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The neurology of saccades and covert shifts in spatial attention
An event-related fMRI study

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Summary
Visual neglect occurs most frequently and persistently after lesions that include the right supramarginal gyrus (SMG), a part of the inferior parietal lobule. Patients with this syndrome make very few saccades to the left, and show abnormal performance on tasks in which they must covertly shift their attention to the left, suggesting that the right SMG is involved in the generation of saccades and attention shifts. Functional imaging studies of saccades and covert attention shifts in the normal brain, however, have shown weak or absent responses in both SMGs. We used event-related functional MRI to re-examine the responses to saccades and attention shifts within a single experiment, and to assess responses to left- and right-sided stimuli independently. When subjects made saccades to peripheral stimuli, the expected responses were seen in striate and prestriate cortex, the superior parietal lobules, the frontal eye fields, the supplementary motor area and the anterior insulae. In addition there was a response in the right SMG but not in the left SMG, as predicted from the clinical literature. When subjects made a covert visual assessment of the peripheral stimulus without any saccade, greater activity was seen in all of the areas in the frontoparietal network. Each area showed a bias towards contralateral stimuli, with two exceptions: the anterior insulae gave mainly ipsilateral responses, whilst the right SMG gave equal responses to right- and left-sided stimuli. These findings are discussed in the context of current theories pertaining to the clinical syndrome of neglect.

Keywords: neglect; saccades; covert attention shifts; functional MRI; parietal cortex

Abbreviations: BOLD = blood oxygen level dependent; FEF = frontal eye field; fMRI = functional MRI; SMA = supplementary motor area; SMG = supramarginal gyrus; SPL = superior parietal lobule

Introduction
Normal individuals can easily obey a request to 'attend to' a particular spatial location without looking at it, as a poker player might do if they wanted to inspect a particular playing card in front of them without betraying their interest to other players through their eye movements. Such a manoeuvre is referred to as a 'covert' shift in spatial attention, to distinguish it from the more usual 'overt' technique of shifting one's gaze to the object of interest.

Clinical evidence suggests that the system that mediates such shifts in spatial attention, whether overt or covert, is distributed asymmetrically across the two cerebral hemispheres. Patients with lesions involving a part of the right inferior parietal lobule called the supramarginal gyrus (SMG) fail to explore the left side of space, make very few saccades to their left, and often completely ignore the left side of the visual world in general and of individual objects. This syndrome has become known as left visual 'inattention' or 'hemi-neglect', and is part of the broader spectrum of abnormalities that many of these patients show across several modalities. Corresponding lesions of the left SMG do not typically result in persistent visual neglect of right-sided stimuli. Less frequently, visual neglect results from lesions outside the parietal cortex, typically in the right frontal lobe (for recent reviews, see Driver and Mattingley, 1998; Mesulam, 1999).

Posner *et al.* tested spatial attention in 13 patients with neglect resulting from parietal lesions (Posner *et al.*, 1984). These patients had to press a button as quickly as possible after the onset of a visual 'target' stimulus, which could appear in either of two boxes, one on each side of the fixation

point. In 'valid cue' trials, one of these boxes became brighter just before the target appeared inside it, in which case patients responded to the target faster, as normal subjects do (Posner, 1980). The reduced reaction time was attributed to a shift in spatial attention to the 'cued' box prior to the appearance of the target. In contrast, in 'invalid cue' trials, the brightening of the box on one side preceded the appearance of the target in the box on the other side, resulting in slower detection, presumably because the patients' attention was directed to the wrong side in these trials. However, in invalid trials, patients with right parietal lesions were much slower at responding to left-sided targets than were patients with left parietal lesions at responding to right-sided targets. This study confirms that patients with neglect resulting from parietal lesions have a deficit of spatial attention as defined by the Posner paradigm, and suggests that the right parietal lobe has a role in spatial attention that is not matched by the left parietal lobe. It should be noted, however, that the deficit in spatial attention alone cannot explain all of the multiple components of the extremely heterogeneous syndrome of visual neglect (Stone *et al*., 1998).

