Evidence for a Two-Stage Model of Spatial Working Memory Processing within the Lateral Frontal Cortex: A Positron Emission Tomography Study

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Previous work in nonhuman primates and in patients with frontal lobe damage has suggested that the frontal cortex plays a critical role in the performance of both spatial and nonspatial working memory tasks. The present study used positron emission tomography with magnetic resonance imaging to demonstrate the existence, within the human brain, of two functionally distinct subdivisions of the lateral frontal cortex, which may subserve different aspects of spatial working memory. Five spatial memory tasks were used, which varied in terms of the extent to which they required different executive processes. When the task required the organization and execution of a sequence of spatial moves retained in working memory, significant changes in blood flow were observed in ventrolateral frontal cortex (area 47) bilaterally. By contrast, when the task required active monitoring and manipulation of spatial information within working memory, additional activation foci were observed in mid-dorsolateral frontal cortex (areas 46 and 9). These findings support a two-stage model of spatial working memory processing within the lateral frontal cortex.

There is considerable evidence that the frontal cortex plays a critical role in certain aspects of working memory. This evidence comes both from the study of patients with excisions of frontal cortex (Petrides and Milner, 1982; Owen et al., 1990, 1995) and from lesion and electrophysiological recording work on nonhuman primates (see Goldman-Rakic, 1987, for review). In the monkey, it has been shown that lesions confined to one part of the dorsolateral frontal cortex, namely the cortex lining the sulcus principalis (i.e., area 46) result in severe impairments on tests of spatial working memory, such as the spatial delayed alternation and delayed response tasks (see Goldman-Rakic, 1987; Fuster, 1989).

On the basis of an analysis of the nature of the impairment on nonspatial self-ordered working memory tasks shown by monkeys with lesions of the mid-dorsal lateral frontal cortex (Petrides, 1991a,b, 1995), a general theoretical framework regarding the role of the frontal cortex in mnemonic processing and its relationship to planning and other executive processes has recently been proposed (Petrides, 1994). According to this view, there are two executive processing systems within the lateral frontal cortex. The middle portion of the ventrolateral frontal cortex (i.e., areas 45 and 47) underlies active comparisons made about stimuli held in short-term memory as well as the active organization of sequences of responses based on conscious, explicit retrieval of information from posterior cortical association systems. In this sense, this region serves as one level of interaction between short-term and long-term memory systems and executive processing. By contrast, the mid-dorsolateral frontal cortex (dorsal area 46 and area 9) is assumed to constitute another level of interaction of executive processes with memory and is recruited only when active manipulation and monitoring of information within working memory is required. By monitoring, we refer to the active checking of information as occurs, for example, when a subject is required to decide which items in a given array of stimuli have been selected previously, and which ones have not. This two-stage model of lateral frontal cortical function describes how both spatial and nonspatial stimuli are retained and manipulated within working memory. The model makes a number of specific predictions, some of which have recently been tested with nonspatial stimuli in functional activation studies with positron emission tomography (PET). Thus, Petrides et al. (1993) have reported significant increases in regional cerebral blood flow (rCBF) within the mid-dorsolateral frontal cortex (areas 46 and 9) on a visual nonspatial self-ordered working memory task in which the subjects were required to monitor which ones of a set of stimuli had been selected and which ones had not. In a related study, when subjects were required to make judgements about, but not to manipulate, similar visual stimuli within working memory, a significant increase in blood flow was observed only in ventrolateral frontal cortex (Petrides et al., unpublished observations).

The present PET study was designed to investigate whether this two-stage model of lateral frontal cortical function may also apply to the contribution of the frontal cortex to spatial working memory. Normal subjects were scanned while performing five different spatial working memory tasks that differed in terms of the extent to which they required active monitoring and manipulation of the stored information. It was predicted that the tasks requiring active judgements about the contents of working memory and the organization of appropriate responses but that had minimal monitoring requirements would only activate ventrolateral areas within the frontal lobe. By contrast, performance on tasks that required monitoring and manipulation of spatial information within working memory would activate areas within the mid-dorsolateral frontal cortex (i.e., areas 46 and 9).

Materials and Methods

Scanning Methods and Data Analysis

PET scans were obtained with the Scanditronix PC-2048 system, which produces 15 image slices at an intrinsic resolution 5.0 × 5.0 × 6.0 mm (Evans et al., 1991a). In this study, the resultant "field of view," within which PET data from all 16 subjects was obtained, extended from 24 mm below the anterior-posterior commissure line (AC-PC line) to 61 mm above it. The relative distribution of regional cerebral blood flow (rCBF) was measured with the bolus $H_2{}^{15}O$ methodology (Raichle et al., 1983), without arterial sampling (Fox and Raichle, 1984). For each subject, a high-resolution magnetic resonance imaging (MRI) study (whole brain, 1 mm^3 voxels, 3-D sagittal acquisition) was also obtained from a Philips Gyroscan 1.5T and resliced so as to be coregistered with the PET data (Evans et al., 1991b). An orthogonal coordinate frame was then established based on the AC-PC line as defined in the MRI volume (Evans et al., 1992). These coordinates were used to apply a trilinear resampling of each pair of MRI and PET data sets into a standardized stereotaxic coordinate system (Talairach and Tournoux, 1988). To overcome residual anatomical variability persisting after stereotaxic standardization, the PET images were reconstructed with a 20 mm filter and then normalized for global rCBF and averaged across subjects within each scanning condition. The mean state-dependent change rCBF image volume was obtained (Fox et al., 1985) and converted to a t statistic volume by

