A large-scale distributed network for covert spatial attention

Further anatomical delineation based on stringent behavioural and cognitive controls

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Summary

Functional MRI was used to examine cerebral activations in 12 subjects while they performed a spatial attention task. This study applied more stringent behavioural and cognitive controls than previously used for similar experiments: (i) subjects were included only if they showed evidence of attentional shifts while performing the task in the magnet; (ii) the experimental task and baseline condition were designed to eliminate the contributions of motor output, visual fixation, inhibition of eye movements, working memory and the conditional (no-go) component of responding. Activations were seen in all three hypothesized cortical epicentres forming a network for spatial attention: the lateral premotor cortex (frontal eye fields), the posterior parietal cortex and the cingulate cortex. Subcortical activations were seen in the basal ganglia and the thalamus. Although the task required attention to be equally shifted to the left and to the right, eight of 10 subjects showed a greater area of activation in the right parietal cortex, consistent with the specialization of the right hemisphere for spatial attention. Other areas of significant activation included the posterior temporo-occipital cortex and the anterior insula. The temporo-occipital activation was within a region broadly defined as MT+ (where MT is the middle temporal area) which contains the human equivalent of area MT in the macaque monkey. This temporo-occipital area appears to constitute a major component of the functional network activated by this spatial attention task. Its activation may reflect the 'inferred' shift of the attentional focus across the visual scene.

Keywords: attention; hemispheric dominance; networks; spatial orientation

Abbreviations: BA = Brodmann area; fMRI = functional MRI; FST = floor of the superior temporal visual area; MST = medial superior temporal area; MT = middle temporal area; SPM = statistical parametric map

Introduction

The flexible orientation of attention to behaviourally relevant events is a function of great importance for adaptive interaction with the environment. We have suggested that spatial attention is mediated by a large-scale neural network, including three monosynaptically interconnected areas in the frontal, parietal and cingulate cortices (Mesulam, 1981). Physiological and behavioural observations in monkeys and humans suggest that each of these regions makes a differential contribution to spatial attention (Chedru *et al.*, 1973; Mesulam, 1981, 1985, 1990; Posner *et al.*, 1984; Fox *et al.*, 1985; Goldberg and Segraves, 1987; Zipser and Andersen, 1988; Galletti *et al.*, 1993). The frontal eye fields and the surrounding premotor cortex provide access to a motor map for the distribution of overt exploratory behaviours, the posterior parietal cortex to a spatially addressed sensorimotor representation of the extrapersonal space and the cingulate cortex to a map for the spatial distribution of expectancy and motivational relevance (Mesulam, 1981). The effective apportionment of attention across the extrapersonal space requires the integrity of all three of these cortical areas, as

well as their connections with each other and with specific subcortical regions in the thalamus and striatum. Lesions in any component of this network can lead to hemispatial neglect.

Hemispheric asymmetry is another characteristic feature of the attentional network: severe contralesional neglect is common after right hemisphere injury but rare after left hemisphere injury (Mesulam, 1981; Heilman *et al.*, 1985; Weintraub and Mesulam, 1987; Spiers *et al.*, 1990). The asymmetry of neglect-causing lesions has been ascribed to hemispheric specialization for the control of spatial attention, such that the right hemisphere regulates the distribution of spatial orientation across the entire extrapersonal landscape whereas the left hemisphere's influence is confined predominantly to the contralateral hemispace (Mesulam, 1981; Heilman *et al.*, 1985).

Several functional imaging studies have examined the anatomical organization of spatial attention (Corbetta *et al.*, 1993; Gitelman *et al.*, 1996a; Nobre *et al.*, 1997; Corbetta, 1998). However, with one exception (Nobre *et al.*, 1997) the previous studies did not have the resolution to analyse activations in individual subjects, and none of them consistently controlled for response-related motor activity, response inhibition, central fixation and working memory. The present functional MRI (fMRI) study was designed to address some of these limitations with the help of a stringent control task.

Methods
Subjects
Twelve volunteers participated in the study. There were seven men and five women, and none had any history of significant medical, neurological or psychiatric illness. Their mean ($\pm$ standard deviation) age was 32.5 ± 7.2 years. All subjects were right-handed by self-report and the mean score on the modified Edinburgh handedness scale was $+75.4 \pm 30.2$ (Ransil and Schachter, 1994). Subjects gave their informed consent, and this study was approved by the Institutional Review Board at Northwestern University.

Behavioural tasks: general design
The behavioural task (Fig. 1) was a variant of one developed by Posner for examining endogenously triggered shifts of spatial attention in the absence of eye movements (Posner, 1980). Centrally (foveally) presented arrow cues were used to generate lateralized expectancy for subsequent target appearance. This task therefore emphasized the sensory–representational rather than the motor–exploratory components of spatial attention.

The background display for all tasks consisted of a small central diamond (1° wide) and two peripheral squares (1.5° wide and 7.5° eccentric in each visual field). Each active-task trial started when one side of the central diamond brightened, forming an arrow which cued the side for subsequent target appearance (Fig. 1, top). The cue stayed on during a cue-to-target interval of 200, 400 or 800 ms. By maintaining the presence of the cue, potential working memory effects during the cue-to-target interval were minimized. A target then appeared for 100 ms, either on the same side as the cue 80% of the time (valid) or on the opposite side 20% of the time (invalid). The target stimulus was a diagonal cross ($\times$) while the foil was an upright cross ($+$). The subject's task was to discriminate the target stimuli covertly (without eye movements) and to respond as quickly and accurately as possible by pressing a response button only when the target was a diagonal cross. Each trial lasted 2 s. Reaction times were recorded in the magnet as well as in a preceding separate pilot session in the cognitive laboratory.

In the baseline condition (Fig. 1, bottom) the central diamond and both side boxes were displayed every 2 s. The central diamond was either bold or not bold. The side boxes contained either a diagonal or an upright cross on both sides. Subjects were told to press the response button during the baseline condition if and only if the central stimulus was bold, regardless of the shape of the peripheral targets. Therefore the maintenance of central fixation to detect a bold diamond (baseline) or central arrow (active-task) and to avoid lateralized saccades to targets were features of both the baseline and the experimental conditions. The baseline task also controlled for the motor response, the conditional (no-go) aspect of responding and the visual display. However, the baseline task did not require shifts of spatial attention for successful performance. The fMRI experimental run itself was designed as a series of paired active and baseline conditions each lasting 30.5 s and alternating a total of eight times.

