Object and Spatial Visual Working Memory Activate Separate Neural Systems in Human Cortex

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Human and nonhuman primate visual systems are divided into object and spatial information processing pathways. In the macaque, it has been shown that these pathways project to separate areas in the frontal lobe and that the ventral and dorsal frontal areas are, respectively, involved in working memory for objects and spatial locations. A positron emission tomography (PET) study was done to determine if a similar anatomical segregation exists in humans for object and spatial visual working memory. Face working memory demonstrated significant increases in regional cerebral blood flow (rCBF), relative to location working memory, in fusiform, parahippocampal, inferior frontal, and anterior cingulate cortices, and in right thalamus and midline cerebellum. Location working memory demonstrated significant increases in rCBF, relative to face working memory, in superior and inferior parietal cortex, and in the superior frontal sulcus. Our results show that the neural systems involved in working memory for faces and for spatial location are functionally segregated, with different areas recruited in both extrastriate and frontal cortices for processing the two types of visual information.

The results of lesion and single-cell recording experiments indicate that the primate visual system is divided into two processing pathways (Ungerleider and Mishkin, 1982; Desimone and Ungerleider, 1989). The ventral occipitotemporal pathway, known as the "what pathway," is essential for perceiving the identity of objects. Cells in extrastriate regions within this pathway are sensitive to the intrinsic properties of objects such as shape, color, texture, and orientation (Desimone and Ungerleider, 1989). In contrast, the dorsal occipitoparietal pathway, known as the "where pathway," is involved in the perception of the spatial relationships among objects, the perception of movement, and in guiding movement toward objects. Cells in extrastriate regions within this pathway are sensitive to visuospatial properties of objects, such as the direction of stimulus motion (Desimone and Ungerleider, 1989). The human visual system also appears to show this segregation in extrastriate cortex for the perception of objects and their locations in space (Haxby et al., 1991, 1994a; Ungerleider and Haxby, 1994).

In the macaque, these two pathways have separate anatomical projections to prefrontal cortex. The occipitotemporal pathway projects to the inferior convexity of prefrontal cortex (Chavis and Pandya, 1976; Ungerleider et al., 1989; Webster et al., 1994), while the occipitoparietal pathway projects to dorsolateral prefrontal cortex (Barbas and Mesulam, 1985; Ungerleider and Desimone, 1986; Cavada and Goldman-Rakic, 1989). These ventral and dorsal prefrontal regions appear, from single cell physiological recording experiments in nonhuman primates, to play a role in working memory for objects and locations, respectively (Wilson et al., 1993). Additional data from delayed response tasks with nonhuman primates (Fuster, 1985, 1990; Goldman-Rakic, 1990) and from human lesion and imaging studies (Ghent et al., 1962; Smith and Milner, 1984; Milner et al., 1985; Schachter, 1987; Shimamura et al., 1990; Petrides et al., 1993b; Haxby et al., 1995) also suggest that the prefrontal cortex plays a role in working memory.

The concept of working memory, as originally proposed by Baddeley and Hitch (1974), has three dissociable components: a phonological rehearsal loop for the storage and manipulation of verbal information, a visuospatial sketch pad for visual and spatial information, and a central executive for attentional control. In light of the physiological data from nonhuman primates and the dissociation of object and spatial information in extrastriate areas in the human, it seems reasonable that the visuospatial sketch pad might be further dissociable into two subsystems: one for object based information, and one for spatial information. However, to our knowledge, no previous imaging study has used both object and spatial working memory tasks within the same study such that the spatial task and the object task used the same set of visual stimuli.

We have investigated the functional organization of human frontal cortex by using positron emission tomography (PET) to measure changes in regional cerebral blood flow (rCBF) associated with working memory for faces and spatial locations. We present the results of an experiment in which the stimuli for the face and location working memory tasks were identical so that differences in the patterns of rCBF changes could be attributed to the difference between the selective retention of face identity or face location in working memory and not to stimulus differences. Our results, together with the results from several previous studies, suggest that working memory in the frontal lobe of humans, like that of the monkey, is functionally segregated, with a dorsal region for spatial location and more ventral regions for object identity.

A preliminary report of this study has appeared in abstract form (Courtney et al., 1994).

Materials and Methods

Subjects

Sixteen (eight male, eight female) healthy, right-handed volunteers participated in this study. Mean age was 27.8 years (SD 4.6). Mean educational background was 16.3 years (SD 2.4). All subjects gave written informed consent.

Visual Tasks

PET scans measuring rCBF were obtained while subjects performed visual working memory and control tasks. All tasks were presented by a Macintosh IIfx computer (Apple, Cupertino, CA) using SuperLab software (Cedrus, Wheaton, MD; Haxby et al., 1993b). Responses for all tasks were button presses made with the right or left thumb. Buttons were interfaced to the Macintosh computer with a National Instruments NB-DIO-24 card (Austin, TX) to record response accuracy and latency.

The stimuli for all tasks had the same spatial configuration. Subjects were presented with 24 gray squares placed in an irregular array on a black background. For the two working memory tasks, three faces would appear, one at a time, each in a different square in the array (Fig. 1). Each face in the memory set was shown for 1500 msec, for a total of 4500 msec. After the third face appeared, the screen

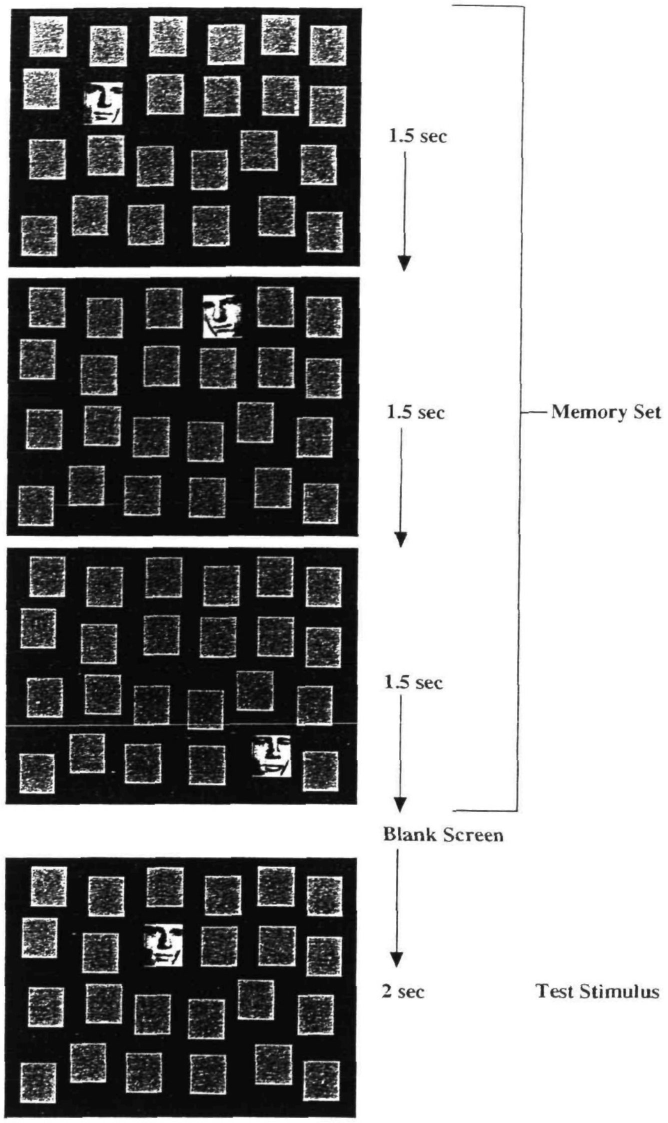


Figure 1. Sample stimuli for the face working memory task. The item shown would require a "yes" response. Stimuli for the locations working memory task were identical except that the test stimulus was never one of the faces used to mark the locations in the memory set. The sensorimotor control task also had identical stimuli except that a scrambled face (not shown) appeared each time in one of the squares instead of a face.