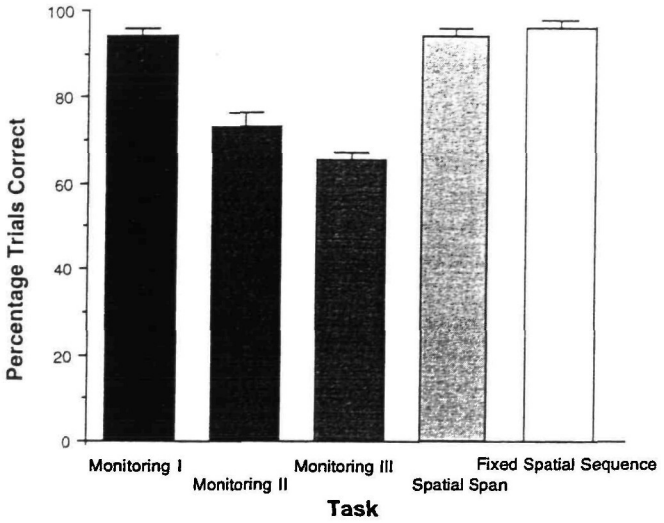

Figure 1. Performance data from the five spatial memory tasks. In each case, the percentage of total trials completed without an error is shown. Errors bars are SEM.

dividing each voxel by the mean standard deviation in normalized CBF for all intracerebral voxels (Worsley et al., 1992).

Individual MRI images were subjected to the same averaging procedure, such that composite stereotaxic image volumes sampled at approximately 1.5 mm in each dimension were obtained for both *t* statistic and MRI volumes. Anatomical and functional images were merged to allow direct localization on the MRI images of *t* statistic peaks identified by an automatic peak-detection algorithm.

The significance of a given change in rCBF was assessed by application of an intensity threshold to the *t* statistic images (Worsley et al., 1992). This threshold, based on 3-D Gaussian random field theory, predicts the likelihood of obtaining a false positive in an extended 3-D field. For an exploratory search involving all peaks within the gray matter volume of 600 cm^3 or 200 resolution elements (resels), the threshold for reporting a peak as significant was set at $t = 3.5$, corresponding to an uncorrected probability of $p < 0.0002$ (one tailed). Correcting for multiple comparisons, a *t* value of 3.5 yields a false positive rate of only 0.58 in 200 resels (each of which has dimensions 20 × 20 × 7.6 mm), which approximates the volume of cortex scanned. For the directed search within the mid-dorsolateral and mid-ventrolateral frontal regions for predicted activation foci in specific cytoarchitectonic areas, we selected a search volume of 150 cm^3 or 50 resels. On this basis, the threshold for significance within these regions was set at a conservative value of $t = 3.00$, corresponding to an uncorrected probability of $p < 0.0013$.

Subjects

Sixteen normal right-handed volunteer subjects, eight male and eight female, participated in the study. Each subject underwent seven, 60 sec PET scans within a single session and an MRI scan on a different day. Six of the seven scanning conditions administered pertain to the current study. The ages of the subjects ranged from 21 to 25 years (mean age, 21.56 yrs). All subjects gave informed, written consent for participation in the study after its nature and possible consequences were explained to them. The study was approved by the Ethics Committee of the Montreal Neurological Institute.

Table 1
Stereotaxic coordinates of activation obtained when spatial monitoring I was compared with the Control condition

Region	Stereotaxic coordinates X	Y	Z	*t* statistic
Spatial monitoring I minus control condition				
Right hemisphere				
Mid-dorsolateral frontal cortex (area 9/46)	35	30	29	3.09
Premotor cortex (area 6)	30	3	50	5.69
Sensorimotor cortex (area 1/2)	54	−26	41	3.97
Intraparietal sulcal cortex (area 7/40)	44	−40	51	7.15
Posterior parietal cortex (area 7)	27	−62	54	7.78
Primary visual cortex (area 17)	16	−64	12	6.72
Parieto-occipital sulcus (area 7/19)	31	−76	30	5.19
Primary visual cortex (area 17)	13	−83	5	5.45
Left hemisphere				
Premotor cortex (area 6)	−28	1	54	5.01
Posterior parietal cortex (area 7)	−21	−49	45	4.45
Medial posterior parietal cortex (area 7)	−12	−69	54	8.09
Primary visual cortex (area 17)	−17	−74	11	4.87
Control condition minus spatial monitoring I				
Right hemisphere				
Cingulate cortex (area 32)	8	30	−11	5.30
Ventrolateral frontal cortex (area 45)	47	22	6	4.98
Inferior frontal cortex (area 44)	47	6	11	5.46
Insula	36	−2	0	3.58
Left hemisphere				
Frontopolar cortex (area 10)	−9	63	12	5.71
Orbitofrontal cortex (area 11)	−21	42	−9	5.38
Ventrolateral frontal cortex (area 45)	−51	18	2	5.22
Supplementary motor cortex (area 6)	−4	−9	62	4.69
Middle temporal cortex (area 21)	−55	−54	5	4.27
Posterior parietal cortex (area 39)	−56	−57	29	5.32

Activation foci in this and the other tables represent peaks of statistically significant (see text) changes in normalized rCBF. The stereotaxic coordinates are expressed in mm. x, medial-to-lateral distance relative to the midline (positive = right hemisphere); y, anterior-to-posterior distance relative to the anterior commissure (positive = anterior); z, superior-to-inferior distance relative to the anterior commissure-posterior commissure line (positive = superior). Significance level is given in *t* test units (see Materials and Methods for details).

Stimuli and Testing Conditions

The stimuli used in all six conditions of this study were colored circles (1 cm in radius) presented, on a black background, on a high-resolution, touch-sensitive screen. The screen was suspended approximately 50 cm above the subject and was therefore within comfortable reach. The order in which the six conditions were administered was randomly arranged across subjects with the restriction that no two subjects performed the tasks in the same order. Each PET scan lasted 60 sec and testing on the task was initiated 10 sec before scanning began. All subjects completed the same fixed number of trials in each condition, the performance lasting for approximately 90 sec in total. Performance data were collected during this 90 sec period. The scans were separated by approximately 10 min, during which time the requirements of the task to be administered in the next scanning condition were explained to the subject and practice problems were administered to ensure that the task had been fully understood.