In attempting to account for the asymmetry of parietal lesions causing a deficit of spatial attention, it has been suggested that the right parietal lobe is capable of shifting attention in either direction, whilst the left parietal lobe is only capable of shifting attention to the right (Heilman and Valenstein, 1979; Weintraub and Mesulam, 1987). According to this explanation, shifts of attention to the left can only be mediated by the right parietal lobe, and therefore damage to this lobe results in left inattention. In contrast, shifts of attention to the right can be mediated by either parietal lobe, and therefore unilateral damage does not result in neglect of the right half of space. If the hypothesis is correct, then one would expect to see this pattern of laterality in functional imaging studies of the normal human brain in which saccades or attention shifts to the right with those to the left are compared.

No previous functional imaging studies of saccades have addressed this issue, since they have all pooled data from leftward and rightward saccades (Melamed and Larsen, 1979; Fox *et al*., 1985; Paus *et al*., 1993, 1995; Petit *et al*., 1993, 1996, 1997; Anderson *et al*., 1994; Nakashima *et al*., 1994; O'Driscoll *et al*., 1995; O'Sullivan *et al*., 1995; Darby *et al*., 1996; Müri *et al*., 1996; Sweeney *et al*., 1996; Bodis-Wollner *et al*., 1997; Corbetta *et al*., 1998; Law *et al*., 1998; Luna *et al*., 1998). These studies have employed 'epoch' designs, in which the regional cerebral blood flow is usually measured over epochs of 30 s or more. It has probably proved impractical to require subjects to make a long series of rightward saccades, for 30 s or so, without any of the corresponding leftward saccades required to return the gaze to a central position. Most studies of covert shifts in spatial attention have also pooled results from the two visual hemifields (Vandenberghe *et al*., 1996; Gitelman *et al*., 1999; Kim *et al*., 1999). The only two studies in which attention shifts within the right and left hemifields have been at least partially dissociated have both suggested that the important asymmetry is in the superior parietal lobules (Corbetta *et al*., 1993; Nobre *et al*., 1997), whilst activity in the SMGs, where the asymmetry is expected from clinical studies, was either absent or too weak to reach significance.

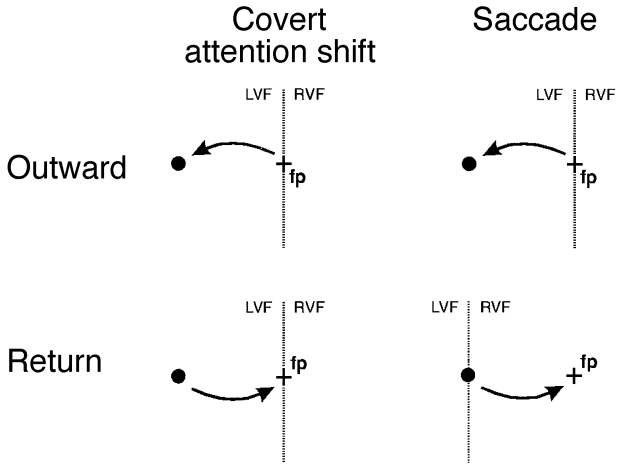

Fig. 1 Diagram to illustrate the difficulty in directly comparing saccades and covert attention shifts in an epoch-based experiment, in which outward and return saccades are pooled. Dotted line represents the central vertical meridian of vision. fp = fixation point; RVF = right visual field; LVF = left visual field. See text for details.

As well as re-examining evidence for a possible hemispheric asymmetry for saccades and covert attention shifts in the normal brain, we were also keen to address the question of whether there are differences in the cortical activity associated with these two types of behaviour. According to the premotor theory of attention (Sheliga *et al.*, 1985), covert attention shifts must require the same cortical machinery as saccades, since they are themselves simply unexecuted saccades. Functional imaging provides an excellent opportunity to test this theory in the human brain. However, although comparison of the results of the saccades studies mentioned above with results from separate studies of covert attention shifts suggests that there is considerable overlap in the cortical systems active during these two behaviours, it is not yet clear whether there are any cortical areas specialized for only one or other of them (Corbetta, 1998).

