-weighted images. The two coronal slices shown for each task are those which contributed to the spatially normalized group mean images. Figure 2a,b represents activations associated with the LOCATION task for the anterior and posterior slice, respectively. Figure 2c,d represents activation associated with the SHAPE task for the same slices; while Figure 2e,f represents activation associated with the DOT task. In the LOCATION task, a cluster of activated voxels was obtained in the right MFG in the anterior slice (Fig. 2a) and on the border of the right MFG and IFG in the posterior slice (Fig. 2b). No activation exceeded the $t$ criterion of 2.0 in the same region of the left MFG, although a small patch of activated voxels occurred more inferiorly in the left IFG (Fig. 2b). The SHAPE task produced larger clusters of activated voxels in the right MFG and IFG bilaterally, most notably in the posterior slice (Fig. 2d). Few activated voxels were obtained in the DOT task compared to the working memory tasks. A few scattered voxels were seen in the right SFG in both the anterior (Fig. 2e) and posterior (Fig. 2f) slices, and in the inferior aspects of the right hemisphere.

Activated voxels were evident at the base of the brain between the eyes in both the LOCATION and SHAPE tasks. This region, which occurred at the most inferior edge of the gradient-echo images, showed an inconsistent pattern across subjects. The proximity of this region to the eyes and to susceptibility artifacts caused by the sinuses suggested that these effects, when observed, were artifactual.

Group Mean Images

The $t$-test analysis performed on the group mean images confirmed the observations in individual subjects. The significantly activated voxels for the LOCATION task are displayed in Figure 3a,b as a red overlay upon the group average anatomical images. The results for the SHAPE and DOT tasks are similarly presented in Figure 3c,d and Figure 3e,f, respectively. Across subjects, the LOCATION task was associated with clusters of activated voxels in the right MFG of both slices with minimal activations of the left MFG of either slice. The SHAPE task also produced clusters of activated voxels in the right MFG of both slices. The distributions of activated voxels were similar to those obtained for the LOCATION task. Unlike the LOCATION task, however, SHAPE was associated with a cluster of activated voxels in the left MFG extending inferiorly into the IFG (Fig. 3c,d). The DOT task produced fewer activated voxels in this analysis. One cluster was evident in the right MFG of the posterior slice (Fig. 3f) and a cluster of activation was evident in the inferior aspect of both slices (Fig. 3e,f).

Region of Interest Analysis

The anatomical extent of activation across subjects was more systematically evaluated in the ROI analyses performed on the spatially normalized data. Figure 4 presents the spatially normalized anterior (Fig. 4a) and posterior (Fig. 4b) group mean anatomical images and the anatomical ROIs used to interrogate the mean image series in each task (because of signal loss caused by the frontal sinuses, ROIs for the gyrus rectus and the orbital frontal gyri were not drawn). Table 1 presents the mean activation in the task analysis interval (i.e., images 23–43) for each ROI. The overall distribution of activation summed across working memory tasks is presented in Figure 5. Mean activation across hemispheres exceeded ± 2 $z$-scores (or standard deviations (SDs)) above the pre-task interval only in the MFG.

<table>
<thead>
<tr>
<th>Task</th>
<th>Location</th>
<th>Shape</th>
<th>DOT</th>
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<tbody>
<tr>
<td>Right</td>
<td>SFG</td>
<td>1.40</td>
<td>1.73</td>
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<tr>
<td></td>
<td>MFG</td>
<td>4.44</td>
<td>4.88</td>
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<tr>
<td></td>
<td>IFG</td>
<td>1.53</td>
<td>1.06</td>
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<tr>
<td></td>
<td>Cing</td>
<td>0.76</td>
<td>1.72</td>
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<tr>
<td>Left</td>
<td>SFG</td>
<td>-1.10</td>
<td>0.85</td>
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<tr>
<td></td>
<td>MFG</td>
<td>2.65</td>
<td>5.33</td>
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<tr>
<td></td>
<td>IFG</td>
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<td>20.68</td>
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<tr>
<td></td>
<td>Cing</td>
<td>-0.15</td>
<td>1.26</td>
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<tr>
<td>Both</td>
<td>SFG</td>
<td>0.19</td>
<td>1.29</td>
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<tr>
<td></td>
<td>MFG</td>
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<tr>
<td></td>
<td>IFG</td>
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<td>1.71</td>
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<tr>
<td></td>
<td>Cing</td>
<td>0.31</td>
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Activation is expressed in $z$-scores (standard deviations) comparing the task interval to the common pre-task baseline. SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; Cing, cingulate gyrus.