would blank for 500 msec and then another face would appear for 2000 msec in one of the squares of the array. After this test face, the screen would blank for 1 sec and then the next set of faces would begin. Pictures of faces were from a fixed set of 24 that were taken from a high school yearbook and cropped to remove hair and clothing. Prior to scanning, the same set of faces was used when the subjects practiced the working memory tasks. In total, subjects saw each of the 24 faces three times during this training session, and therefore, were familiar with the faces before the PET scanning began.

Before each task began, subjects were instructed to remember either the three faces in the memory set, or the three locations in which the faces appeared. Subjects were instructed to look directly at each face as it appeared. For the face memory task, the subject indicated whether the test face was the same as one of the three faces seen in the memory set, regardless of the location in which the face appeared. For the location memory task, the subject indicated whether the test location was the same as one of the three locations indicated in the memory set, regardless of which face appeared. For the face memory task, the test face never appeared in one of the locations used in the memory set. For the location memory task, the test face was never one of the faces that had appeared in the memory set. This was done to discourage covert storage of unattended information during the working memory tasks. A "yes" response was indicated by pressing a button with the right thumb, a "no" response by pressing a button with the left thumb.

For the sensorimotor control task, three scrambled pictures of faces (filtered to remove the high frequencies) would appear, one at a time, each in a different gray square in the array, using the same timing as for the working memory tasks. After the third scrambled face, the screen would blank for 500 msec and then another scrambled face would appear in a different square in the array. Again, the subjects were instructed to look directly at each scrambled face as it appeared. The fourth (test) stimulus was never the same picture nor in the same location as any of the previous three stimuli. After the screen blanked and the fourth scrambled face appeared, subjects would press either the left- or right-hand button, on alternating trials, so that the total number of motor responses was identical for the control and working memory tasks. The control task was always used for the first and last scans of each session. The order for the working memory tasks was counterbalanced across subjects, with two scans obtained for each task.

Stimuli were presented on a computer-monitor positioned approximately 60 cm from the subject's eyes and tilted to be perpendicular to the subject's line of sight. The full stimulus array subtended approximately 15.5° × 12° of visual angle. Each small square in the array subtended approximately 1.8° × 2.1° of visual angle.

Positron Emission Tomography

Measurement of rCBF was accomplished with a Scanditronix PC2048-15B tomograph (Milwaukee, WI). This tomograph acquires 15 contiguous, cross-sectional images simultaneously, each 6.5 mm thick. Within-plane resolution is 6.5 mm (full-width at half-maximum). Head movement was minimized by using a thermoplastic mask that was molded to the subject's head and attached to the scanner bed.

Each scan was obtained while the subject performed one of the three tasks described above. Subjects began each task 15 sec before the intravenous injection of 37.5 mCi of $H_2{}^{15}O$. Scanning began when the brain radioactivity count reached a threshold value and continued for 1 min thereafter. The task was stopped at the end of scanning. A transmission scan was used to correct images for attenuation. Local radiation counts (counts/min/cc) were used as an index of local blood flow. Blood flow increases are known to be a linear function of radiation counts for scans of less than 1 min duration (Herscovitch et al., 1983; Fox et al., 1984; Fox and Mintun, 1989). Changes in tissue radioactivity will be referred to as changes in blood flow.

Data Analysis

The voxel dimensions in the original scans were 2 × 2 × 6.5 mm. Using linear interpolation, scans were converted to 43 slice images with 2 × 2 × 2.27 mm voxels. Alignment of the first scan in the y (anterior-posterior) and z (superior-inferior) dimensions was rectified using the maximum zero-crossover method described by Minoshima et al. (1992). The remaining scans were aligned to the rectified first scan using an iterative procedure that also tested fit using the maximum zero-crossover method (Lee et al., 1991) and found the optimum alignment by iterating seven parameters (scale and six movements: roll, pitch, yaw, x-translation, y-translation, z-translation) with the simplex search algorithm (Nelder and Mead, 1965). These procedures corrected all scans for roll, yaw, and between-scan head movements. These programs were implemented on an Intel iPSC860 parallel supercomputer.

Task-related differences in rCBF were tested using statistical parametric mapping (SPM; Friston et al., 1989, 1990, 1991a,b). SPM consists of three steps: stereotactic normalization, correction for global flow, and task comparisons. Stereotactic normalization is a fully automated procedure that scales each scan to the dimensions of the Talairach and Tournoux (1988) stereotactic atlas brain, aligns the scan to the estimated location of the line connecting the anterior and posterior commissures (AC-PC line), and reshapes the scan, using a nonlinear resampling, to the conformation of a template PET scan. Stereotactic normalization resamples each scan into voxels that are 2 × 2 × 4 mm in the x, y, and z planes, respectively. Scans are then smoothed using a Gaussian filter with a full-width at half-maximum

Table 1
Mean accuracies and response times for the working memory tasks

Task	Accuracy (% correct)	Response time (msec)
Faces working memory		
Practice	83.3 ± 18.0**	1367 ± 377*
PET scan	84.4 ± 12.0*	1311 ± 320*
Location working memory		
Practice	90.4 ± 24.0	959 ± 305
PET scan	98.4 ± 5.0	893 ± 249

Data are mean ± SD.

*Significantly different from location working memory, $p < 0.0001$.

**Significantly different from location working memory, $p < 0.002$.

of 2 cm in x and y, and 1.2 cm in z. After each individual's scan has been resampled into a standard brain coordinate space, statistics are calculated for each voxel sampled in all subjects. rCBF for each voxel is corrected for variations in global blood flow by dividing each voxel value by the global mean for that scan (McIntosh et al., in press). The significance of rCBF differences between sets of task conditions is tested by calculating t tests using the pooled estimate of error variance. Values of t were converted to standard Z values to provide a measure of statistical significance that is independent of sample size.