Ideally one would wish to compare saccades and covert attention shifts within the same experiment, but the use of epoch-based designs has made such a comparison difficult. For example, a series of saccades or covert attention shifts might be made back and forth between a central fixation point and a target on the left, as illustrated in Fig. 1. In this case, each outward covert attention shift is directly comparable with each outward saccade: both are made centrifugally into the left visual field. However, the return shifts are not comparable. The return covert attention shift is made centripetally, from the left visual field to the centre of vision. The return saccade, in contrast, is made centrifugally, from the centre of vision to the original fixation

point (fp), which now lies in the right visual field. Thus, in epoch-based experiments in which outward and return saccades have been pooled, the cerebral responses to covert attention shifts and to saccades are not directly comparable. Other more complex epoch designs result in similar difficulties (e.g. Corbetta *et al*., 1998; see Discussion). The direct comparison should therefore be between outward saccades and outward covert attention shifts, without contamination by return saccades or attention shifts.

This requirement is fulfilled by the new technique of event-related functional MRI (fMRI) (Josephs *et al*., 1997; Friston *et al*., 1998), which has allowed us to examine the responses to outward saccades and covert attention shifts within the same experiment, whilst return shifts are modelled out as events of no interest. We were therefore able to make a valid comparison of saccades and covert attention shifts, and examine shifts to the left and to the right independently, without contamination of the fMRI signal by the opposite saccade or attention shift back to a central position at the end of each trial. A preliminary report of these results has been published (Perry and Zeki, 1999).

Methods

fMRI image acquisition and subjects

Seven subjects (three male) between the ages of 20 and 45 gave informed consent to be studied, and were trained on the task prior to scanning in a 2-T Magnetom Vision whole-body MRI scanner (Siemens, Erlangen, Germany) equipped with a head volume coil. A gradient EPI (echo-planar imaging) sequence, with a TE (echo time) of 40 ms and a TR (repetition time) of 4.1 s, was selected to maximize blood oxygen level-dependent (BOLD) contrast and to minimize inflow effects. Each brain image was acquired in 48 slices, each 2 mm thick (with 1 mm gaps between) and consisting of 64 × 64 pixels. Visual stimuli were back-projected by an LCD (liquid crystal display) video projector onto a screen which the subject viewed through an angled mirror. Eye-tracking within the scanner was not possible because of the strong magnetic field. An infra-red eye-tracking system (Applied Science Laboratories, Bedford, Mass., USA) was therefore used outside the scanner, whilst six subjects (three male) performed the task, viewing exactly the same blocks of stimuli on an ordinary computer monitor, whilst head-immobilized, as in the scanner. Approval for the study was granted by the Ethics Committee of the National Hospital for Neurology and Neurosurgery, London, UK.

Experimental paradigm

Each subject performed two blocks of 96 trials, with a short break in between. The total length of each trial was 9 s; a non-integral multiple of the TR (4.1 s) was chosen in order to give an effective sampling frequency, over the whole experiment, of ~1 s (see Josephs *et al*., 1997). Two types of