Behavioural tasks: cognitive laboratory
In order to train subjects and derive some measure of eye movement during the task, all subjects performed an initial set of studies in the cognitive psychophysics laboratory outside the magnet. In the cognitive laboratory we assessed (i) whether subjects could maintain central fixation throughout all phases of the task, and (ii) whether subjects showed evidence of the invalidity effect by having a larger reaction time when the cue and target were in different locations. The presence of an invalidity effect proved that the cue induced a covert shift of the attentional focus. Stimuli were presented using Superlab software (Cedrus, Phoenix, Ariz., USA) running on a Macintosh PowerPC computer (Apple, Cupertino, Calif., USA). Subjects viewed the stimuli 40 cm away from a 21-inch monitor. Eye movements were recorded using an ISCAN® infra-red monitoring system (ISCAN, Burlington, Mass., USA). The eye movement data were examined using the ILAB software (D. Gitelman), which displayed a map of eye position overlaid on the stimuli the subjects were viewing (Fig. 2). The reaction time data were analysed by a repeated measures ANOVA (analysis of
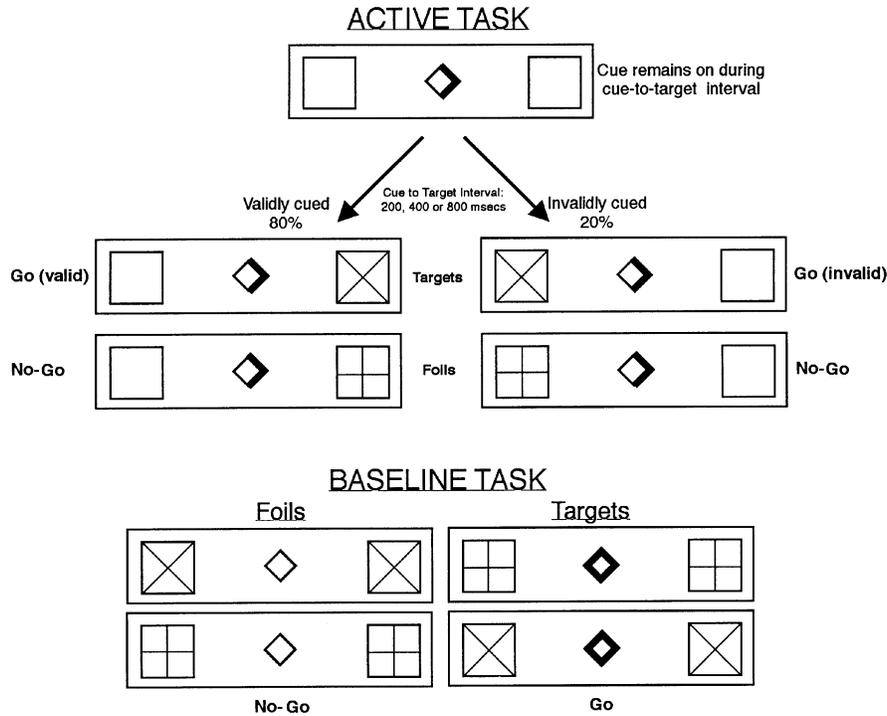
ACTIVE TASK

Cue remains on during
cue-to-target interval

Validly cued
80%

Cue to Target Interval:
200, 400 or 800 msecs

Invalidly cued
20%

Go (valid)   Targets   Go (invalid)

No-Go   Foils   No-Go

BASELINE TASK

Foils   Targets

No-Go   Go

Fig. 1 Graphical outline of the display sequence for the active and baseline tasks. The active task was initiated by making bold one side of the central diamond, forming an arrow cue (in this case towards the right). 80% of the time targets or foils appeared in the box indicated by the arrow (valid cue); 20% of the time the target or foil appeared in the box opposite the arrow (invalid cue). Subjects pressed the response button only when the diagonal cross (×) appeared in either box. The cue remained on during the cue-to-target interval. In the baseline task, the display was refreshed every 2 s and subjects pressed the response button only to a bold central diamond, regardless of the stimuli in the side boxes.
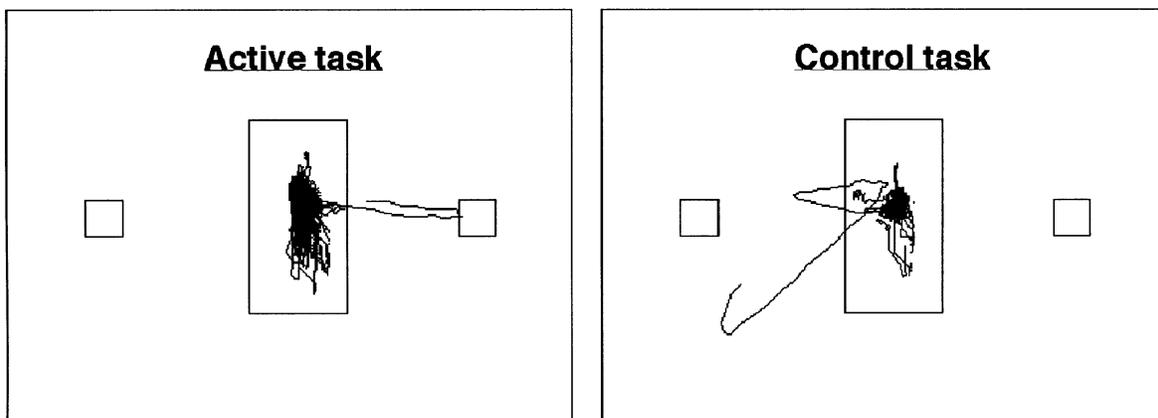

Fig. 2 Eye movements in one subject recorded in the cognitive laboratory during the active (left) and baseline (right) conditions. The positions of the central region of interest and the target boxes are shown. There was no difference in saccades between the two conditions.

variance) with factors for side and validity. Subjects who did not show the invalidity effect or those who could not maintain fixation within 2° of the centre in >90% of the trials did not undergo fMRI.

Behavioural tasks: functional imaging
Reaction times for the subjects' performance in the magnet were also analysed; subjects had to show an invalidity effect of at least 30 ms for their data to be included in the analysis.