Individual voxel statistics were corrected for multiple comparisons using a particle analysis method developed by Friston et al. (1994). The experiment-wise probability of a region of activation may be determined from the number of contiguous voxels, all of which exceed some threshold for an individual voxel Z value. Thus, a larger region with a lower Z threshold may have the same probability as a smaller region with a higher Z threshold. The calculation of probabilities is dependent on the size of the search space and the estimated spatial smoothness of the statistical parametric map. Because the estimate of smoothness can vary dependent on the size, number, and intensity of cerebral activations, we used a standard estimate of smoothness that we calculated from comparisons between repeated task conditions in this and other experiments (Haxby et al., 1994a,b). This estimate corresponded to a smoothness (full-width at half-maximum) of 10.2 mm in x , 11.2 mm in y, and 12.7 mm in z (Friston's $W = 2.69$). The search space for this analysis was 70,633 voxels (1130.1 cm^3). The field of view in z was from 24 mm below the AC-PC line to 52 mm above. We set the Z threshold at 2.4, which, for this value of spatial smoothness and size of search space, requires that a region of activation contain at least 236 voxels (3.78 cm^3) to have an experiment-wise probability less than 0.05. Foci for areas demonstrating maximal rCBF differences were identified by finding local maxima, defined as voxels that demonstrated significant rCBF differences and that had Z values higher than any other voxel in a $1.8 \times 1.8 \times 2$ cm ($9 \times 9 \times 5$ voxels) space centered on that voxel.

rCBF values during performance of the two working memory tasks were compared both to the control task rCBF and to each other. Significant increases as compared to the control task were taken to indicate activity that could be attributed to either general visual processing and memory operations, shared by both working memory tasks, or to visual processing and memory operations specific to object or spatial information. Significant differences between the working memory tasks were taken to indicate those areas that were more specifically associated with perceptual and working memory operations related to face identity than to spatial location or vice versa.

Results

Cognitive Testing Performance

Mean response accuracies and reaction times for the two working memory tasks are presented in Table 1. Reaction times were shorter and accuracies were better for the location working memory task than for the face working memory task ($p < 0.002$). Because we equated stimulus parameters for all tasks, performance data could not be equated.

Table 2
Local maxima within areas demonstrating significantly greater rCBF for working memory than for sensorimotor control

	Talairach coordinates			
Area	x	y	z	Z score
Face working memory greater than sensorimotor control				
Bilateral occipitotemporal (94.6 cm^3, $p < 0.0001$)[a]				
Left fusiform gyrus (19)[b]	−35	−78	−5.6	>7.98
Right fusiform gyrus (19)	28	−78	−12	6.93
Midline cerebellum	2	−42	−16	4.09
Right frontal (25.4 cm^3, $p < 0.0001$)				
Middle frontal (45/46)	32	36	20	5.63
Orbital or inferior frontal (11/47)	22	40	−4	3.87
Anterior cingulate (32)	0	20	36	4.07
Left frontal (5.12 cm^3, $p < 0.05$)				
Inferior frontal (44)	−40	8	28	4.12
Location working memory greater than sensorimotor control				
Bilateral occipitoparietal (41.0 cm^3, $p < 0.0001$)				
Right middle occipital (19/7)	26	−76	20	5.08
Left superior parietal (7)	−16	−62	44	4.97
Right superior parietal (7)	14	−62	44	4.79

[a] *Activation volume and probability.*

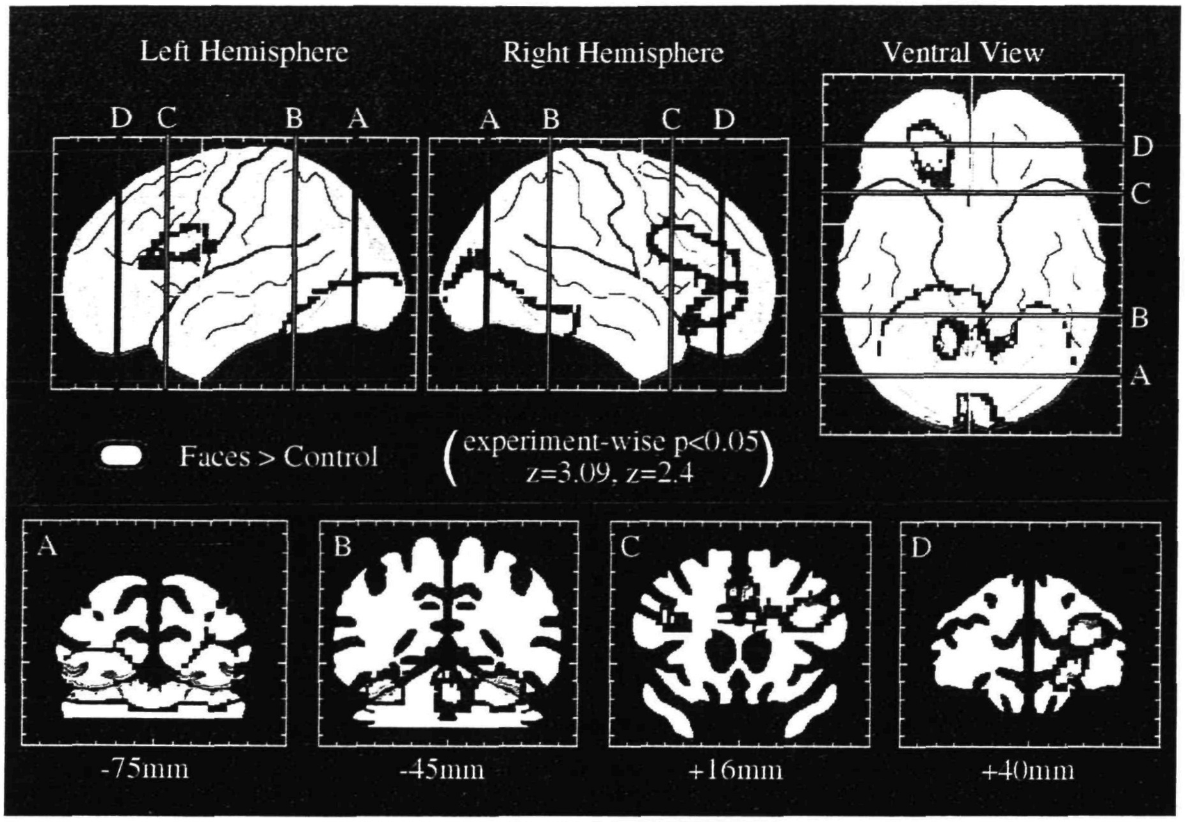
[b] Brodmann area from Talairach and Tournoux atlas.

rCBF Differences

Areas demonstrating significant increases in rCBF during performance of the face working memory task, relative to the sensorimotor control task (experiment-wise $p < 0.05$), are shown in Figure 2. Areas demonstrating significant increases in rCBF during performance of the location working memory task, relative to the control task, are shown in Figure 3. Significant regions of activation are listed in Table 2 with local maxima for each region.