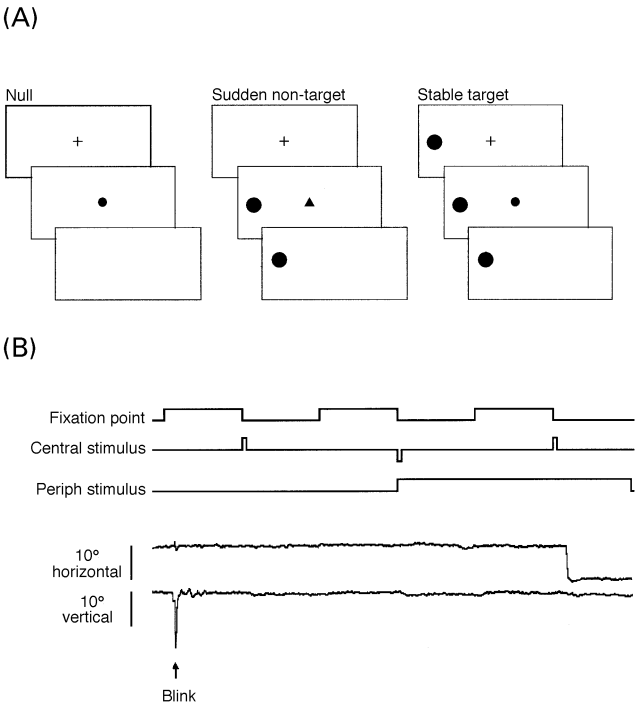

Fig. 2 Schematic diagram of one trial triplet, with eye-tracking traces from one subject. (**A**) For each trial the first frame (duration 4.5 s) is shown at the top, the second frame (duration 0.2 s) in the centre and the third frame (duration 4.3 s) is shown at the bottom. The three trials shown followed consecutively (see **B**). All shapes were actually white on a black background. (**B**) Timing of events in same trial triplet as illustrated in **A**, with eye-tracking traces from the left eye of one subject. Downward deflection in horizontal eye trace indicates saccade to the left. Eye blinks were easily detected by their characteristic artefact in the vertical trace, as shown.

'test' trials appeared during the experiment: 'target' trials, in which subjects made a saccade towards a peripheral visual stimulus, and 'non-target' trials in which a peripheral stimulus appeared but no saccade was made. In a third type of trial, called a 'null' trial, there was no peripheral stimulus (see Fig. 2).

At the start of each trial the subject fixated a central cross. After 4.5 s the cross was replaced by a 'central' cue stimulus, which was either a circle or a triangle, and which was flashed up for 200 ms. In null trials this was the only stimulus present on the screen, and subjects simply maintained central fixation throughout the trial. In test trials, however, a peripheral stimulus was also visible. If this peripheral stimulus was of the same form (circle or triangle) as the central stimulus, then subjects made a saccade to this 'target' stimulus. If, on the other hand, the peripheral stimulus did not match the central stimulus in form (a 'non-target' trial), the subject maintained central fixation. After a further 4.3 s the central cross reappeared and subjects made a saccade back to this cross for the start of the next trial. The reason for extinguishing the fixation cross during the second half of each trial was that in left target trials, for example, the cross would have moved into the right visual field, confounding

the responses to leftward saccades with visual responses to right-sided stimuli (see bottom right panel of Fig. 1).

Test trials (whether target or non-target) took one of two forms. In 'sudden-onset' trials, the peripheral stimulus appeared at the same moment as the central stimulus. In stable trials, on the other hand, the peripheral stimulus had already been present for 9 s by the time the central stimulus appeared (although the subject did not know, until the appearance of the central stimulus, whether or not the peripheral stimulus was a target). This was achieved by arranging trials in rotation, in a series of trial 'triplets': null trial, then sudden-onset trial, then stable trial, then null trial again, and so on throughout the experiment. One example of such a trial triplet is shown in two formats in Fig. 2. Peripheral stimuli could appear on the left or the right, and at an eccentricity of either 2.5° or 10°. Thus the design of the study may be thought of as a $2 \times 2 \times 2 \times 2$ factorial design, the four factors being: target versus non-target; sudden onset versus stable; right versus left; and eccentricity (2.5° versus 10°). The addition of the null trials gave a total of 17 types of trial. Each peripheral stimulus had a small black cross at its centre (not shown in Fig. 2) to aid fixation.

The trials were pseudorandomized with the following constraints. Within each trial triplet, the same peripheral stimulus persisted from the sudden-onset trial through into the stable trial (see Fig. 1). There were 64 possible types of trial triplet, each of which was presented once during the course of the whole experiment, in a pseudorandom order, giving a total of 192 trials. These were divided into two blocks of 96 trials, with a short break in between, both in the eye-tracking study and in the functional imaging study. Prior to eye-tracking or scanning, each subject performed as many practice trials as they required to feel totally confident with the task (30–60 trials). All subjects reported after the end of the experiment that they were able to perform the task correctly almost all of the time, making only one or two errors (always erroneous saccades to non-targets) in each block of trials, a conclusion which is supported by the off-line eye-tracking data (see Results). Such errors would tend to result in an underestimate of the difference between targets and non-targets, but in spite of this we were able to demonstrate highly significant differences between them.