This requirement ensured that subjects were performing the task as requested during the imaging and that the task was producing the desired attentional shifts. For the fMRI group, reaction time data were analysed by a repeated measures ANOVA with factors for side and validity.

Stimuli were presented using software and hardware similar to that described above. The images were projected by a Proxima active matrix LCD (liquid crystal display) projector onto a custom-designed, non-magnetic rear-projection screen. Subjects viewed the screen located ~170 cm from their eyes via a mirror.

MRI: anatomical scans

T_1-weighted anatomical images were obtained on a 1.5 T Siemens Vision scanner, using a 3D FLASH (fast low angle shot) sequence with the following parameters [repetition time/echo time (TR/TE) 15 ms/6 ms, flip angle 20°, field of view (FOV) 220 mm, matrix 256×256, slice thickness 1.0 mm]. All anatomical and functional scans were obtained in transaxial planes parallel to the anterior commissure–posterior commissure (AC–PC) line.

MRI: functional scans

Functional MRI volumes were acquired as thirty-two 4 mm slices using a single-shot EPI (echo planar imaging) method (TR/TE 4350/40 ms, flip angle 90°, matrix 64×64, FOV 220 mm). For all functional runs, the signal was allowed to equilibrate over four initial volumes that were excluded from the analysis.

Subjects had their head immobilized with a vacuum pillow (Vac-Fix, Bionix, Toledo, OH, USA) and the restraint callipers built into the head coil. They were given a non-magnetic button which enabled recording of their responses. A vitamin E capsule was taped to the left temporal region to mark laterality for image processing.

MRI: data analysis

Analysis of fMRI data was performed using SPM-96 software (Wellcome Department of Cognitive Neurology, London, UK) running under the MATLAB environment (Mathworks, Sherborn, Mass., USA) (Friston *et al.*, 1995*a, b*, 1996; Worsley and Friston, 1995) on a HP-UX workstation (Hewlett-Packard, Palo Alto, Calif., USA). Application Visualization System software (Advanced Visual Systems, Waltham, Mass., USA) was used for scalp editing, volume rendering and image display. The Application Visualization System also enabled us to localize activations with respect to sulcal landmarks by using custom-designed software that projected a mark made on the 'surface' of a three-dimensional ray-traced image to the corresponding two-dimensional slice, and vice versa (Damasio and Frank, 1992).

The MRI data were subjected to a number of preprocessing steps. All functional images were realigned to the image taken proximate to the anatomical study (Friston *et al.*, 1995*a*) using affine transformation routines built into SPM-96. Subject movement was always <0.44 mm in any direction during each run (Parrish *et al.*, 1998). The realigned scans were then normalized using the template image supplied with SPM-96. This template conforms to the space defined by the International Consortium for Brain Mapping project (ICBM) (NIH P-20 grant), and closely approximates the space described in the atlas of Talairach and Tournoux (Talairach and Tournoux, 1988). Functional data were then smoothed with a 7 mm isotropic Gaussian kernel.

SPM-96 uses the technique of statistical parametric mapping and references the probabilistic behaviour of a stationary Gaussian field for defining an image's probability density function. It employs the general linear model for testing hypotheses at each voxel. Contrasts were set up to test for voxelwise effects of signal differences between the baseline and active conditions, and SPM{t} and SPM{Z} maps were calculated (Friston *et al.*, 1995*b*). We examined contrasts both for individual subjects and for the group as a whole.

All SPM{Z} values were thresholded at $P \leqslant 0.001$ ($Z = 3.09$). The threshold for reporting activations in areas of no anatomic hypothesis was $P \leqslant 0.05$ (corrected for multiple comparisons over the entire brain volume). In regions of a priori hypothesis, this correction was made using the unified approach described by Worsley and colleagues (Worsley *et al.*, 1996) for the specific volumes of interest. The a priori regions of hypothesis included the bilateral frontal eye fields, posterior parietal cortex, supplementary eye fields, anterior cingulate cortex, basal ganglia and posterior thalami.

In order to compare hemispheric differences in activation on a regional level, we defined regions of interest in homologous areas of each hemisphere based on our a priori hypotheses, and counted the number of activated voxels in these regions of interest at a mapwise threshold of $P \leqslant 0.001$. A lateralization index (LI) was computed for each subject according to the formula $LI = (V_R - V_L)/(V_R + V_L)$, where V_L and V_R are the number of activated voxels in each hemisphere in the left and right regions of interest, respectively. A sign test was then performed across subjects for those with positive (i.e. rightward) versus negative (i.e. leftward) lateralization indices (Desmond *et al.*, 1995; Binder *et al.*, 1996).

Results

Behavioural data

In the cognitive laboratory, all subjects included in the analyses were able to maintain gaze within 2.0° of the centre on >90% of the trials. In addition there was no significant difference in eye movements between the rest and active conditions ($P > 0.3$, two-tailed on a paired t test for any movements beyond the specified region of interest). The eye movements of one subject in the cognitive laboratory are
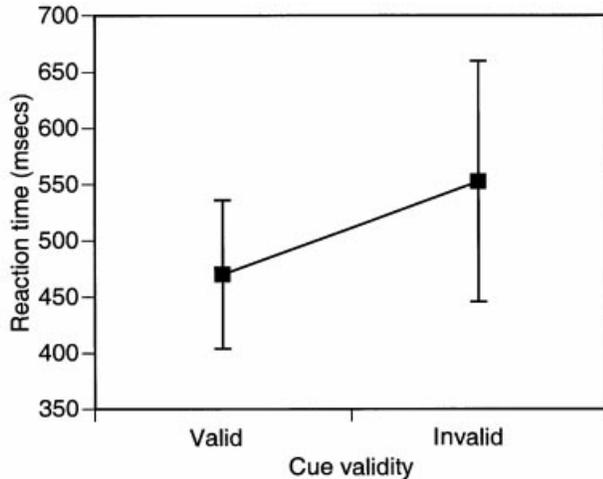
Fig. 3 Reaction times and standard deviations to validly and invalidly cued trials. Data are reported for the 10-subject group. Faster reaction times to the valid trials ($P < 0.001$) indicate that attention was shifted.