Both tasks showed activation in the right posterior fusiform gyrus [Brodmann area (BA) 19]. In addition to the posterior fusiform gyrus, face, but not location, working memory activated more anterior areas bilaterally in ventral occipitotemporal cortex centered along the fusiform gyrus (BA 18). Activation extended more anteriorly in the right hemisphere than in the left. In the right hemisphere, activation extended anteriorly to 27 mm posterior to the anterior commissure, through the fusiform gyrus, the lingual gyrus (BA 37), and into the parahippocampal gyrus (BA 20/36). In the left hemisphere, activation extended to 37 mm posterior to the anterior commissure. In the right frontal lobe, face working memory activated areas in the middle frontal gyrus (BA 45/46) and in the sulcus between orbital and inferior frontal cortices (BA 11/47). Activation was also seen in left inferior frontal cortex, but this was more posterior (BA 44) than was the inferior frontal activation in the right hemisphere. Increases in rCBF for the face working memory task, relative to the control task, were also seen in anterior cingulate cortex (BA 32) and midline cerebellum. Location, but not face, working memory showed increases in rCBF, relative to the control task, in the right dorsolateral occipital cortex (BA 19/7) and bilaterally in the superior parietal cortex (BA 7).

Comparison of rCBF during performance of each of the two working memory tasks to each other revealed differences in activation between the tasks that were not apparent when comparing each task to the sensorimotor control. As will be presented later, there were areas that showed significantly less activation during the working memory tasks than during the control task. We refer to these areas as being "deactivated." A direct comparison of face and location working memory would produce areas that showed significantly different de-



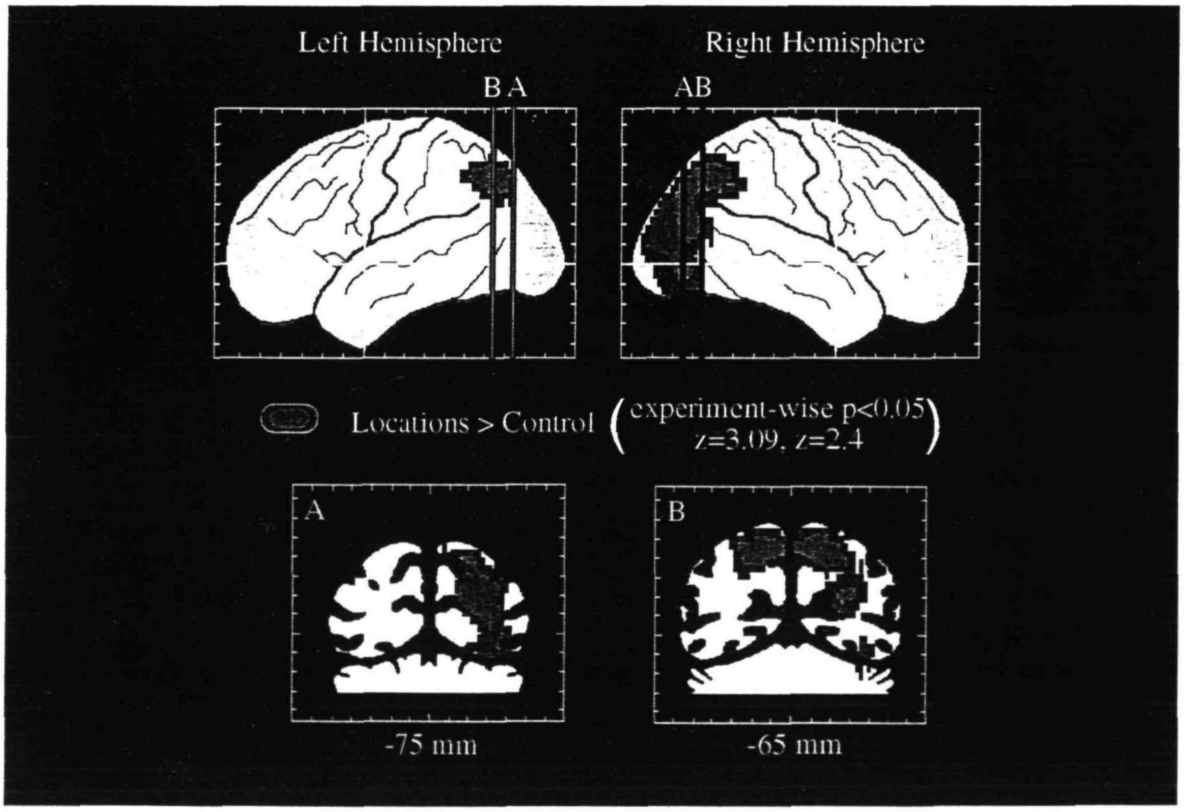


Figure 2. **(top)** Areas showing significantly increased rCBF during the face working memory task as compared to the sensorimotor control task. Lateral and ventral views are maximum intensity projections onto the surface of the brain. *Tick marks* indicate 1 cm intervals. *Longer white lines* indicate the locations of the interhemispheric fissure and anterior commissure, the major axes defining the coordinate space for the Talairach and Tournoux (1988) stereotactic brain atlas. Coronal sections are adapted from the Talairach and Tournoux stereotactic atlas. In the coronal sections the right hemisphere is shown on the right and the left hemisphere is on the *left*. The plane for each coronal section is indicated on the lateral and ventral views.

Figure 3. **(bottom)** Areas showing significantly increased rCBF during the location working memory task as compared to the sensorimotor control task.