There were five experimental conditions and one control condi-

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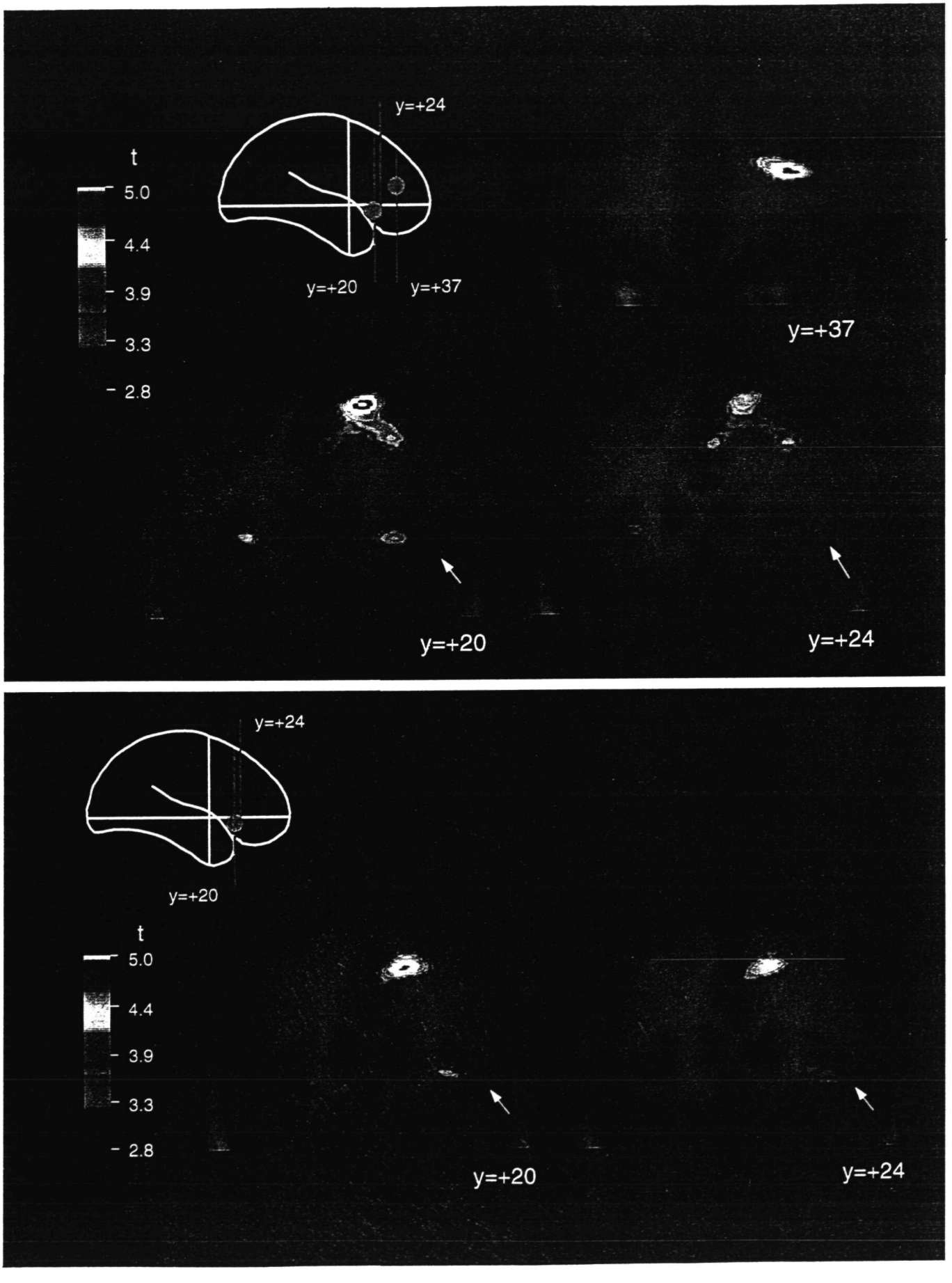
Figure 2. Spatial monitoring II minus control condition: merged PET-MRI sections illustrating rCBF increases averaged for all 16 subjects. The schematic outline of the brain indicates, in *red*, the level (y-coordinate) of the coronal sections rostral to the anterior commissure. The *green dots* indicate the sites of activation within the mid-dorsolateral and ventrolateral frontal cortex presented in these sections. The subject's left is on the left side of the images. The *top right section* (y = +37) shows activation within the right mid-dorsolateral frontal cortex (area 46). The *bottom left* (y = +20) and *bottom right* (y = +24) images show bilateral activation within the ventrolateral frontal cortex (area 47). The activation foci within the ventrolateral frontal cortex are located directly below the horizontal ramus, which is marked on the images with a *white arrow*. Significant activation foci within the premotor cortex (area 6), the mid-dorsolateral frontal cortex (area 9), and the anterior cingulate cortex are also clearly visible on these lower images.