shown in Fig. 2. The positions of the central regions of interest and the target boxes are also illustrated. Nine subjects showed a significant effect of validity in the magnet ($P < 0.05$, one-tailed) with 33–217 ms (mean 81.2 $\pm$ 58.0 ms) slower response times to invalid trials. One additional subject showed 34 ms of slowing to invalid trials and a trend towards a significant difference between the valid and invalid conditions ($P = 0.075$). His data were therefore included in the analysis. Two other subjects were excluded from fMRI analysis as they failed to show an invalidity effect in the magnet ($P > 0.1$). Thus, for the entire group of 10 subjects that were retained, the mean reaction times were 470 $\pm$ 66.1 ms for valid trials and 553 $\pm$ 109.0 ms for invalid trials ($P < 0.001$, Fig. 3). Reaction times did not show an interaction with target hemispace. During the rest condition, subjects had a mean reaction time of 431 $\pm$ 71.2 ms to the bold central diamond.

fMRI data
Parietal activations
The group activation results are shown in Fig. 4A, and coordinates of representative activations are given in Table 1. The greatest area of parietal activation in the group was over the interparietal sulcus/superior parietal lobule junction. The other frequent region of parietal activation in the group was the precuneus.

Analysis of the individual subjects demonstrated activations in all 10 subjects in the posterior parietal cortex (Tables 1 and 2 and Fig. 4A, B, D and E). The activation of subject 6 is shown in Fig. 4B. In order to localize more precisely the activations relative to parietal lobe anatomy, the interparietal sulcus was traced on the cortical surface of each subject's three-dimensional brain image, and then projected onto the two-dimensional horizontal slices. The

interparietal sulcus was defined according to the guidelines of Critchley (Critchley, 1953). The interparietal sulcus included a horizontal ramus (the interparietal sulcus proper), an anterior vertical limb (the inferior postcentral sulcus) and a posterior vertical limb (the descending interparietal sulcus including its junction with the interoccipital sulcus up to the transverse occipital sulcus). An activation was labelled as originating from the banks of the interparietal sulcus if its coordinates fell within a full width at half-maximum (FWHM $\approx$8 mm) of the interparietal sulcus as determined by each subject's traced interparietal sulcus line. Figure 4E demonstrates the tracing results in subject 3. Most of the parietal activations in this subject involved the interparietal sulcus cortex as defined above. There was also a single area of superior parietal lobule/precuneus activation best seen on section ii of Fig. 4E.

The other nine subjects also showed activations within the interparietal sulcus region. In addition, activations were seen in the superior parietal lobule in seven subjects and in the precuneus in six subjects. Two subjects showed very small activations (13 and 10 voxels, respectively) in the inferior parietal lobule (supramarginal gyrus). Figure 5 plots the lateralization index for voxels in the parietal lobe for each subject. Eight out of 10 subjects showed a rightward bias of this index [$P < 0.05$ by the sign test for a rightward (positive) versus leftward (negative) lateralization index].

Frontal activations
Group analysis demonstrated activation of premotor cortex (frontal eye fields) along the precentral sulcus involving the posterior part of the middle frontal gyrus and, less frequently, the posterior part of the superior frontal gyrus bilaterally (Table 1 and Fig. 4A). This activation site was consistent with identified sites of frontal eye field activation in previous studies (Paus, 1996; Nobre *et al.*, 1997). Supplementary motor cortex activation was also seen in the group analysis.

Nine of 10 individuals displayed activation of the frontal eye fields. Consistent hemispheric asymmetry was not evident at this site, as most subjects showed approximately symmetrical activations. In the medial frontal cortex, small areas of activation were seen in the supplementary motor region (6/10 subjects). Other small, individual frontal areas of activation included the inferior and middle frontal gyri bilaterally in four individuals. The locations of these prefrontal activations would correspond to the inferior aspects of Brodmann areas (BA) 44, 45 and 46. The prefrontal regions of activation were not seen in the group analysis, probably because of the interindividual variability and small size of the activations.