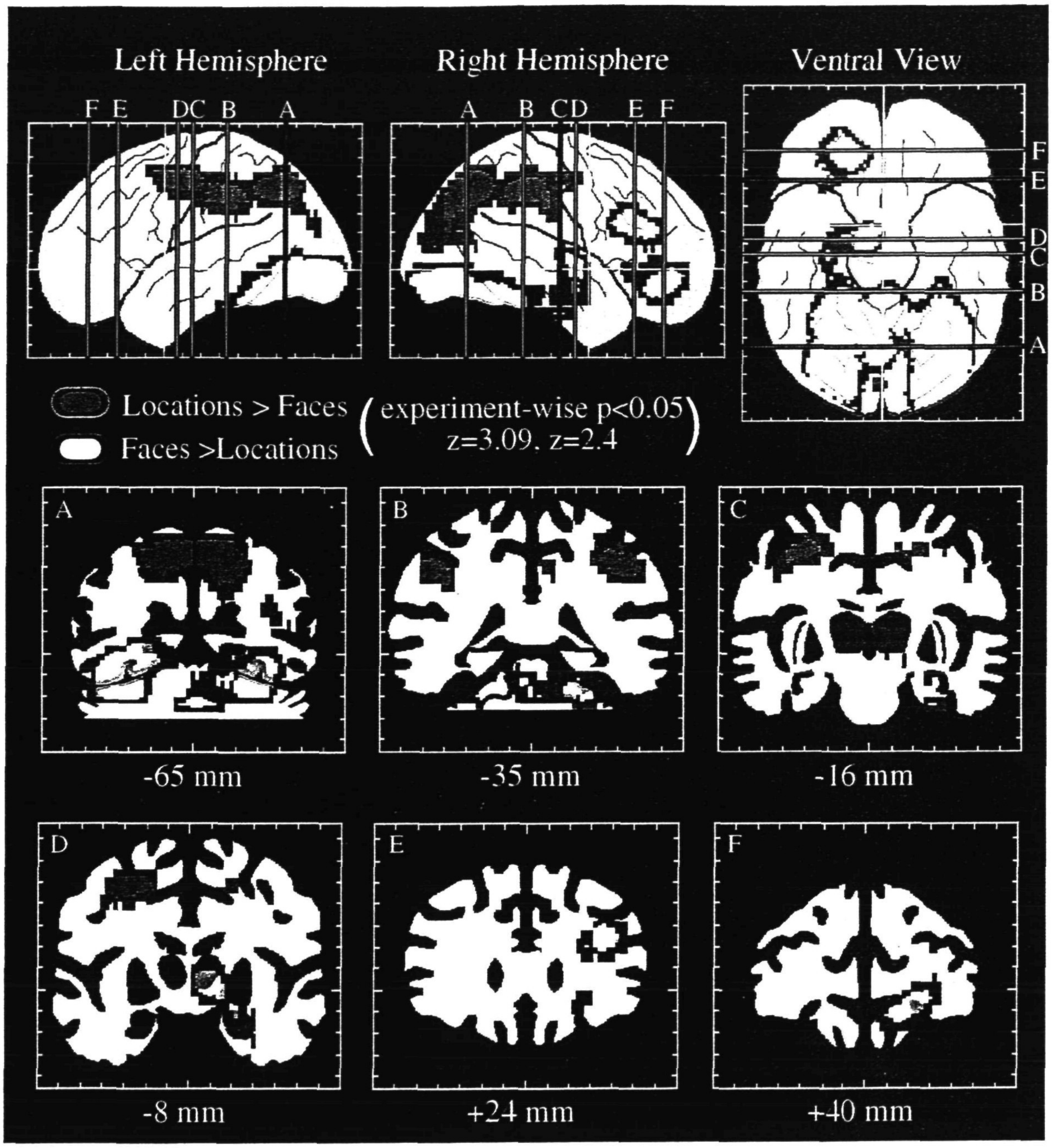


Figure 4. Areas showing significantly increased rCBF during each of the working memory tasks as compared to the other working memory task.

activations as well as significantly different activations. In order to isolate the differences in activations from the differences in deactivations, the statistical maps for the comparisons of the two working memory tasks to each other were masked as follows, using the comparison to the sensorimotor control. After the Z scores were computed for differences between object and spatial working memory, the statistical maps were masked so that voxels that showed a decrease for both tasks relative to the sensorimotor control were eliminated from the analysis. As will be presented later, these included auditory, motor, and somatosensory cortices. Figure 4 shows significant differences in rCBF from direct comparisons between the two working memory tasks. Significant regions of activation are listed in Table 3 with local maxima for each region.

The occipitotemporal region of significant rCBF increase for face as compared to location working memory extended farther anteriorly than when face working memory was compared to the sensorimotor control. This finding suggests that small increases in rCBF during face working memory (in the thalamus: 1.74 cm^3; p = 0.54; local maximum, 6, −4, 4; Z score, 3.55; in the parahippocampal gyrus: 0.18 cm^3; p = 0.99; local maximum, 28, −16, −24; Z score, 2.78) were enhanced by small decreases during location working memory in nearby cortex (1.74 cm^3; p = 0.54; local minimum, 30, −2, −20; Z score, 3.16), although neither activation reached significance

Table 3
Local maxima within areas demonstrating significantly greater rCBF for working memory for faces versus working memory for spatial location

Area	Talairach coordinates x	y	z	Z score
Face working memory greater than location working memory				
Bilateral occipitotemporal (89.1 cm^3, $p < 0.0001$)[a]				
Left fusiform gyrus (18)[b]	−34	−76	−8	6.84
Right fusiform gyrus (18)	28	−78	−12	4.84
Cerebellum or lingual gyrus (37)	24	−46	−20	4.25
Midline cerebellum	4	−68	−24	4.38
	−4	−42	−16	3.90
Thalamus	6	−4	4	4.20
Right parahippocampal gyrus (20/36)	29	−17	−24	3.31
Right orbital frontal (6.66 cm^3, $p < 0.01$)				
Orbital frontal (11)	16	38	−8	4.16
Right inferior frontal (6.27 cm^3, $p < 0.01$)				
Inferior frontal (9/45/46)	36	26	24	4.02
Location working memory greater than face working memory				
Bilateral occipitoparietal, and right frontal (43.9 cm^3, $p < 0.0001$)[a]				
Calcarine fissure (17)[b]	2	−82	12	3.81
Left middle occipital (19)	−26	−80	24	2.68
Left inferior parietal (40)	−44	−32	40	4.52
Right inferior parietal (40)	42	−32	40	4.43
Left superior parietal/precuneus (7)	−14	−64	44	5.08
Right superior parietal/precuneus (7)	8	−60	44	5.41
Right superior frontal sulcus (6/8)	20	−14	48	2.79
Left precentral/superior frontal (11.4 cm^3, $P < 0.0001$)				
Left superior frontal sulcus (6/8)	−30	−8	48	4.90

[a] Activation volume and probability.

[b] Brodmann area from Talairach and Tournoux atlas.

Table 4
Local maxima within areas demonstrating significantly more rCBF for sensorimotor control than for working memory

Area	Talairach coordinates x	y	z	Z score
Sensorimotor control greater than face working memory				
Left parietal and temporal (54.4 cm^3, $p < 0.0001$)[a]				
Left middle temporal (21)[b]	−50	−6	−12	3.76
Left inferior parietal (40)	−48	−36	24	5.90
Right temporal (26.8 cm^3, $p < 0.0001$)				
Superior temporal (22)	48	−36	16	5.62
Insula	34	−2	4	4.12
Posterior medial frontal (18.5 cm^3, $p < 0.0001$)				
Posterior cingulate (7/31)	−4	−42	40	4.87
Posterior medial frontal (6)	0	−6	52	3.26
Right posterior medial or superior frontal (6)	18	−1	52	2.87
Anterior medial frontal (11.2 cm^3, $p < 0.0001$)				
Anterior medial frontal (9)	−4	52	20	4.02
Left frontal (4.08 cm^3, $p < 0.05$)				
Superior or middle frontal (6/8)	−24	14	48	4.09
Sensorimotor control greater than location working memory				
Left temporal (16.75 cm^3, $p < 0.0001$)[a]				
Inferior temporal (20)	−58	−22	−20	3.53
Superior temporal (22)	−42	8	−12	3.33
	−54	−26	8	3.21
Middle temporal (21)	−54	−46	4	3.31
	−48	−8	−4	3.22
Inferior parietal (40)	−52	−44	24	2.90
Right temporal (4.42 cm^3, $p < 0.05$)				
Superior temporal (22)	48	−34	16	3.72
(21)	46	−24	0	3.32
Right frontal (6.33 cm^3, $p < 0.05$)				
Anterior medial or superior frontal (9)	12	48	24	3.27

[a] Activation volume and probability.

[b] Brodmann area from Talairach and Tournoux atlas.

when the working memory tasks were compared to the sensorimotor control. The additional areas of activation for the face working memory task include more extensive activation of the right parahippocampal gyrus, amygdala, and thalamus.