Analysis of functional imaging data

The raw fMRI data was pre-processed using the software package SPM98, and statistically analysed using SPM97 (Wellcome Department of Cognitive Neurology, London, UK, see http://www.fil.ion.ucl.ac.uk/spm) which runs with MATLAB (Math Works Inc., Mass., USA). The methods have been described in detail elsewhere (Josephs *et al*., 1997; Friston *et al*., 1998) and are only briefly summarized here. The series of brain images acquired during the course of each block of trials was spatially realigned to the first image in the block, and then normalized to a standard average brain included within SPM97 (from a series of MRI scans performed at the Montreal Neurological Institute, McGill University, Montreal, Canada), which approximates to that described in the atlas of Talairach and Tournoux (1988). The data were then spatially smoothed with a 10 mm isotropic Gaussian kernel and temporally smoothed with a 4 s Gaussian kernel prior to statistical analysis.

The event-related analysis was performed using the standard haemodynamic response function provided within SPM97. For each of the 17 types of trial, an artificial time series was created modelling the expected haemodynamic response to every central stimulus (for this trial type) throughout the whole scan series. These were treated as events of interest. The ends of each trial type were modelled separately, as events of no interest, since whether a stimulus disappeared at this moment and whether the subject made a 'return' saccade back to the centre of the screen depended on the type of trial that had occurred. Low frequency effects (less than one cycle per 64 s) were modelled as covariates of no interest (similar to preprocessing with a high-pass filter, see Fig. 5 of Turner *et al*., 1997).

All of the results derive from a 'fixed effects' analysis of the whole group of seven subjects; it is well established that this is the appropriate analysis for establishing typical features of the human brain (Friston *et al*., 1999). The *P* values we quote have been corrected for multiple comparisons (using Gaussian field theory), with one exception, which is in the assessment of the laterality of a given brain area. The procedure here was to select an individual voxel from the non-targets versus null trials contrast (the voxel which gave the most significant *P* value, see Results), and then use the contrast right non-targets versus left non-targets, and its converse, to assess whether this voxel (or the nearest one for which data was available) gave a significantly greater response to non-targets in one hemifield than in the other. Since the statistical test was applied to only one voxel (selected using an orthogonal contrast), uncorrected statistics are used to assess significance in this case.

A feature of SPM97 is that the design matrix is identical for every voxel (Holmes *et al*., 1997), and this does not allow for the fact that the top slice of the brain was acquired 4.1 s before the bottom slice (see Friston *et al*., 1998). Two solutions were applied to overcome this problem. For all of the figures and for Tables 2 and 3, the data were adjusted to obtain, for each slice, the time series that would have been expected if all of the slices had been acquired instantaneously at the start of each scan ('temporal realignment'), using sinc interpolation in time (Schanze, 1995) prior to spatial realignment. The advantage of this approach is that statistical parametric maps can be shown for the whole brain, whilst the disadvantage is a slight loss of statistical power. For one particularly critical contrast, comparing non-targets with targets, data that had not been temporally realigned were also analysed, with the events specified correctly for the top slice. The resulting map is only correct for dorsal areas within the brain, so no figure is shown for this comparison, although the resulting statistics are quoted alongside the

Table 1 *Hypothetical classification of neural activity during each type of trial*

	Null trials	Non-target trials	Target trials
Phasic visual responses to peripheral stimuli; non-visual responses common to execution of saccades and of covert attention shifts	−	+	+
Responses specific to saccade execution	−	−	+
Tonic visual responses to peripheral stimuli	−	+	−
Responses specific to covert attention shifts; saccade inhibition in presence of peripheral stimulus	−	++	?+/−

statistics from the temporally realigned analysis in the Results section.