Cingulate activations
Activation of the anterior cingulate gyrus was seen both in the group analysis and in 6/10 individuals. This activation was primarily located over the dorsal aspect of the gyrus and
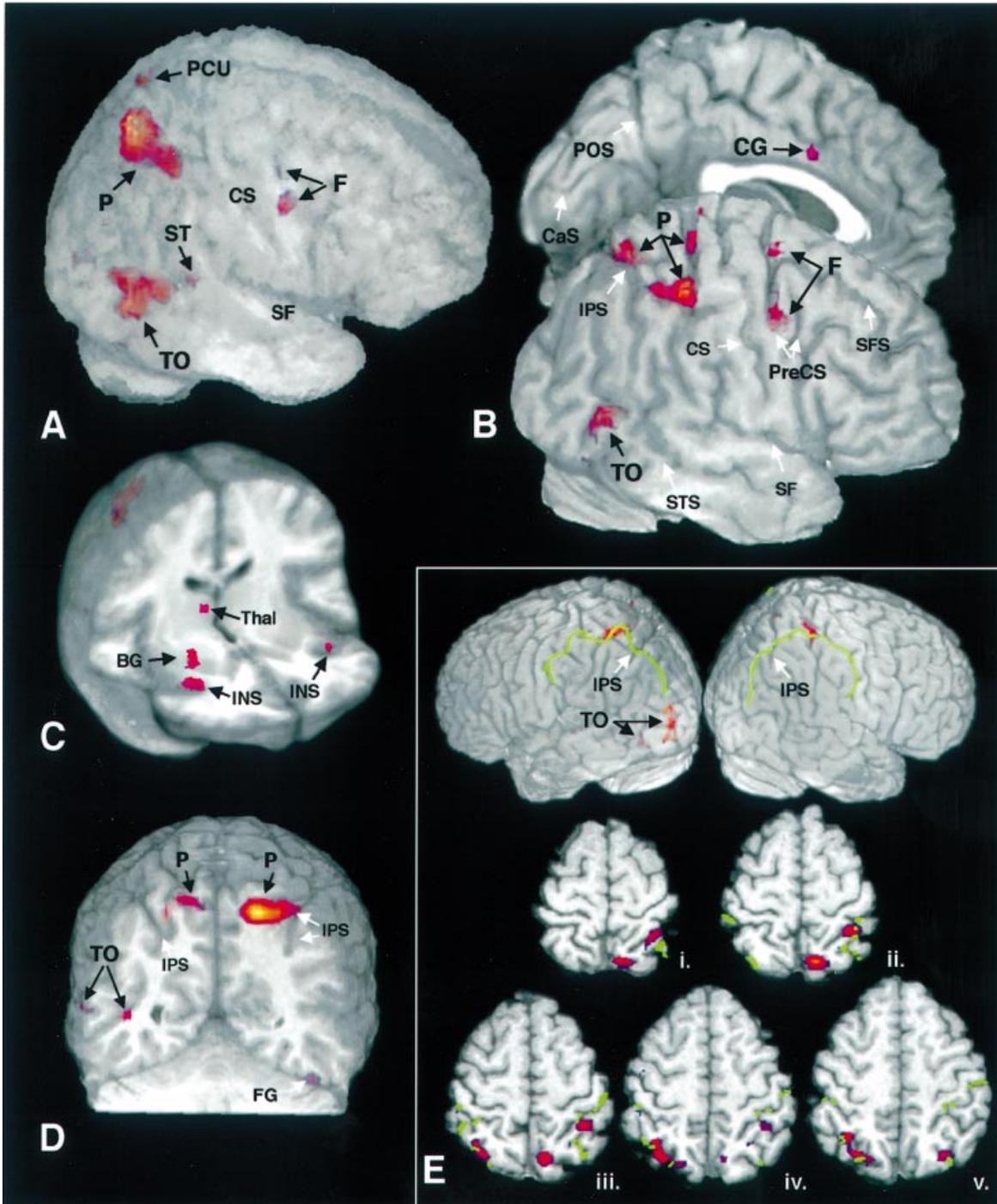
Fig. 4 Representative areas of activation for group and individual analyses. (**A**) Group (*n* = 10) cortical activations in the right hemisphere overlaid on an average of all 10 brains. (**B**) Right hemisphere and midline activations in subject 6 merged with this subject's normalized brain image. (**C**) Group subcortical and insula activations overlaid on the same averaged brain as in **A**. The brain is sectioned in both the coronal and the axial plane to show simultaneously all subcortical activations. (**D**) Parietal, temporal and temporo-occipital activations in subject 8. On the right, the parietal activation is at the superior parietal lobule/interparietal sulcus junction and lies in a superior branch sulcus of the interparietal sulcus. On the left, the activation extends into the superior parietal lobule. (**E**) Course of the interparietal sulcus (green line) in subject 10 traced on three-dimensional renderings of each hemisphere, and then viewed horizontally to delineate the interparietal sulcus location on each slice. Right is on the right side of all images. BG = basal ganglia; CaS = calcarine sulcus; CG = cingulate gyrus activation; CS = central sulcus; F = frontal eye field activation; FG = fusiform gyrus; INS = insula; IPS = intraparietal sulcus; P = parietal activation; POS = parieto-occipital sulcus; PCU = precuneus activation; PreCS = precentral sulcus; SF = sylvian fissure; SFS = superior frontal sulcus; ST = superior temporal activation; STS = superior temporal sulcus; Thal = thalamus; TO = temporo-occipital activation.

Table 1 *Regional cortical activations for the group analysis*

Cortical region of activation	ICBM-Talairach coordinates			Group Z value	Number of subjects with activation (L or R)
	x	*y*	*z*		
Parietal					
Left intraparietal sulcus/superior parietal lobule	−21	−60	51	6.59	10
Right intraparietal sulcus/superior parietal lobule	27	−60	57	7.66	
Left precuneus	−6	−60	57	6.77	6
Right precuneus	3	−54	57	4.76	
Frontal					
Left premotor cortex	−27	−6	42	6.26	9
Right premotor cortex	51	0	36	5.65	
Left anterior insula	−33	27	−9	4.89	1
Right anterior insula	36	27	−6	5.79	
Midline frontal					
Left supplementary motor cortex	−3	9	45	4.83	6
Right supplementary motor cortex	3	18	39	4.68	
Cingulate					
Anterior cingulate cortex	0	24	24	4.46	6
Temporal					
Right posterior superior temporal gyrus	63	−39	12	4.83	7
Left posterior middle/inferior temporal gyrus	−45	−69	−6	6.93	9
Right posterior middle/inferior temporal gyrus	51	−60	−6	6.74	
Visual					
Left inferior occipital gyrus	−33	−87	−3	6.66	5
Right posterior fusiform gyrus	48	−69	−24	5.27	

The Talairach coordinates are based on the ICBM, NIH P-20 template brain. The Z scores are all significant at $P < 0.05$ after correcting for the regions of interest in areas of a priori hypothesis, or the whole brain in areas of no hypothesis. See Methods for the definition of these regions.

Table 2 *Areas of parietal activation by subject*

Subject	Superior parietal lobule	Interparietal sulcus	Precuneus	Inferior parietal lobule (supramarginal gyrus)
1		+		+
2			+	
3	+	+	+	
4		+		
5	+	+		
6	+	+		
7	+	+	+	
8	+	+	+	
9	+	+	+	+
10	+	+	+	

Fig. 5 Lateralization index for total number of right versus left voxels in the parietal cortex. Note that more subjects (8/10) showed a rightward bias in this index ($P < 0.05$).

within the cingulate sulcus itself (Fig. 4B). No hemispheric asymmetry was noted for this activation.

Temporal and insular activations

Activations were seen in the posterior temporal lobes bilaterally. While activation at this site was not hypothesized a priori, the height and size of the activations did survive correction for multiple comparisons. The largest region of posterior temporal activation was seen overlying the middle and inferior temporal gyri in BA 21 and 37 bilaterally (indicated by TO in Fig. 4A, B, D and E). Nine subjects
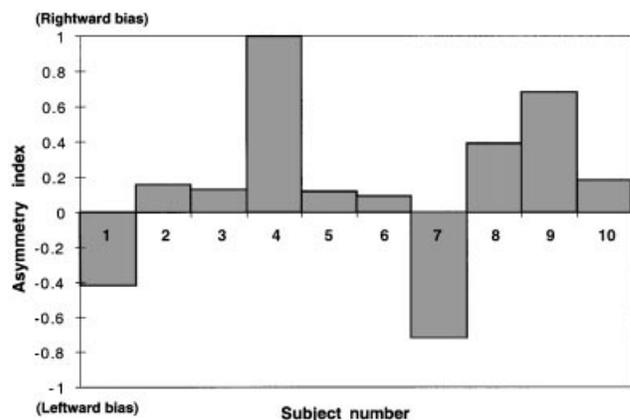
showed activation in this area, and there was no consistent hemispheric asymmetry.