The comparison of the location to the face working memory task also revealed additional areas of activation not seen in the comparison to the control. These additional areas included bilateral inferior parietal cortex (BA 40), the precuneus (BA 7), and bilateral superior frontal sulcus (BA 6/8). There was also a suggestion of activation in the left superior frontal sulcus in comparison to the sensorimotor control task, but in that comparison the area did not reach significance (1.71 cm^3; $p = 0.50$; local maxima, −22, 2, 24; $Z = 3.20$). The additional areas seen in the direct comparison of location to face working memory are in or near regions showing decreased rCBF during faces working memory, relative to the sensorimotor control. These decreases are detailed below. As with the comparison of face working memory to location working memory, it is the combination of increases and decreases in rCBF (relative to the sensorimotor control) that occurs when the working memory tasks are compared directly to each other, that causes these additional areas of activation to become significant.

The areas that demonstrated significant rCBF decreases during performance of the working memory tasks, relative to the sensorimotor control, are shown in Figures 5 and 6. Local maxima for areas with decreased rCBF are listed in Table 4. Decreased rCBF was seen for both the face and location working memory tasks in bilateral superior temporal cortex (BA 22), left middle (BA 21) and inferior (BA 20) temporal cortex, left inferior parietal cortex (BA 40), and the anterior medial frontal gyrus (BA 9). In addition, face, but not location, working memory showed decreases in posterior cingulate cortex (BA 7/31), right insular cortex, and bilateral posterior superior frontal cortices (BA 6/8). rCBF decreases in inferior parietal cortex were more extensive during face working memory than during location working memory, and included postcentral somatosensory cortex. The posterior superior frontal rCBF decreases (local maxima: −24, 14, 48, $Z = 4.09$; 0, −6, 52, $Z = 3.26$; 18, −1, 52, $Z = 2.87$) were close to the superior frontal sulcus rCBF increases (local maxima: −30, −8, 48, $Z = 4.90$; 20, −14, 48, $Z = 2.79$) seen in the comparison of location to face working memory. These decreases probably contributed to the significant rCBF increases in both the left and right superior frontal sulci obtained when the location working memory task was compared to the face working memory task. In general, the areas demonstrating significant rCBF decreases were in primary and association cortices for unattended sensory modalities, namely audition and somesthesis.

Discussion

Results from the present study demonstrated that both face and location working memory tasks activate frontal cortex, but that the regions activated by each task are distinct. The frontal area activated by location working memory, in the superior frontal sulcus, was dorsal to the middle, inferior, and orbital frontal areas activated by face working memory. In addition to the segregation in frontal cortex, the face and location working memory tasks also activated distinct areas in extrastriate cortex. Whereas both tasks showed activation in the right posterior fusiform gyrus, only face working memory activated more anterior areas bilaterally in ventral occipitotemporal cortex centered along the fusiform gyrus, and only location working memory activated the right dorsolateral occipital cortex, and the precuneus and superior and inferior parietal cortices bilaterally. The segregation of spatial and object processing into dorsal and ventral streams in extrastriate cortex as well as their segregation within frontal cortex agrees well with the organization of these areas in the macaque brain (Ungerleider and Mishkin, 1982; Wilson et al., 1993), suggesting a common primate plan.

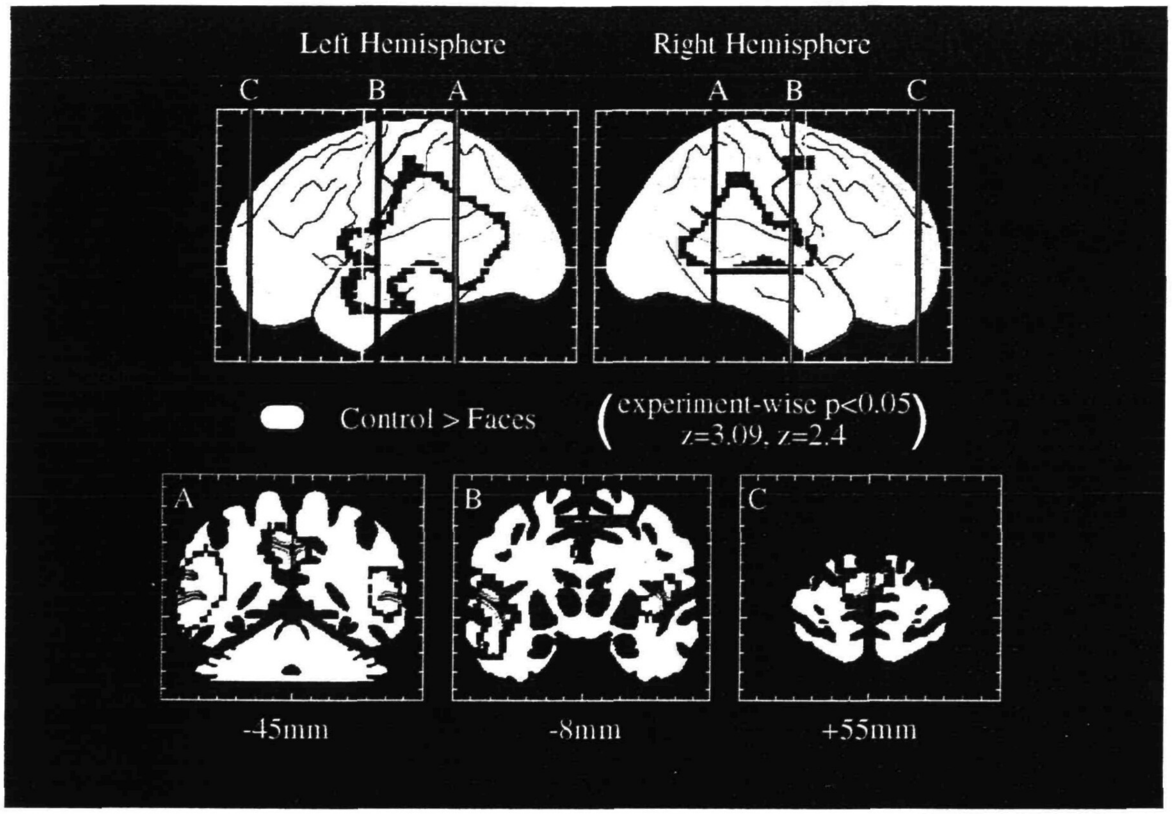
Based on work in monkeys as well as our prior imaging studies in humans (Haxby et al., 1995), the activations in extrastriate cortex appear to reflect primarily perceptual processes, whereas activations in frontal lobe reflect primarily the working memory aspects of the tasks. There is, for example, extensive evidence from studies of delayed response tasks in nonhuman primates that the frontal lobes are involved in maintaining an active representation of a stimulus after it has been removed from view (Fuster, 1985, 1990; Goldman-Rakic, 1990; Wilson et al., 1993). Although the present study cannot distinguish regions involved in the perceptual aspects of the task from those involved in the working memory aspects, in a separate report of face working memory we showed a dissociation between perceptual functions associated with extrastriate areas and working memory functions associated with frontal areas. This dissociation was demonstrated by parametrically varying the length of the delay between the stimulus to be remembered and the test stimulus. Extrastriate areas were shown to have a negative correlation with delay length, indicating that they were primarily involved in perceptual processing. Frontal areas, however, did not decline systematically with delay length, indicating more involvement with the working memory aspects of the task (Haxby et al., 1995).