Time-Course of Activation for MFG

The $t$-test analyses for the group-averaged data (Fig. 3) suggested a hemispheric difference between the activation patterns of the LOCATION and SHAPE tasks. This was investigated further in the anatomical ROI analysis (see Fig. 4 for regions interrogated). Since the ROIs integrate activity over a large number of voxels, they should be maximally sensitive to small but consistent activations which might produce few significant $t$-values in the presence of noise. The time-courses of activation obtained for the right (red ROI, Fig. 4a,b) and left MFG are shown in Figure 6a,b, respectively. The activation time-courses were combined for both the anterior and posterior slices for clarity since the signal changes associated with each task were similar in both slices. For the right MFG (Fig. 6a), the activation time courses for all three tasks rose above 2.0 SDs above the pre-task baseline within 3 s and reached a plateau by -6 s. This level of activation was maintained until 6 s after the task interval, at which time the activation slowly declined. The mean activation over the task analysis interval was similar for both working memory tasks (see Table 1) but only reached slightly more than half of this level for the DOT task. In contrast to the robust activation time course for the MFG, the ROIs drawn for the adjacent white matter (blue...
ROI, Fig. 4a,b) did not show any consistent task-related activation (Fig. 7a,b).

**Hemispheric Differences in MFG Activation.** The time-courses of activation in the left MFG (Fig. 6b) showed a similar onset latency as the right MFG. The SHAPE task produced a slightly greater mean level of activation for the left MFG (5.33 SDs) than it did for the right MFG. The DOT task produced a mean activation of 2.12 SDs—also similar to its value for the right MFG. However, the LOCATION task produced a mean activation of only 2.65 SDs in the left MFG—a value half that produced by SHAPE and similar to that produced by DOT. The differential
Figure 6. Group mean time-courses of activation for the right (a) and left (b) MFG averaged over the anterior and posterior slices (LOCATION = heavy solid line, SHAPE = light solid line, DOT = dotted line). In this and Figures 6 and 7, the image number appears on the x-axis and image intensity (expressed as a z-score relative to the pre-task baseline) is shown on the y-axis. The vertical lines demarcate task onset and offset.

Figure 7. Group mean time-courses of activation for the right (a) and left (b) white matter averaged over the anterior and posterior slices (LOCATION = heavy solid line, SHAPE = light solid line, DOT = dotted line).

Figure 8. Activated voxels are shown overlaid upon T1-weighted anatomical images for an individual subject performing the SHAPE task using a gradient-echo imaging sequence. (a) Convolution analysis showing clusters of activation in the left and right middle frontal gyri. (b) Split-map (t > 2) showing two clusters of activation in the left middle frontal gyrus. Color scale: yellow (t = 2) to red (t = 5).

in the immediate post-task interval, with somewhat greater activation following the cessation of the SHAPE task (Fig. 10). This difference was pronounced in the left cingulate where the activation produced by the SHAPE task persisted longer than for the other two tasks. This more persistent activation for SHAPE was also apparent in the left MFG (Fig. 6b).
activation produced in the left MFG for the SHAPE compared to LOCATION working memory tasks was consistent with the t-test analysis shown in Figure 3.

Although the overall level of activation was smaller, the SHAPE task also produced a stronger activation (Table 1) of the left inferior frontal gyrus (2.36 SDs) than of the right (1.06 SDs). In contrast, no activation of the left inferior frontal gyrus was observed for the LOCATION task. The more inferior extent of activation for the SHAPE task in the left hemisphere was seen in the group t-test analysis (Fig. 3d) and in individual analyses (Fig. 2d). Activation produced by the DOT task showed a hemispheric asymmetry in the SFG. The right side showed a mean activation of 3.42 SDs while the left showed no activation.