A smaller region of temporal activation was located near the intersection of the posterior superior temporal gyrus (BA 22) and the inferior parietal lobule (BA 40). Although activations were seen in this area in four subjects on the left and five subjects on the right (seven individuals in total), the group analysis showed this superior temporal activation as significant only on the right side (ST in Fig. 4A).
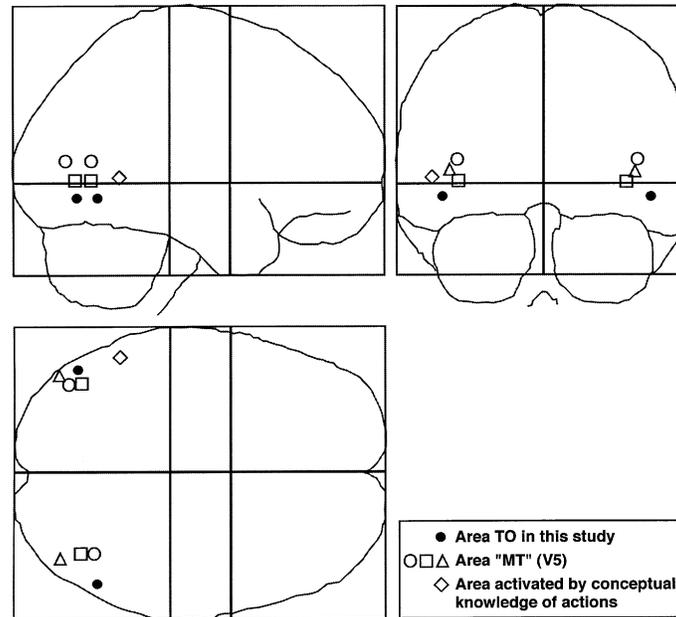
Figure 6 plots the primary focus of the group temporo-

Fig. 6 Foci of activations in the temporo-occipital region. Filled circles (●) denote the locations found in the current study. The foci of activations in MT (E, G, C) and an area subserving movement-related knowledge (◇) are taken from several previous studies (Zeki *et al.*, 1991; Martin *et al.*, 1995; Beauchamp *et al.*, 1997; Dupont *et al.*, 1997; Chawla *et al.*, 1998).

occipital activation, along with foci of activations previously identified as human area MT (middle temporal area), and a left hemisphere region found to subserve movement-related knowledge (Martin *et al.*, 1995). As shown in Fig. 6, the maximum focus of temporo-occipital activation in the current study was located more inferiorly and laterally to the area identified as MT. It had a vector distance of 18 mm from the average of the MT regions on either side. The overall area of the temporo-occipital activation would overlap a region designated as MT+ (DeYoe *et al.*, 1996; Tootell *et al.*, 1998).

Bilateral activations were seen in the anterior insula in the group analysis (Fig. 4C). Only one subject had a suprathreshold activation (accounting for multiple comparisons) in this area in the individual analyses. However, an additional three subjects showed subthreshold activations of the insula (Z scores ranging from 4.05 to 4.62).

Visual activations
Activations in visual cortex survived correction for multiple comparisons in six subjects. In the group analysis, the left-sided visual cortex activation was seen overlying the inferior occipital gyrus corresponding to BA 19, whereas right-sided activation was located in the fusiform gyrus (Table 1). In individual subjects, these activations occurred in regions corresponding to BA 18 and 19 and included the inferior occipital and fusiform gyri (FG in Fig. 4D).

Subcortical activations
Subcortical regions of activation included the thalamus in five subjects and the basal ganglia in seven subjects. Thalamic

activation was difficult to localize precisely owing to the limited resolution of the functional data. The group analysis showed right thalamic activation possibly overlapping the ventral lateral nucleus (x, y, z = 12, –3, 3; Z = 4.73). However, individual activations appeared to overlap variably the mediodorsal, anterior pulvinar and ventral lateral or intralaminar thalamic nuclei.

Basal ganglia activation showed no consistent hemispheric asymmetry and was located in the caudate in two subjects and the putamen in five. In the group analysis, basal ganglia activations were seen in the left putamen (x, y, z = –18, –6, 15; Z = 5.62) and the right putamen/globus pallidus, with respective coordinates of x, y, z = 27, 6, –6; Z = 5.27 and 18, –3, 12; Z = 5.00 (Fig. 4C).

Discussion
We have previously proposed a network approach to the anatomical organization of spatial attention (Mesulam, 1981, 1990). This model was based on three major assumptions: (i) spatial attention is co-ordinated by a network of interconnected cortical areas, the epicentres of which are located in the frontal eye fields, posterior parietal cortex and cingulate gyrus; (ii) the frontal eye field has a relative specialization for the overt motor–exploratory aspect of spatial attention, the posterior parietal cortex for the sensory–representational and sensorimotor aspects, and the cingulate gyrus for the limbic–motivational aspect; and (iii) the right hemisphere co-ordinates attentional deployment across the entire extrapersonal space, whereas the left hemisphere primarily influences contraversive orientation in the right

hemispace. These hypotheses were addressed in this study, based on a task that emphasized the sensory–representational aspect of spatial attention.

In our task, foveally presented visual cues triggered covert shifts of the attentional focus, without any head or eye movements. Activations were seen in all major components of the cortical network originally hypothesized to control spatial attention: the posterior parietal cortex, the frontal eye fields and the cingulate gyrus. Although the task required symmetrical shifts of attention to both sides of space, 80% of subjects showed a greater area of right-sided parietal activation, consistent with the hypothesized specialization of this hemisphere for spatial attention.

Similar sites of activation (frontal, parietal and cingulate) have been seen in several previous studies of spatial attention. These studies were based on tasks that included visual targets, auditory targets, spatial priming, expectancy shifts and manual exploration (Corbetta *et al.*, 1993; Gitelman *et al.*, 1996*a*; Pugh *et al.*, 1996; Kim *et al.*, 1997; Nobre *et al.*, 1997; Tzourio *et al.*, 1997). The substantial overlap in activations among these studies of attention suggests that these three cortical regions provide a flexible large-scale substrate for all spatial attentional behaviour.