Figure 3. Spatial span minus control condition: merged PET-MRI sections illustrating rCBF increases averaged for all 16 subjects. The schematic outline of the brain indicates the level (*red lines*) of the coronal sections shown and the *green dot* indicates the site of activation within the ventrolateral frontal cortex (area 47) presented in those sections (y = +20 and +24). The subject's left is on the left side in these images. Note that the activation foci are located directly below the horizontal ramus, which is marked on the images with a *white arrow*. A significant activation focus within the premotor cortex (area 6) is also clearly visible on these images.


y=+24
t
5.0
4.4
3.9
3.3
2.8
y=+20
y=+37
y=+37
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y=+24
y=+24
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t
5.0
4.4
3.9
3.3
2.8
y=+20
y=+24

Table 2
Stereotaxic coordinates of activation obtained when spatial monitoring II was compared with the control condition

Region	Stereotaxic coordinates X	Y	Z	t statistic
Spatial monitoring II minus control condition				
Right hemisphere				
Frontopolar cortex (area 10)	34	51	6	3.53
Mid-dorsolateral frontal (area 9)	39	25	36	3.52
Mid-dorsolateral frontal (area 46)	39	37	20	4.86
Anterior cingulate cortex (area 32)	5	25	36	3.55
Ventrolateral frontal cortex (area 47)	35	18	−3	3.75
Premotor cortex (area 46)	25	10	56	6.47
Posterior parietal cortex (area 7/40)	40	−44	51	6.53
Posterior parietal cortex (area 7)	20	−64	53	8.01
Posterior parietal cortex (area 7/19)	25	−73	38	6.26
Lateral prestriate cortex (area 18)	34	−83	23	6.36
Primary visual cortex (area 17)	8	−88	5	7.16
Medial prestriate cortex (area 18)	9	−90	20	5.43
Left hemisphere				
Ventrolateral frontal cortex (area 47)	−29	20	−1	3.54
Premotor cortex (area 6)	−27	1	54	5.85
Medial posterior parietal cortex (area 7)	−5	−69	53	8.15
Posterior parietal cortex (area 7)	−20	−69	44	5.80
Lateral prestriate cortex (area 19)	−38	−71	0	4.56
Primary visual cortex (area 17)	−11	−81	12	6.11
Lateral prestriate cortex (area 19)	−24	−85	27	4.95
Control condition minus spatial monitoring II				
Right hemisphere				
Primary motor cortex (area 4)	48	1	11	6.45
Superior longitudinal fasc.	34	−30	27	3.74
Left hemisphere				
Frontopolar cortex (area 10)	−13	65	18	6.02
Medial orbitofrontal cortex (area 11)	−17	39	−9	6.30
Anterior cingulate cortex (area 32)	−4	36	−5	7.12
Ventrolateral frontal cortex (area 45)	−51	32	3	5.25
Insula	−34	1	11	5.48
Postcentral cortex (area 43)	−44	−14	20	4.77
Middle temporal cortex (area 21)	−59	−52	6	5.90

See Table 1 note.

Table 3
Stereotaxic coordinates of activation obtained when spatial monitoring III was compared with the control condition

Region	Stereotaxic coordinates X	Y	Z	t statistic
Spatial monitoring III minus control condition				
Right hemisphere				
Premotor cortex (area 6)	29	6	51	6.76
Anterior paracingulate cortex (area 32)	3	24	39	3.60
Mid-dorsolateral frontal (area 9/46)	31	37	23	5.14
Mid-dorsolateral/frontopolar cortex (area 9/10)	28	49	9	3.40
Parieto-occipital sulcus (area 7/40)	40	−42	50	6.28
Precuneus (area 31)	21	−59	23	5.45
Lateral prestriate cortex (area 19)	27	−85	22	6.60
Primary visual cortex (area 17)	13	−85	3	9.01
Left hemisphere				
Ventrolateral frontal cortex (area 47)	−28	20	−3	3.27
Premotor cortex (area 6)	−24	5	54	5.42
Posterior parietal cortex (area 7)	−7	−69	53	8.50
Primary visual cortex (area 17)	−12	−76	10	7.36
Lateral prestriate cortex (area 19)	−29	−85	24	5.94
Control condition minus spatial monitoring III				
Right hemisphere				
Ventrolateral frontal cortex (area 47)	39	39	−8	3.78
Ventrolateral frontal cortex (area 45)	47	32	6	3.83
Primary motor cortex (area 4)	47	−1	12	6.66
Superior temporal sulcus (area 21/22)	60	−31	3	5.88
Inferior parietal cortex (area 40)	4	−31	27	4.10
Left hemisphere				
Medial orbitofrontal cortex (area 11)	−17	39	−12	7.53
Ventrolateral frontal cortex (area 45)	−47	37	3	6.41
Cingulate cortex (area 32)	−3	32	−5	7.08
Ventrolateral frontal cortex (area 45)	−46	20	12	5.07
Insula	−31	3	11	6.82
Superior temporal cortex (area 22)	−64	−21	0	4.39
Middle temporal cortex (area 21)	−58	−52	5	5.96

See Table 1 note.

tion in this study. Three of the five experimental tasks required various degrees of monitoring and manipulating of spatial information in working memory. We refer to these three conditions as spatial monitoring I–III, respectively. All three spatial monitoring conditions required that the subject monitor the contents of working memory in order to make various judgements, such as whether particular stimuli had or had not been presented (spatial monitoring I) or which ones of a set of defined locations had already been selected (spatial monitoring II and III). These tasks have mnemonic requirements that are similar to those that have been shown to be critical in accounting for the impairment after mid-dorsolateral frontal lesions in the monkey (Petrides, 1991a,b, 1995). It was predicted that performance of these tasks would result in a greater blood flow response within the mid-dorsolateral frontal cortex in comparison with the control task. The other two experimental conditions also involved spatial working memory, but these tasks were not expected to activate mid-dorsolateral frontal cortex, but, rather, the ventrolateral frontal region. One of these tasks, the spatial span task, required that the subject remember a given sequence of spatial locations and then reproduce them immediately afterward. The other task, the fixed spatial sequence, required that the subject reproduce a fixed sequence of locations that had been learned prior to scanning. Note that these two tasks *do not require* any manipulation of spatial information within working memory but only the retention of a perceived or learned spatial sequence and the organization of its execution. The fixed spatial sequence task was similar to a fixed sequence tasks that monkeys with mid-dorsolateral frontal lesions perform normally (Petrides, 1995).