**Application of Group Activation Time-Course to New Subjects**

The group mean activation time-courses from the MFG (Fig. 6a,b) for the LOCATION and SHAPE tasks were averaged, low-pass filtered to remove noise, and then used in a convolution analysis of the data obtained for four additional subjects. This analysis was performed to test the reliability of the ROI time-course analyses obtained in the group analysis. Figures 8 and 9 present the results for subject AP who performed eight runs of the SHAPE task using gradient-echo echoplanar acquisition. Figure 8a shows the result of the convolution analysis. Several clusters of activated voxels appear in the left MFG, and two smaller clusters appear in the right MFG. A few additional clusters appear near the bottom of the image. Figure 8b shows the result of the t-test analysis performed on these same data. Two clusters of activated voxels were obtained in the left MFG, and one small cluster was obtained in the right MFG. The activated regions identified by the t-test overlapped with those identified by the convolution analysis.

The results for this individual showed a predominantly left MFG activation for the SHAPE task which extended more inferiorly in the left hemisphere, and thus replicated two of the main findings from the primary study. Subject AP was not run on the spatial working memory task in this new study, but had previously demonstrated a strong right dominant activation for spatial working memory tested previously by McCarthy et al. (1994—see their fig. 4).

The time-courses of activation (Fig. 9) were determined for the activated voxels from the left MFG from the convolution (Fig. 8a) and t-test analysis (Fig. 8b), respectively. A mean activation of 1.43 and 1.9% was calculated for each method for the gradient-echo images (solid lines). These same voxels were interrogated in the spin-echo image series and showed mean activations of 0.60 and 0.77%, respectively (broken lines). These values were 42 and 41% of the measures obtained for gradient-echo imaging.

The convolution and t-test analyses revealed similar clusters of activation in the MFG with gradient-echo imaging in all four subjects, and similar activation time-courses were obtained for both gradient and spin-echo images in three of four subjects. Of the three subjects with concordant activation time-courses for gradient and spin-echo imaging, the mean signal changes obtained for spin-echo were 37% (range 35–42%) of those obtained for gradient-echo.

**Time Course of Activation for Cingulate Cortex**

The ROI analysis for the cingulate gyri (pink ROI, Fig. 4a,b) showed a distinct pattern in which little or no activation occurred during the task, but all three tasks produced activation...
Figure 9. Time-courses of activation for ROIs in the left middle frontal gyrus from Figure 8. (a) Convolution ROI from Figure 8a. (b) Split t-test ROI from Figure 8b. Solid line = gradient-echo sequence; dotted line = spin-echo sequence.

Figure 10. Group mean time-courses of activation for the right (a) and left (b) cingulate gyri averaged over the anterior and posterior slices (LOCATION = heavy solid line, SHAPE = light solid line, DOT = dotted line).
Discussion
The present study demonstrated that the middle frontal gyri were consistently activated during the performance of working memory tasks, and that the hemispheric pattern and extent of activation was dependent upon the working memory domain. Activation commenced by 3 s after task onset and declined at a slower rate, beginning ~6 s after task completion. This pattern of activation was not observed in items, and similar levels and/or patterns of activation were not observed in the superior and inferior frontal gyri, or in the cingulate gyrus. The pattern of activation in the MFG was reliable in that the group activation time course of this region successfully identified activation in the MFG in data collected subsequently in four additional subjects.

Differential Hemispheric Activity Related to Location and Shape
The present findings replicate our previous study performed at 2.1 T where we found that spatial working memory preferentially activated the right MFG (McCarthy et al., 1994). The spatial memory (LOCATION) task produced a right MFG activation which was 168% of that produced in the left MFG in the group-averaged data. The nonspatial memory (SHAPE) task produced nearly equal activation of the right MFG as the spatial task, but even greater activation was produced in the left MFG where the average level of activation was more than twice the level measured for the spatial task. Thus while the greatest levels of activation for the working memory tasks were consistently found in the MFG, the activation showed a different hemispheric pattern as a function of the memory task performed (see Smith et al., 1996, for a related discussion).