The current experiment was designed to address a number of conceptual and methodological issues that were incompletely examined in previous studies. The issues we considered to be of particular importance included (i) in-scanner task performance, (ii) achieving a better anatomical characterization of the activations in individual subjects, and (iii) controlling for task requirements that could potentially confound the interpretation of frontal eye field activations. These confounds included (a) the requirement for push-button responses, (b) the conditional (no-go) aspect of the required response, (c) the working memory load of the task, (d) the need for intense central fixation, and (e) the need to inhibit eye movements. Each of these considerations is addressed below.

All 10 subjects showed a slowing of reaction time of >30 ms to invalid cues during their performance of the task in the magnet. Our requirement that reaction times to validly cued stimuli be faster than to invalidly cued stimuli ensured that the cues shifted the focus of attention.

The role of the frontal eye fields in the attentional network has generated controversy. Conceivably, its activation in tasks of covert attention could be contingent on the requirement for responding (Corbetta *et al.*, 1993), the undetected occurrence of eye movements (Sweeney *et al.*, 1996; Bodis-Wollner *et al.*, 1997; Luna *et al.*, 1998), the intensity of central fixation (Anderson *et al.*, 1994; Law *et al.*, 1997), the need to inhibit eye movements (Corbetta *et al.*, 1993; Law *et al.*, 1997), the no-go contingency of the response (Kawashima *et al.*, 1996*b*) or the working memory load of the task (Sweeney *et al.*, 1996).

In the current study, subjects had to make push-button responses in both the active and the baseline conditions. Furthermore, responses had a conditional (no-go) component

during both conditions, such that subjects had to inhibit reactions to the + sign during the active task, and to the ◇ (non-bold diamond) during the baseline task. The active and baseline conditions also had similar requirements for intense central fixation (i.e. to detect if the central diamond was wholly or partly bold) and for inhibition of eye movements in the presence of peripheral stimuli. Given these controls, the frontal activations in our subjects are unlikely to have been secondary to factors such as the motor response, go/no-go contingency or central fixation. However, the cognitive subtraction model used in this study cannot entirely rule out the possibility that the frontal eye field activation reflected an interaction between one of these factors and attention, rather than the effect of spatial attention alone.

The contribution of undetected eye movements to frontal eye field activations was a potential concern. There is currently no available method for monitoring eye movements of <5° during the acquisition of fMRI data without also introducing major artefacts in the imaging of the frontal lobes. Nevertheless, there are several reasons for proposing that the frontal eye field activation seen in this study should not be attributed to eye movements. First, as noted above, our subjects were highly trained to maintain central fixation. Secondly, in another study (Nobre *et al.*, 1998) we specifically tested the possibility that eye movements could account for frontal eye field activations in a covert spatial attentional task similar to that used in the current study. The baseline task in that study required subjects to make vigorous horizontal saccadic eye movements of 4.2° or 24.3° every 400–1200 ms, with no specific emphasis on shifting spatial attention. When the activation elicited by this saccade task was subtracted from that of the covert attention shifting task, residual activity was still seen in the frontal eye fields, indicating that at least some of the frontal eye field activation during covert spatial attentional shifts could be attributed to the attentional rather than the oculomotor aspects of the task. A recent visual–motion study came to similar conclusions regarding attentional influences on frontal eye field activity (Buchel *et al.*, 1998).

Some paradigms that have been used for the investigation of spatial attention contain a potentially confounding requirement for working memory. The study by Corbetta *et al.*, for example, included cue-to-target delays as long as 2000 ms, requiring the subject to hold the spatial information in working memory during that interval (Corbetta *et al.*, 1993). By contrast, in the present study the cue was visible until the target appeared, eliminating spatial working memory requirements. This is a very important consideration since the region of the frontal eye fields may also be activated by working memory (Cohen *et al.*, 1997; Courtney *et al.*, 1997; LaBar *et al.*, 1998), a possibility that was minimized in this study by the design of the task.

Activation was also noted in visual association cortices such as the inferior occipital gyrus on the left and the fusiform gyrus on the right. These regions both potentially overlap areas of the visual cortex that appear to be active in

processing object form (Tootell *et al.*, 1998). Thus, in the current task, activity in these regions may have reflected the need to discriminate between the diagonal cross (×) and the vertical cross (+) during the active but not the baseline task.

An area that showed prominent activation despite the stringent controls was centred around the temporo-occipital junction, at the posterior part of the middle temporal gyrus (TO in Fig. 4A, B, D and E). This region does not overlap the location of areas activated by form discrimination (Van Essen and Drury, 1997). Its activation is thus unlikely to reflect the requirement to discriminate between the × and the +. Therefore, we conclude that the temporo-occipital activation is linked to the covert shifts of attention required by the experimental task. In some subjects, this activation extended into the adjacent parts of the superior and inferior temporal sulci. A similar region of activation was noted in the study by Nobre and colleagues (Nobre *et al.*, 1997). The centroid for the temporo-occipital activation was in the vicinity of two motion-related areas: the movement-sensitive area V5 (MT) and an area activated by the evocation of knowledge related to action (Martin *et al.*, 1995). Figure 6 shows the anatomical relationships among these activation sites.

The temporo-occipital activation does overlap the region designated as MT+ (DeYoe *et al.*, 1996; Tootell *et al.*, 1998). This area probably includes the human homologues of area MT as well as MST (medial superior temporal area), FST (floor of the superior temporal visual area) and other motion-related areas initially identified within the superior temporal sulcus of the macaque (Boussaoud *et al.*, 1990; DeYoe *et al.*, 1996). In the macaque monkey, area MST (and perhaps also FST) is interconnected with all three cortical epicentres of the attentional network: the frontal eye fields, the inferior parietal lobule–intraparietal sulcus and the cingulate cortex (Mesulam *et al.*, 1977; Barbas and Mesulam, 1981; Mesulam, 1981; Boussaoud *et al.*, 1990). Areas MST and FST are also interconnected with adjacent inferotemporal polysensory areas of the superior temporal sulcus and TEO (temporo-occipital area) (Boussaoud *et al.*, 1990). This region therefore provides a synaptic bridge between the dorsal and ventral streams of visual processing, a level of integration that may be important for moving the focus of attention among objects in the extrapersonal space.