Finally, there was a control condition that provided a baseline against which to examine the extent of activation within the frontal cortex in the other five experimental conditions. The control condition had similar visual, spatial, and motor requirements as the five experimental tasks, except for their specific mnemonic requirements. Eight identical red circles were presented, scattered randomly, except for one of these circles that occupied the central location. Once every second the central circle changed its color from red to blue and, at this point, the subjects were required to touch it. Once touched, the central circle turned red again.

Spatial Monitoring I

Within each trial, three blue circles were presented on the computer screen, one at a time and in random locations. Each of these circles remained on the screen for 0.25 sec and then disappeared as the next circle appeared. After the third circle had been presented, a delay of 3 sec ensued, during which time the screen remained blank. At the end of the delay period, eight red circles appeared simultaneously on the screen. The location occupied by three of these circles was identical to the location of the three blue circles shown before the 3 sec delay, the remaining five being randomly positioned. The subjects were required to touch, in any order they wished, each one of the three locations that were presented before the delay. Immediately after the third response, the screen cleared for 1 sec and the next trial began. Within the testing period, each subject completed 12 trials. Note that the requirements of this task are similar to those of the nonspatial working memory tasks that monkeys with mid-dorsal lateral frontal lesions fail (Petrides, 1991a, 1995) and, in this sense, it is procedurally quite different from the spatial span task and fixed spatial sequence task described below. Thus, during stimulus presentation, each of the three locations to be remembered is selected randomly from a large number of possible positions on the screen. At this stage, the subject has no information about the subset of eight locations from which these three target stimuli are to be selected. Consequently, during recall, subjects must consider each of these eight locations in turn, and decide, with reference to the contents of working memory, whether each location has been presented previously or not. The fact that the three target stimuli cannot be

Table 4
Stereotaxic coordinates of activation obtained when spatial span was compared with the control condition

Region	Stereotaxic coordinates X	Y	Z	t statistic
Spatial span minus control condition				
Right hemisphere				
Ventrolateral frontal cortex (area 47)	36	20	−5	3.47
Premotor cortex (area 6)	25	8	50	4.44
Posterior parietal cortex (area 7)	24	−64	56	7.78
Posterior parietal cortex (area 7)	27	−73	35	6.72
Primary visual cortex (area 17)	13	−83	3	5.88
Medial prestriate cortex (area 18)	11	−90	20	6.23
Left hemisphere				
Premotor cortex (area 6)	−21	5	59	4.31
Medial posterior parietal cortex (area 7)	−12	−69	54	8.68
Precuneus (area 7)	−19	−69	24	3.63
Primary visual cortex (area 17)	−12	−73	9	6.52
Lateral prestriate cortex (area 18)	−38	−85	17	3.70
Control condition minus spatial span				
Right hemisphere				
Ventrolateral frontal cortex (area 45)	46	39	3	4.65
Primary motor cortex (area 4)	48	3	11	5.64
Superior temporal cortex (area 22)	60	−30	5	3.80
Left hemisphere				
Frontopolar cortex (area 10)	−11	65	14	4.98
Ventrolateral frontal cortex (area 45)	−46	41	6	4.75
Superior temporal cortex (area 22)	−46	8	−17	3.77
Insula	−34	−1	11	4.53
Supplementary motor area (area 6)	−4	−11	60	4.48
Superior temporal cortex (area 22)	−47	−28	12	4.58
Middle temporal cortex (area 21)	−55	−50	5	3.89
Posterior parietal cortex (area 39)	−55	−57	29	6.14

See Table 1 note.

encoded as part of a known array effectively removes the tendency for subjects to simply remember the stimuli as a spatial sequence, a strategy that clearly is used in the spatial span task included in this study (see below). Analysis of response patterns during the spatial monitoring I task supports this suggestion and demonstrates that subjects tend to respond according to the position of target stimuli on the screen (i.e., left to right), rather than according to the temporal order in which they were presented.

Spatial Monitoring II

This task is based directly on one used previously to assess spatial working memory in neurosurgical patients with frontal or temporal lobe damage (Owen et al., 1990, 1995). On each trial, eight red circles were presented in random locations on the screen. The subjects were required to "search through" these red circles by touching each one of them until one of the touched circles turned blue. The circle, then, returned to its original red color and the subject was required to initiate a new "search" through the circles until another one turned blue. The subjects knew that once a particular location had turned blue, it would never turn blue again and therefore the point of the task was to avoid touching locations that had turned blue on earlier "searches." The subjects could search the boxes in any order they wished, but were explicitly instructed to search in random fashion and not to use any systematic spatial strategies. When all eight locations had turned blue, a new random arrangement of the eight red circles was presented, and the subject had to "search though" them, as before, until each one had turn blue. In order to keep the number of searches consistent across individuals, the number of locations visited before each location turned blue was determined by the computer. Within the testing period, each subject completed four trials, each of which required eight searches. Thus, in this spatial monitoring condition (and also in spatial monitoring III; see below), the subject was required to refer to a continually updated on-line record of which of a defined set of previously selected locations had been marked with a blue circle.

Spatial Monitoring III

This condition was exactly the same as the spatial monitoring II condition described above, except for the fact that 12, rather than 8, spatial locations were used. Consequently, within each trial, 12 searches were required and a total of 12 circles would have to turn blue to complete the trial. Within the testing period, each subject completed three trials, each of which required 12 searches.