Activation of prefrontal cortex during working memory tasks has been reported in several PET and fMRI studies (e.g., Jonides et al., 1993; Petrides et al., 1993a,b; Cohen et al., 1994; Swartz et al., 1994, 1995; Smith et al., 1995, 1996; see review by McCarthy, 1995). This region has also been activated by tasks which, though not presented in the context of working memory, nevertheless required the transient storage of sensory information (e.g., Corbetta et al., 1991; O’Sullivan et al. 1994). However, reports have differed with regard to the hemispheric distribution of effects, and in the relative extent of dorsal and ventral prefrontal activation.

Activation of the right PFC has been observed during the performance of spatial working memory tasks (Jonides et al., 1993; McCarthy et al., 1994; Smith et al., 1995), and in memory tasks using spatially oriented stimuli (Petrides et al., 1993a). Of these studies, Petrides et al. (1993a) and McCarthy et al. (1994) showed bilateral but right dominant activation of the dPFC, while Jonides et al. (1993) found activation in right inferior PFC (area 47). Smith et al. (1995) replicated the findings of Jonides et al. (1993) with regard to the right inferior PFC, but also found activation of dPFC area 46 in one variant of their task. More recently, this latter group (Smith et al., 1996) reported activation of dPFC area 46 when the spatial working memory task was made more continuous. Activation was bilateral but was greater in the right hemisphere. These results and the present study support the conclusion that working memory tasks primarily involving spatial memory preferentially activate the right PFC. However, others have not found this relationship. Sweeney et al. (1996) found bilateral activation of dPFC area 46 using an oculomotor spatial delayed-response task similar to that employed in the nonhuman primate studies. Courtney et al. (1996) found predominantly right dPFC activation for a face working memory task, but not for a location working memory task where more posterior activation in premotor cortex was found when comparing their location and face tasks. Thus, at present, it is not possible to incorporate all studies of spatial working memory within a common framework.

In contrast to the spatial working memory tasks reviewed above, nonspatial tasks have shown a different hemispheric pattern of activation. Cohen et al. (1994) used a letter monitoring task to demonstrate bilateral activation of dPFC and Swartz et al. (1994, 1995) showed bilateral activation of dorsal PFC (including dPFC and dorsal pole) in a visual memory task similar to the SHAPE task used here. Smith et al. (1995) found activation of left prefrontal cortex in an object working memory task.

The degree to which bilateral activation may represent the addition of verbal mediation to the subject's task strategy remains undetermined. Petrides et al. (1993b) found bilateral activation of dPFC using a verbal working memory task, and Smith et al. (1996) showed predominantly left prefrontal activation in their verbal working memory study. In the present study we attempted to limit verbal mediation by using shapes without obvious verbal labels. Nevertheless, some subjects reported using verbal labels as a mnemonic aid. However, the argument that differential verbal processing in working memory tasks determines completely the hemispheric pattern of dPFC activation is challenged by those PET studies of working memory which explicitly required phonological processing and in which differential activation of Broca’s area rather than dPFC was obtained (Zatorre et al., 1992; Paulesu et al., 1993).

It is noteworthy that activation of the PFC has also been obtained in long-term recognition memory tasks (e.g., Grasby et al. 1993; Moscovitch et al. 1995; Shallice et al., 1994). For example, Moscovitch et al. (1995) have reported increased activation of the right PFC (including areas 44, 45, and 46) for both spatial and object recognition tasks. It has been argued that the PFC is critical for episodic memory and, furthermore, that there is hemispheric specialization with regard to episodic memory function (Shallice et al., 1994; Tulving et al., 1994). Both Shallice et al. (1994) and Tulving et al. (1994) have proposed that the right PFC is important for episodic retrieval while the left PFC is important for encoding into episodic memory. In the model of Tulving et al. (1994), the left PFC is also involved in retrieving information from semantic memory. These studies are not necessarily in conflict with the present study in that it is likely that working memory plays a role in encoding to and retrieval from episodic memory. However, the present results and prior literature (e.g., Smith et al. 1995) indicate that the spatial or object domain tested by the working memory task is important in determining the hemispheric pattern of frontal lobe activation.