The anatomical location of the location working memory frontal activation deep in the superior frontal sulcus makes assigning a designation of prefrontal or premotor cortex premature. The Talairach atlas is ambiguous as to whether this area corresponds to Brodmann area 6 or 8. However, what is clear is that this same area has been seen in several different studies of spatial working memory and other visuospatial tasks. The location working memory task in the present study activated an area bilaterally that was nearly identical to the right dorsal frontal area found in earlier studies of location working memory (Jonides et al., 1993) and location matching (Haxby et al., 1994a). A similar, though slightly more anterior, area of activation was seen bilaterally in a study of shifting spatial attention (Corbetta et al., 1990). A study of spatial working memory using functional magnetic resonance imaging by McCarthy et al. (1994) could not have seen this activation because only a single image was collected at 4 cm anterior to the anterior commissure and therefore would not have included this portion of the superior frontal sulcus.

During all of the tasks in the present study, subjects were instructed to look directly at each picture as it appeared, but eye movements were not monitored. Although we cannot rule out the possibility that rCBF differences between the two working memory tasks are due to differences in eye movements, comparison of our results to PET rCBF studies of eye movements suggests that the areas in the superior frontal sulcus associated with our location working memory task are distinct from the frontal eye fields, which are known to be associated with saccades (Bruce and Goldberg, 1985). A recent PET-rCBF study of voluntary saccades found a network of areas associated with them, including the precentral gyrus, supplementary motor area, midcingulate cortex, lenticular nucleus, and thalamus (Petit et al., 1993), none of which was selectively activated by our location working memory task. The putative frontal eye field in this recent study and in two earlier PET-rCBF studies (Fox et al., 1985; Colby and Zeffiro, 1990; but see Anderson et al., 1994) was located in the precentral gyrus, and thus more lateral than the frontal area, located in the superior frontal sulcus, that was selectively activated by location working memory in this and a previous study (Jonides et al., 1993) and by spatial location matching (Haxby et al., 1994a). Because of the proximity of the superior frontal sulcus area to premotor cortex, it may be tempting to dismiss this activation as related to motor preparedness rather than to working memory. However, because of the agreement of our results with other studies of spatial working memory, all of which controlled for motor aspects of the tasks, and the difference between the superior frontal area of activation and that of previous studies of eye movements, we believe that this area participates in spatial working memory.

Some might argue that the middle frontal cortical area (BA 9/45/46) may be a more likely human homolog to the principal sulcus and arcuate area, which appears to be involved in spatial working memory in the macaque. Indeed, this middle frontal area was activated in studies of location working memory by McCarthy et al. (1994) and by Owen et al. (1995). McCarthy et al. found that this area was also significantly activated by their control tasks, which required attention to peripheral locations. However, other studies of nonspatial working memory have also found activation in or near Brodmann area 46, suggesting that this area may play a more general role in working memory (Grasby et al., 1993; Petrides et al., 1993a; Cohen et al., 1994). The present study showed a small, statistically insignificant increase in the middle frontal gyrus for location working memory relative to the control task (0.22 cm^3; p = 0.99; local max, 32, 40, 16; Z score, 2.50), indicating that although this area may participate in spatial working memory, its participation is weaker than the more dorsal area in the superior frontal sulcus. It may be that the middle frontal area is more strongly activated by more difficult working memory tasks. It is also possible that our control task, which included a delayed alternation component in the motor response, may have partially masked the participation of this area in spatial working memory. In the present study, however, the middle and inferior frontal areas seem to participate more vigorously in object working memory and the superior frontal sulcal area seems to participate more selectively in spatial working memory. McCarthy et al. might also have found a much stronger and more selective activation for location working memory in the superior frontal sulcus had they included more posterior slices in their analysis. In summary, the locations of the human homologs for the nonhuman primate functional areas in prefrontal cortex are still unclear.

The right anterior inferior frontal area activated only by face working memory in the present study was also seen in both the location working memory study by Jonides et al. (1993) and the face working memory study by Haxby et al. (1995). This finding may indicate a more general role in visual working memory for the inferior frontal region, or, alternatively, it may indicate that the spatial working memory task used by Jonides et al. could have been mediated, in part, by an object working memory strategy. Their task involved remembering the location of three simultaneously presented dots and could be performed by remembering the shape of the triangle defined by the three dots. The present study used a sequential, instead of simultaneous, presentation of locations, which was intended to reduce subjects' tendency to use an object-based strategy. More importantly, however, the location and face working memory tasks were done within the same study using the same stimuli, so that rCBF differences could be unambiguously attributed to the difference between