Spatial Span

This task was based directly on the Corsi block tapping test described by Milner (1971). On each trial, eight red circles were presented in random locations on the screen. One of these red circles would then turn blue, for 0.5 sec, before returning to its red color. Another circle would then turn blue in the same manner until five of the eight stimuli had changed color in this way. Immediately following the presentation of the fifth stimulus, the subjects were required to touch each of these five "target" locations in any order they wished. After five responses by the subject, the screen was cleared and the next trial began with the eight red circles occupying new locations, five of which would sequentially turn blue. Within the testing period, each subject completed seven trials.

Note that in this spatial span task, the subject has merely to watch a spatial sequence, hold it in short-term memory and program its reproduction. In this sense, it is quite different from the spatial monitoring I task described above in that, during presentation, the five target stimuli are encoded as a subset of a *known* array. This provision effectively encourages subjects to encode the target stimuli as a sequence, and then reproduce that sequence in exactly the same temporal order. Thus, no manipulation of the stored sequence is required. Analysis of response patterns during the spatial span task supports this suggestion and demonstrates that subjects invariably reproduce the target stimuli in the same temporal order in which they were presented.

Fixed Spatial Sequence

In this condition, a single array of eight randomly positioned red circles were presented on the computer screen. Prior to scanning, the subjects learned to touch each one of these red circles in a fixed random sequence. Scanning did not begin until each subject could reproduce this sequence perfectly from memory, five times in a row. During scanning, the subjects were required simply to reproduce the sequence by touching each one of the circles in the correct order, returning to the beginning once the end of the sequence had been reached. When a circle was touched, it changed color from red to blue for 0.5 sec and then returned to red to indicate that the next circle in the sequence should be touched. In this way, the rate of response was controlled and kept approximately the same as in the other conditions. Within the testing period, each subject completed seven trials. Again, this task requires very little monitoring or manipulation of information within working memory but simply the retention and reproduction of a learned sequence of responses.

Results

Performance

The proportion of trials completed without an error on each one of the five behavioral tasks is presented in Figure 1. Of the three monitoring tasks, the first one was clearly the easiest, with subjects making very few errors, whereas the spatial monitoring II (eight boxes) and spatial monitoring III (12 boxes) tasks were more difficult, the subjects completing 73% and 65%, respectively, of all trials without an error. During the spatial span task, 96% of all trials were completed without an error, which is exactly the same as the mean score for the spatial monitoring I condition. Finally, in the fixed spatial sequence task, 98% of all performed sequences were without error.

Blood Flow

This study was designed to permit specific previously designed comparisons, accomplished via subtractions, between each one of the five experimental conditions and the control condition. The results of these subtractions, in terms of statis-

Table 5
Stereotaxic coordinates of activation obtained when the fixed spatial sequence condition was compared with the control condition

Region	Stereotaxic coordinates X	Y	Z	*t* statistic
Fixed spatial sequence minus control condition				
Right hemisphere				
Ventrolateral frontal cortex (area 47)	50	24	−9	3.38
Posterior parietal cortex (area 7)	25	−62	54	4.44
Primary visual cortex (area 17)	12	−66	9	6.36
Posterior parietal cortex (area 7)	16	−74	42	5.56
Lateral prestriate cortex (area 18)	16	−76	5	6.86
Medial prestriate cortex (area 18)	11	−85	20	5.28
Left hemisphere				
Ventrolateral frontal cortex (area 11/47)	−26	18	−5	3.16
Medial posterior parietal cortex (area 7)	−9	−69	54	6.55
Posterior parietal cortex (area 7)	−20	−71	42	3.69
Medial prestriate cortex (area 18)	−1	−74	24	5.67
Primary visual cortex (area 17)	−15	−78	11	5.84
Control condition minus fixed spatial sequence				
Right hemisphere				
Precentral cortex (area 6)	52	6	12	3.96
Superior temporal cortex (area 22)	62	−30	5	4.28
Superior temporal sulcus (area 21/22)	62	−52	11	3.91
Left hemisphere				
Ventrolateral frontal cortex (area 10/47)	−48	39	−3	4.67
Thalamus	−3	−14	14	3.85
Posterior parietal cortex (area 40)	−59	−45	27	3.72
Middle temporal cortex (area 21)	−56	−52	5	4.45

See Table 1 note.

tically significant changes in rCBF are given in Tables 1–5, together with the corresponding stereotaxic coordinates. These coordinates are based on the system used in the brain atlas of Talairach and Tournoux (1988).

When activity in the spatial monitoring I condition was compared with that in the control condition, there was significantly greater rCBF, as predicted, in the mid-dorsolateral frontal cortex (i.e., areas 46 and 9) in the right hemisphere (Table 1). Other significant rCBF changes were located mainly in primary visual cortex, posterior parietal region, and premotor cortex bilaterally. No significant changes in blood flow were observed in the mid-ventrolateral region of the frontal cortex following this subtraction, the maximum t value observed in this region of cortex being $t = 0.45$ (see summary in Table 6).

The results of the comparisons between spatial monitoring II and the control conditions (Table 2, Fig. 2) and between spatial monitoring III and the control conditions (Table 3) are very similar and will be discussed together. Again, our predictions were clearly confirmed as both the spatial monitoring II (eight-location) and the spatial monitoring III (12-location) tasks resulted in significantly greater rCBF in the right mid-dorsolateral frontal cortex (areas 46 and 9). In both conditions, significant changes in blood flow were also observed in right frontopolar cortex (area 10) and in ventrolateral frontal area 47. In the eight-location version of the task this change was clearly bilateral (see Fig. 2), while in the 12-location version it failed to reach statistical significance in the right hemisphere ($t = 2.66$). Again, nonfrontal peaks of activation were largely confined to visual cortical areas, the posterior parietal region, and lateral premotor cortex. Finally, in both conditions a significant change in blood flow was observed within area 32 of the cingulate region.