Comparison of Perceptual Control and Working Memory Tasks
Although not clearly evident in the t-test images (Fig. 3e,f), the ROI time-course analyses showed that the non-memory-guided DOT task also produced bilateral activation of the MFG, although at approximately half the level of the SHAPE task. This is consistent with our previous study in which non-memory color detection and dot detection tasks both produced activation of the right MFG, but at a level less than that obtained for a spatial working memory task using identical stimuli (McCarthy et al., 1994). The present study revealed bilateral MFG activation for the DOT control task, although the activation of the right MFG was somewhat greater than the left.
We note that the level of activation produced by the LOCATION task in the left MFG was similar to that produced by the DOT task. Pardo et al. (1991) have reported a PET study in which increases in blood flow in the PFC occurred during performance of vigilance tasks requiring sustained attention, such as the DOT task used here. If the level of activation produced by the DOT task represents processes related to attention, motor preparation, and/or other common task requirements, and if the difference between the DOT and working memory tasks represents additional processes related to the maintenance of memory for past items, then the hemispheric dissociation between the spatial and nonspatial working memory tasks becomes even more apparent. A comparison of the activation time-courses (see Fig. 6a, b) shows that subtraction of the DOT task would leave residual activation of the left MFG only for the nonspatial SHAPE working memory task. However, both spatial and nonspatial working memory tasks would show residual activation of the right MFG.

The monitoring of visually presented stimuli might be expected to activate the MFG in humans as studies in nonhuman primates have shown that neurons in the PFC (particularly dorsolateral areas 8 and 46) respond to attended visuospatial stimuli—whether or not they are to be recalled (Funahashi et al., 1991; Wilson et al., 1993). Furthermore, quantitative 2-deoxyglucose metabolic studies in monkeys performing cognitive tasks have consistently shown that the difference between control and experimental tasks is one of degree rather than of anatomical location (Friedman and Goldman-Rakic, 1988). Therefore, the present findings are entirely in line with expectations based upon cortical physiology.

**Task Difficulty**

Other task differences or systematic artifacts may, however, underlie the difference in activation between the DOT and working memory tasks. One concern is task difficulty. The percentage of correct responses made during performance of the DOT task was not significantly different from either working memory task, but the RT for DOT detection was significantly faster. This is not surprising as one would expect that scanning a memory buffer to identify targets (as in the working memory tasks) would take longer than detecting a brightened pixel. Thus, the operation of the very process of interest (memory) is the likely basis for the RT difference. While perceptual tasks can be made arbitrarily difficult to equalize RTs, the difficulty level in each task would be based upon different processes. An argument that greater difficulty would lead to greater activation due to a non-specific process such as arousal is countered by the results of the LOCATION task, which, though showing a trend for a greater error rate, nevertheless produced less overall activation than SHAPE. Thus while differences in task difficulty may underlie some activation differences, activation levels did not correlate with the performance measures obtained in the working memory tasks.