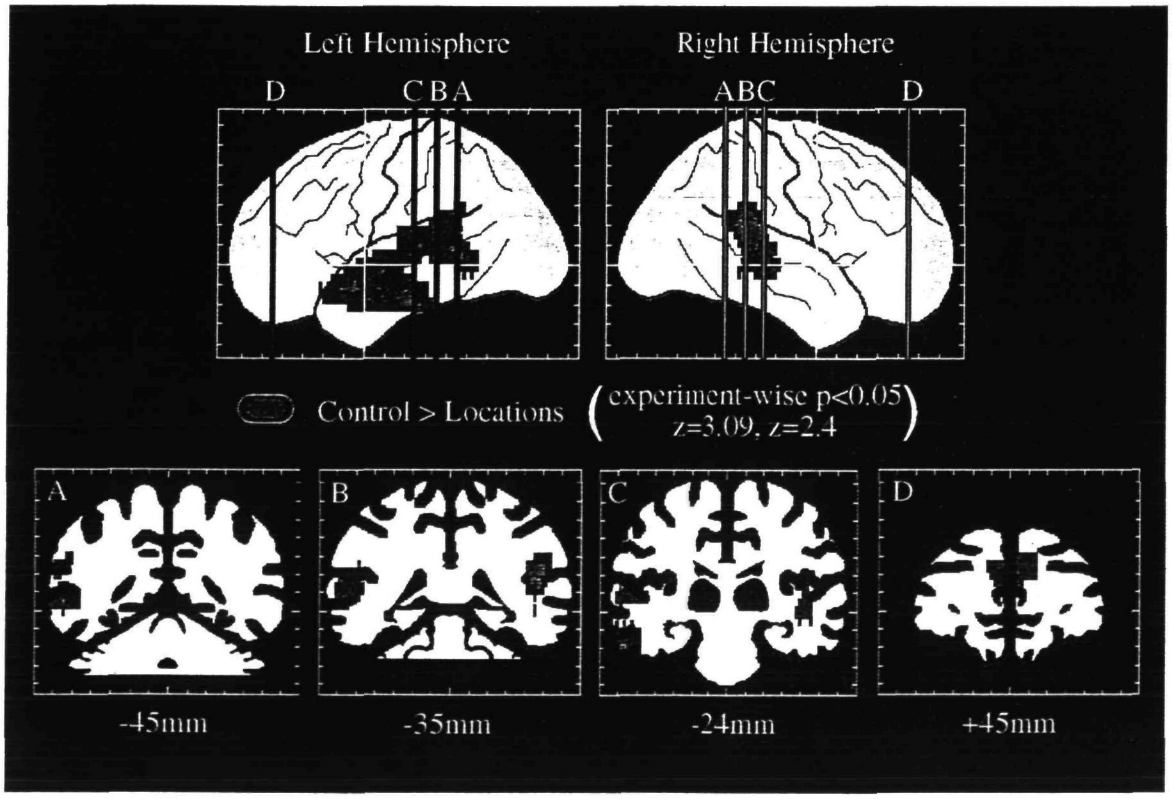


Figure 5. (top) Areas showing significantly decreased rCBF during the face working memory task as compared to the sensorimotor control task.

Figure 6. (bottom) Areas showing significantly decreased rCBF during the location working memory task as compared to the sensorimotor control task.

the cognitive demands of face and location working memory task differences, and not to stimulus differences. Therefore, it seems likely that the inferior frontal area is associated more with object working memory than with a more general working memory function.

In addition to the prefrontal and extrastriate areas mentioned above, the face working memory task activated other cortical and subcortical regions not seen in previous studies using the same face pictures in simultaneous match-to-sample tests of face perception (Haxby et al., 1995). These regions included more anterior extrastriate areas and the thalamus. The activation of these additional regions may reflect a deeper level of face processing or their direct participation in working memory (Miller et al., 1991; Sergent et al., 1992; Haxby et al., 1994a, 1995), or both.

The present study showed significant rCBF increases in both left and right superior frontal cortices for location working memory as compared to face working memory. The rCBF increase was greater in the left hemisphere. In the studies of Jonides et al. (1993) and Haxby et al. (1994a), however, only the activation in the right hemisphere was statistically significant, although nonsignificant rCBF increases were also apparent in a homologous area on the left. Corbetta et al. (1990) found bilateral superior frontal activation in their study of shifting spatial attention. While these hemispheric differences between studies may be due to cognitive differences between the tasks, in general, the superior frontal spatial vision area appears to be bilateral.

The midfrontal area activated by the face working memory task appeared to be bilateral also, although only the rCBF increases in the right hemisphere reached statistical significance. The more anterior inferior frontal area activated by the face working memory task was present only in the right hemisphere. The middle and inferior frontal cortical areas in the right hemisphere have also been activated by long-term memory retrieval for faces (Haxby et al., 1993a), working memory for faces with a 1 sec delay (Haxby et al., 1995), and face matching (Haxby et al., 1994a). In a separate report, we have suggested different roles for the right and left hemispheres during working memory for faces (Haxby et al., 1995), with the right hemisphere retaining an image-based representation of the face that is viable only over brief delays, and the left hemisphere maintaining an analytical representation that is more durable. The relatively brief delays (0.5-3.5 sec) in the present study may have allowed for the more image-based working memory strategy. In addition, because the faces were familiar, right frontal activity may reflect recognition of familiarity and the retrieval of associations previously made for each face (Haxby et al., 1993a; Tulving et al., 1994). On the left, the inferior frontal activation for face working memory was in Broca's area, more posterior than the activation in the right hemisphere. The activation of both of these right and left prefrontal areas is consistent with the subjects' reports of using either an imagery-based strategy (presumably right hemisphere dominant), or a feature-based verbal strategy (presumably left hemisphere dominant), or both.

We also found increases in rCBF during the face working memory task in midline cerebellum. The motor components of all the tasks were equivalent, indicating that this activation is cognitive rather than motor. There is a growing body of evidence for the involvement of the cerebellum in cognitive, nonmotor tasks, including memory and attention (Leiner et al., 1993; Kim et al., 1994). However, these previous reports have focused on the role of the dentate nucleus, whereas the activation seen in the present study is in midline cerebellum. We have no explanation at this time for the role of the activation of the cerebellum during the face working memory task.

In addition to the rCBF increases that were seen during the working memory task, significant rCBF decreases were also seen. These reductions were observed during performance of both working memory tasks, although they were more extensive for face working memory than for location working memory. The region showing greatest rCBF reductions for both working memory tasks was in the superior temporal gyrus and included primary auditory and auditory association cortices. Both tasks also showed significant reductions in anterior medial frontal cortex. The face working memory task, but not the location working memory task, showed reductions in supplementary motor cortex, specifically in the posterior medial frontal gyrus. The face working memory task also showed decreases in rCBF in postcentral somatosensory cortex, inferior parietal cortex, and in the posterior cingulate. These reductions replicate an earlier finding from this laboratory (Haxby et al., 1994) and support our previous conclusion that selective attention to visual stimuli may be associated with suppression of neural activity in areas that process input from unattended sensory modalities. This conclusion is supported by evidence from the animal literature (Hernandez-Peon et al., 1956; Hocherman et al., 1976; Oatman, 1976) and from previous PET-rCBF studies in humans (Mazziotta et al., 1982; Kawashima et al., 1993).

More extensive activation was observed in the present experiment when the two working memory tasks were compared to each other than when each was compared to the sensorimotor control task. This difference can be explained by the existence of small activations during one working memory task, compared to the control task, and small deactivations during the other working memory task. Thus, for the face working memory task, the increased cortical extent of the activation in the temporal lobe was probably due to decreased rCBF in the anterior fusiform and parahippocampal gyrus during the location working memory task relative to the control task, although these decreases were not significant. The reason for this small decrease during location working memory relative to the control task is unclear. For the location working memory task, the additional extrastriate regions of activation, in bilateral inferior parietal cortex, are probably due to their proximity to the superior temporal gyrus deactivation and to the postcentral somatosensory deactivation during the face working memory task. The additional frontal regions of activation, in the bilateral superior frontal sulcus, during the location working memory task, are probably due to their proximity to the superior frontal/posterior cingulate deactivation.

The proximity of these areas of activation and deactivation may, likewise, explain why the cross-modality suppression appears to be much greater for the face working memory task than for the location working memory task. If the location working memory task produced cross-modal deactivations that are similar to those in the face working memory task, then these areas of deactivation would be very close to some of the areas of activation. Spatial smoothing (before the statistical analysis) and intersubject averaging may cause these areas of activation and deactivation during the location working memory task to cancel each other out.

Conclusion

Our results show that the neural systems involved in working memory for faces and for spatial location are functionally segregated, with different areas recruited in both extrastriate and frontal cortices for processing the two types of visual information. This finding indicates that one of the three components in the Baddeley and Hitch (1974) model of working memory, the visuospatial sketch pad, can be further divided into two functionally and anatomically distinct systems for visual object working memory and visual spatial working memory.

Notes

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