The results of the comparison between the spatial span condition and the control condition (Table 4, Fig. 3) also clearly confirmed our prediction that a significant change in blood flow would be observed in the mid-ventrolateral frontal cortex (area 47) in the right hemisphere but not in the mid-dorsolateral frontal region. The maximum t value observed in the mid-dorsolateral frontal cortex was $t = 1.58$ for this comparison (see summary in Table 6). Elsewhere in the cortex, the peaks of activation observed were very similar to those seen in the other subtractions, namely occipital visual areas, the posterior parietal cortex, and in the lateral premotor cortex.

Table 6
Summary of results

	Maximum *t* value: Mid-dorsolateral frontal cortex	Mid-ventrolateral frontal cortex
Spatial monitoring I	$t = 3.09$	$t = 0.45$ NS
Spatial monitoring II	$t = 4.86$	$t = 3.75$
Spatial monitoring III	$t = 5.14$	$t = 3.27$*
Spatial span	$t = 1.58$ NS	$t = 3.47$
Fixed spatial sequence	$t = 1.53$ NS	$t = 3.38$

NS, nonsignificant. All peaks reported are in the right hemisphere except the one marked with an asterisk (*), which was in the left hemisphere. The t values shown represent the maximum values observed in the mid-ventrolateral and mid-dorsolateral frontal regions when the control condition was compared with each one of the five experimental tasks. See also Table 1 note.

The comparison between the fixed spatial sequence condition and the control condition revealed a significant change in blood flow in mid-ventrolateral frontal cortex, as predicted (Fig. 4, Table 5). Again, t values in the mid-dorsolateral frontal cortex were low, the maximum value being $t = 1.53$ (see summary in Table 6). Other significant regions of activation were observed again, in occipital visual areas and in the posterior parietal cortex.

Discussion

The present study used positron emission tomography with magnetic resonance imaging to demonstrate the existence, within the human brain, of two functionally distinct subdivisions of the lateral frontal cortex that subserve different aspects of spatial working memory. Five spatial memory tasks were used that were similar in the type and mode of stimulus presentation and response required, but differed in terms of their executive processing requirements. The tasks were designed to test the hypothesis that the middle sections of the dorsolateral and ventrolateral frontal cortex are differentially involved in executive processes (Petrides 1991a,b, 1994). The first major issue addressed in the present investigation was whether frontal activation would be confined to the mid-ventrolateral region of the frontal cortex when the experimental task (in comparison with the control task) required the organization and execution of a remembered series of spatial moves. In the spatial span task, the subject was required to organize a sequence of spatial moves in order to reproduce a sequence of spatial stimuli previously presented and currently held in working memory. In the fixed spatial sequence task, the subject had to organize and guide the execution of a fixed learned sequence of moves. As predicted, in comparison with the control task that did not require the organization of a sequence of responses, but controlled for the motor component of reaching and touching the stimuli displayed, both the spatial span and the fixed spatial sequence tasks activated ventrolateral frontal cortical area 47 (Tables 4, 5; Figs. 3, 4). It is important to note here that, in the spatial span task, the subject is simply required to hold the presented sequence of moves in working memory until its reproduction is organized and executed. As can be seen from the summary in Table 6, this requirement was clearly not sufficient to yield any significant activation in mid-dorsolateral frontal areas 46