Neurones in MST and FST have larger receptive fields than those in MT. Furthermore, MST neurones have response properties which suggest that they use information about motion to generate signals for smooth pursuit eye movements (Dürsteler and Wurtz, 1988). The other three cortical components of the attentional network (posterior parietal cortex, frontal eye fields and cingulate cortex) play critical roles in the control of saccadic eye movements (Petit *et al.*, 1996). Involvement in the generation of eye movements may therefore be an important common property of all cortical areas playing a critical role in spatial attention, even when the attentional shifts are done without actual eye movements (Nobre *et al.*, 1998). This relationship emphasizes the tight

interactions between the 'perceptual' and 'exploratory' components of spatial attention (Mesulam, 1981). It has also been hypothesized that area MST is sensitive to the inferred movement of occluded targets (Maunsell, 1995). Thus, it is possible that the activation of this area reflects an inferred movement of the attentional focus across the visual scene.

In the monkey, areas MST and FST are located in the posterior part of the superior temporal sulcus, a region that was included in the 'parietal' component of the large-scale network for spatial attention (Mesulam, 1990). Lesions in the inferior parietal lobule in the monkey elicit contralesional extinction and reaching deficits whereas lesions along the banks of the superior temporal sulcus (probably including MST and FST) elicit neglect even for unilaterally presented stimuli (Lynch and McLaren, 1989; Watson *et al.*, 1994). In humans, posterior cortical lesions that yield extinction and other components of contralesional neglect tend to be centred within the posterior parietal cortex, and may extend into the region of the temporo-occipital activation (Bisiach *et al.*, 1981; Friedrich *et al.*, 1998). Hasselbach and Butter (Hasselbach and Butter, 1997) reported a 53-year-old patient with a lesion confined to the region corresponding to the temporo-occipital (TO) activation in Fig. 4. This patient had no visual field cut or extinction but did show moderate left-sided neglect in a target cancellation task, even 4 years after sustaining a stroke. In view of these considerations, it appears that the posterior part of the middle temporal gyrus (TO in Fig. 4) may play a prominent role in spatial attention. Additional work will be required to determine if the role of this temporo-occipital area is confined to visually guided attentional tasks or if it also has a multimodal scope, similar to that of the other three cortical components of the attentional network.

The literature based on focal lesions contains a controversy concerning the location of the parietal area which is critical for spatial attention. Some authors suggest that the critical area is in the superior parietal lobule (Posner *et al.*, 1984; Vallar, 1993) while others emphasize a location in the inferior parietal lobule (Vallar, 1993; Karnath, 1997; Driver and Mattingley, 1998). This study, as well as the previous functional imaging experiment of Nobre *et al.* and a meta-analysis by Corbetta, shows that the 'parietal' epicentre for the attentional network is centred along the posterior interparietal sulcus and that its extension into other parts of the posterior parietal cortex occurs predominantly in the direction of the superior parietal lobule (Nobre *et al.*, 1997; Corbetta, 1998).

In the monkey, the interparietal sulcus contains a mosaic of discrete areas known as LIP (lateral intraparietal area), AIP (anterior intraparietal area), VIP (ventral intraparietal, MIP (medial intraparietal area) and PIP (posterior intraparietal area). Neurones of the LIP encode the head-centred coordinates of visual events and the intention to make them the targets of saccadic eye movements (Zipser and Andersen, 1988; Snyder *et al.*, 1998). Furthermore, in a covert spatial attention task similar to the one we used, many interparietal

sulcus neurones responded best when attention was directed towards the contralateral hemifield (Robinson *et al.*, 1995). Areas AIP and MIP play important roles in visuo-somatosensory integration, visuomotor control and visual reaching (Gallese *et al.*, 1997; Johnson *et al.*, 1997), and movement-sensitive neurones in area VIP participate in the encoding of optic flow and self-motion (Bremmer *et al.*, 1997). In the human, the banks of the interparietal sulcus have been activated by tasks of visually guided saccadic eye movements and visually guided manual reaching (Clower *et al.*, 1996; Kawashima *et al.*, 1996*a*; Luna *et al.*, 1998). The interparietal sulcus region thus displays physiological specializations that are consistent with its role as one of the most critical areas in the control of spatial attention.

Control tasks based on passive rest have suggested that covert shifts of spatial attention could lead to frontal eye field and posterior parietal activations of comparable magnitude (Gitelman *et al.*, 1996*b*). The introduction of more stringent controls in the current experiment, however, shows that the activations in the banks of the interparietal sulcus and in the temporo-occipital region are far more prominent than those in the frontal eye fields, highlighting the greater involvement of posterior association cortices in tasks of covert spatial attention which emphasize the sensory–representational rather than the motor–exploratory aspects of the task. Additional work will be needed to show if the reverse relationship will be identified in tasks that emphasize the exploratory (i.e. overt) aspects of spatial attention.

In previous studies in which the baseline task consisted of passive viewing without motor responses, we detected prominent activation in the supplementary motor area and cerebellum during covert attentional shifts (Kim *et al.*, 1997; Nobre *et al.*, 1997). In the present set of experiments, covert shifts of attention did not elicit cerebellar activation and the activation in the supplementary motor area was quite modest. Thus, the use of stringent controls helped to show that the cerebellum is unlikely to play a major role in covert shifts of spatial attention and that the role of the supplementary motor area is not as prominent as might have been surmised on the basis of earlier work. In fact, the investigation of patients with focal lesions shows that cerebellar lesions do not impair the covert shifting of spatial attention (Yamaguchi *et al.*, 1998).

Basal ganglia activations were seen in seven subjects: five in the putamen and two in the caudate. Activation of the thalamus occurred in the region of the ventral lateral nucleus. A recent functional imaging study has reported the activation of this nucleus in relation to attention and arousal (Portas *et al.*, 1998). Its activation may therefore reflect sustained attentional effort rather than shifts of spatial attention. However, individual subjects also showed activation of the dorsomedial and pulvinar nuclei, areas known to be heavily interconnected with the cortical epicentres of the spatial attentional network and to participate in the control of visual attention (Mesulam, 1981; LaBerge and Buchsbaum, 1990). Additional experiments will be necessary to better define the localization of the subcortical activations associated with spatial attention.

Table 1 shows the presence of interindividual differences in the distribution of parietal activations. Such individual patterns may reflect variations in the strategies used to accomplish the experimental task (Mazziotta *et al.*, 1982) or in the anatomical organization of the relevant neural network. Exploring individual differences in the functional organization of the brain will undoubtedly become one the most challenging directions for future research.

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