**Differential Dorsal and Ventral Prefrontal Activation**

While the present study strongly indicates differential activation of the PFC for spatial and nonspatial working memory tasks as a function of hemisphere, the question of differential dorsal and ventral distribution of activation within a hemisphere for the spatial and nonspatial working memory tasks is less clear. The largest and most consistent activations associated with the working memory tasks occurred in the MFG, which cytoarchitectonic studies in human cortex have shown correspond primarily to area 46 (Rajkowska and Goldman-Rakic, 1995). This region is thus analogous to the principal sulcus of monkey shown to be active in working memory tasks (Funahashi et al., 1989; Goldman-Rakic, 1987). In the present study, activation was also seen in the left IFG for the nonspatial SHAPE working memory task, while the spatial LOCATION task showed no consistent activation of this same region. The degree of activation was small relative to the MFG and requires further study to assess its reliability. Nevertheless, it is consistent with prior monkey studies (Wilson et al., 1993) which showed that nonspatial memory tasks involve more ventral prefrontal regions than spatial memory tasks. It is also consistent with prior neuroimaging working memory studies in humans: Cohen et al. (1994), for example, reported activation extending into more ventral prefrontal regions in their letter monitoring task. It is also consistent with Courtney et al. (1996) who used face stimuli in a nonspatial working memory task and found activation extending into the inferior PFC, albeit predominantly in the right hemisphere.

**Activation of the Cingulate Gyrus**

An unexpected finding in the present study was the pattern of activation in the cingulate gyrus. While little or no activation occurred during task performance, significant activation occurred for all three tasks upon task cessation. The reason for this nonspecific post-task activation is not clear, but the temporal dissociation of activity between the cingulate and prefrontal region is striking. PET studies have reported co-activation of the anterior cingulate and dorsolateral PFC in tasks with working memory components (e.g., Petrides et al., 1993a, b), and we have observed similar co-activation, though not reliably across replications (McCarthy et al., 1994). Pardo et al. (1990) have implicated the anterior cingulate in selecting processing systems necessary for task execution. Simple sustained attention, however, did not activate this region (Pardo et al., 1991). Interpretation of the cingulate activation observed in the present experiment is difficult because it occurred at a point when the tasks ended and when performance feedback was provided. This suggests that the post-response activation may be related to performance feedback or, alternatively, to the disengagement of sustained attention. It is unlikely to reflect response selection, the mnemonic content of the working memory task, or attention per se, which would have been maximal during the tasks themselves. Of possible relevance are recent single-unit recordings in the posterior cingulate cortex of rhesus monkeys which have revealed a population of neurons that consistently respond only after the delay of delayed-response trials, independent of the direction of the response (Carlson et al., 1994). This neuronal temporal profile is distinctly different from that recorded in prefrontal neurons, just as the fMRI activation of the cingulate cortex differs from that of the prefrontal cortex. Both findings open new questions on the contribution of the cingulate cortex to cognitive functions.

**Gradient-Echo versus Spin-Echo Imaging Sequences**

The degree to which fMRI can distinguish activity in closely adjacent anatomical regions that are nonetheless functionally distinct (as determined by other methods such as single unit recording) remains to be determined. One issue that has been raised is the degree to which fMRI performed at 1.5 T using gradient-echo acquisition may partly reflect increased signals in large venules and veins which may be distant to the activated neurons (e.g., Constable et al., 1994; Lai et al., 1993). Spin-echo
acquisition is less sensitive to magnetic susceptibility effects, especially those arising from large vessels. While activation effects in spin-echo images emphasize smaller vessels relative to gradient-echo images, the overall sensitivity is reduced, making functional imaging with spin-echo difficult at 1.5 T. In the present study, we identified voxels activated by the working memory tasks using gradient-echo sequences, but then interrogated these same voxels in spin-echo sequences. Using this procedure, activation effects were observed in the spin-echo images with signal changes 37% of those obtained in the gradient-echo images. This value is within the range expected from theoretical calculations of the relative signal changes in microvascular structures (Kanen et al., 1994). Moreover, the time-courses of activation for the gradient-echo and spin-echo sequences were similar. One might expect a delay in the gradient-echo time-course if the activity primarily reflected flow downstream of an activated region of cortex. It is therefore unlikely that the activation effects found in the MFG are greatly displaced from the true locus of activation. Nevertheless, until the precise anatomical size and proximity of spatial and nonspatial visual processing centers in human PFC are established, the resolution of the imaging method remains an issue.

Notes
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Address correspondence to Dr Gregory McCarthy, Neuropsychology Laboratory/116B1, VA Medical Center, West Haven, CT 06516, USA.

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