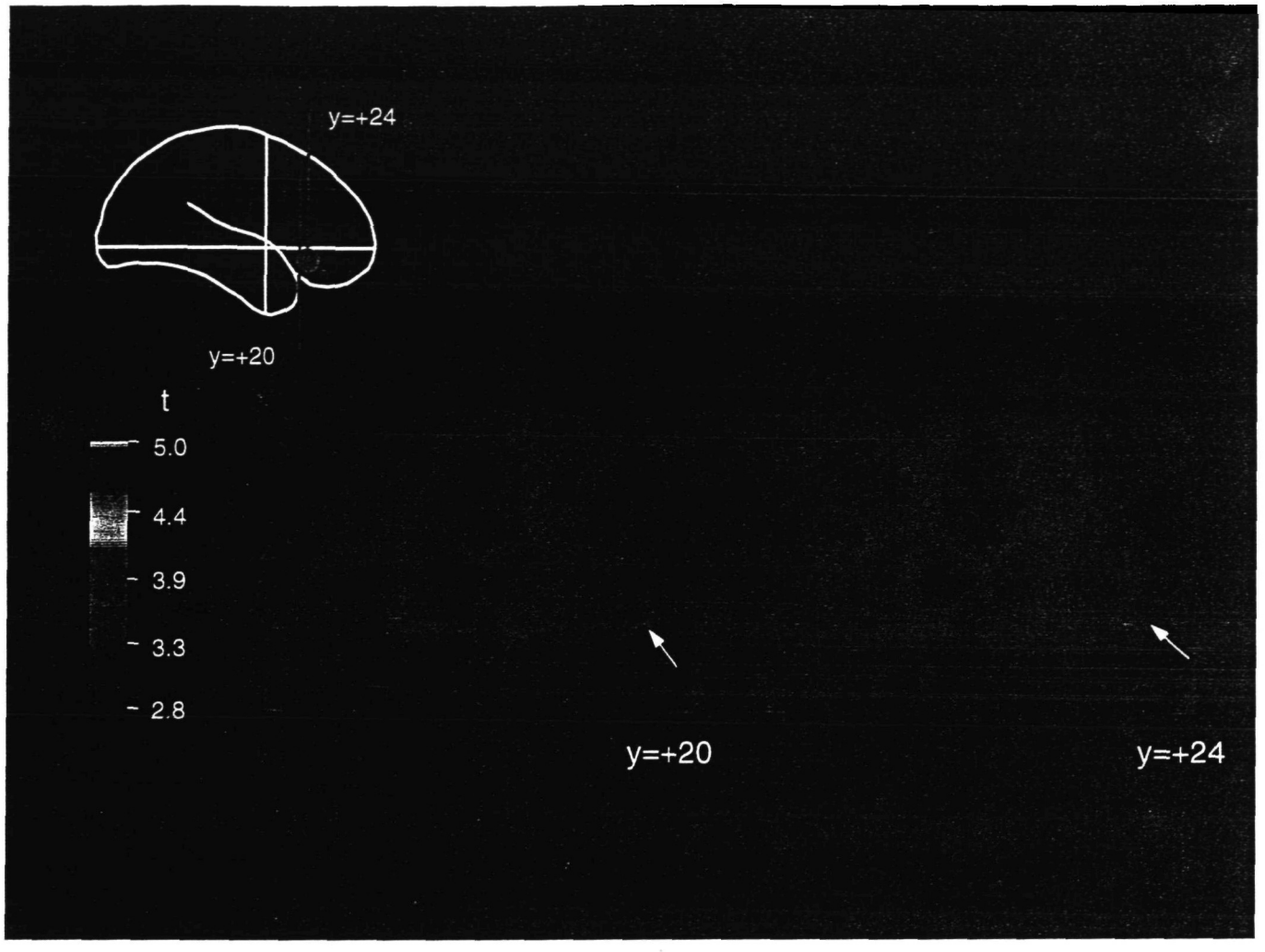

Figure 4. Fixed spatial sequence minus control condition: merged PET-MRI sections illustrating rCBF increases averaged for all 16 subjects. The schematic outline of the brain indicates the level (*red lines*) of the coronal sections shown and the *green dot* indicates the site of activation within the ventrolateral frontal cortex (area 47) presented in these sections (y = +20 and +24). The subject's left is on the left side of images. The activation foci are located directly below the horizontal ramus, which is marked on the images with a *white arrow.*

and 9 when either the spatial span task or the fixed spatial sequence task were compared with the control condition.

The second major question addressed in the present investigation was whether there would be activation within the mid-dorsolateral frontal cortex (i.e., areas 46 and 9) when the executive requirements of the spatial working memory tasks were changed to increase the monitoring and manipulation of information required within working memory. By monitoring, we refer to the active checking of information as occurs, for example, when the subject is required to decide which of a given array of locations have been selected and which ones have not (e.g., spatial monitoring I). The three monitoring tasks (spatial monitoring I–III) differed in terms of the number of such moves that had to be monitored, but they all involved this process to a considerable extent. In all three tasks, activation foci were observed in mid-dorsolateral frontal cortex (i.e., areas 46 and 9) when blood flow in these conditions was compared with the control condition (see Table 6). Furthermore, there were clear differences in the extent to which mid-ventrolateral frontal cortex was also activated. The spatial monitoring I task required that the subjects decide which ones of a set of eight stimuli had been presented earlier, but, unlike the spatial span task (see Materials and Methods), had minimal requirements (compared with the control condition) in terms of the organization of a sequence of responses. As expected, this task activated only mid-dorsolateral frontal cortex (see Table 6). By contrast, the spatial monitoring II and III tasks required that the subject monitor which ones of a set of spatial stimuli had been marked with a blue circle *and also* that a sequence of selections through the set be organized and executed. These tasks activated *both* mid-dorsolateral and mid-ventrolateral frontal cortex. It is important to note that task difficulty was not related to the observed activation of mid-dorsolateral or ventrolateral frontal cortex. For instance, the proportion of trials completed without an error was the same in the spatial monitoring I and the spatial span conditions, yet one of these conditions resulted in activation in mid-dorsolateral frontal cortex and the other in the mid-ventrolateral frontal cortex.

In light of these findings, some of the apparently conflicting results from previous functional neuroimaging studies of spatial working memory can be understood. For example, McCarthy et al. (1994) used functional MRI to measure changes in rCBF while subjects judged whether each of a series of 14 or 15 stimuli was located in a position that had already been occupied earlier in the sequence. The single slice chosen for

the functional MRI study allowed examination of frontal areas 9, 46, 23, and often 47, and revealed a significantly increased MR signal in area 46 across all eight subjects tested. This paradigm is conceptually similar to the spatial monitoring II and III conditions used in the present study, and therefore the two studies concur with respect to the observed activation foci in area 46. Contrasting results, however, have been reported by Jonides et al. (1993), who used PET and a behavioral task that was intended to simulate a paradigm that has been used to test spatial working memory in nonhuman primates (Funahashi et al., 1989, 1990). The subjects were required to remember the location of three dots presented simultaneously on a computer screen for a delay period of 3 sec and then to decide whether or not a probe circle was presented in one of those same three locations. Within the frontal cortex, significant changes in blood flow were observed, ventrolaterally, in area 47 in the right hemisphere. Interestingly however, no significant activity was reported in area 46 in the mid-dorsolateral frontal cortex. Unlike the task described by McCarthy et al. (1994) and the three spatial monitoring conditions included in the present experiment, the task used by Jonides et al. (1993) had minimal monitoring requirements. It simply required that the subject carry out an active comparison between the probe presented and the information stored in working memory in order to decide whether or not the two matched. Our results concur fully therefore with both former studies and clearly demonstrate that both ventrolateral and dorsolateral frontal areas can be activated in spatial working memory tasks, depending on the precise executive processes that are called upon by the task being performed. Thus, whereas the ventrolateral frontal cortex appears to be involved when working memory tasks require comparisons with, or reproduction of, stored information, the mid-dorsolateral frontal cortex becomes involved when active decisions about the occurrence or nonoccurrence of stimuli from a given set are required.

Notes

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