Results

Eye-tracking study

As subjects themselves reported, they were able to perform the task with a high degree of accuracy; the overall frequency of errors in all test trials (target and non-target) was 3%. The overall frequency of erroneous saccades was 7% for sudden-onset non-targets and 3% for stable non-targets. In the other non-target trials, there was no detectable change in horizontal eye position (above noise of amplitude 0.5–1°, see Fig. 2B). Subjects always made the appropriate saccade in target trials, although in two test trials (1%), in different subjects, the latency of the saccade exceeded 1.5 s; these were arbitrarily defined as 'errors' for the purposes of the statistics given above, although they are still included in the following mean latency estimates (the actual latencies were 2.05 and 2.50 s). The mean latency of saccades (measured from the onset of the central stimulus) was 591 ms for sudden targets and 620 ms for stable targets, the difference mainly being attributable to a few express saccades (latency <200 ms) to sudden-onset stimuli. The modal latency was 600 ms in each case.

Types of neural activity and expected BOLD responses

Table 1 gives a hypothetical classification of types of neural activity which may occur during each type of trial, to help explain our rationale for the various contrasts applied to the data. We have only included those neural responses that we expected to differ between trial types. A '+' sign in any box within the table indicates the putative engagement of that type of neural activity during a particular trial type, and '++' indicates even greater engagement (i.e. a larger BOLD signal). For example, if a particular brain area has at least one '+' under 'Target trials', and a '–' under 'Non-target trials', then we expect this area to be revealed in the targets versus non-targets comparison.

Targets versus null trials

The question implicit in previous epoch-based studies of saccades has been: 'what is the complete ensemble of brain areas involved in planning and executing visually guided saccades?'. In the present study this question was addressed using the contrast targets versus null trials, which should demonstrate all of the visuomotor responses during a visually guided saccade (i.e. top two rows of Table 1). During target trials, however, subjects also have to make a brief 'covert' assessment of the peripheral stimulus prior to the saccade, and so areas involved in covert attention shifts may or may not show up in this comparison (hence the entry '+/−' in the bottom row of Table 1).

Fig. 3A shows the contrast targets versus null trials, which demonstrates that the areas engaged during the generation of visually guided saccades included: the striate and prestriate cortices, the superior parietal lobules (SPL), the right supramarginal gyrus (R SMG), the right precentral sulcus close to the location expected for the frontal eye field (R inf FEF) and the supplementary motor area (SMA). The significance levels are given in the first rows of Tables 2 and 3. This result confirms previous (epoch-based) studies of saccades using PET (Fox *et al*., 1985; Paus *et al*., 1993, 1995; Petit *et al*., 1993, 1996; Anderson *et al*., 1994; Nakashima *et al*., 1994; O'Driscoll *et al*., 1995; O'Sullivan *et al*., 1995; Sweeney *et al*., 1996; Law *et al*., 1998) and fMRI (Darby *et al*., 1996; Müri *et al*., 1996; Bodis-Wollner *et al*., 1997; Petit *et al*., 1997; Luna *et al*., 1998).

As shown in Table 2, the activation in both superior parietal lobules reached significance at a level of $P < 0.001$ 'corrected' (i.e. when the correction for multiple comparisons is applied). The clusters in or near the precentral sulcus were much less pronounced and exceeded the corrected level of significance only at the right inferior locus ($P < 0.02$). We will refer to these precentral areas (within Brodmann area 6) as 'frontal eye fields' (FEF), although whether they are analogous to the frontal eye fields described from physiological studies in the monkey (within Brodmann area 8) remains controversial (see Paus, 1996, for a detailed discussion). The functional anatomy will be discussed in more detail in the context of later comparisons, where these areas are shown more clearly.

The cluster in the supplementary motor area (SMA) was located slightly anterior to the expected position of the supplementary eye fields deduced from previous studies (eg. 5, 1, 55 in Luna *et al*., 1998), and failed to reach corrected significance (although $P < 0.001$ uncorrected). Target trials therefore do not appear to be very potent stimuli for the putative frontal and supplementary eye fields in the

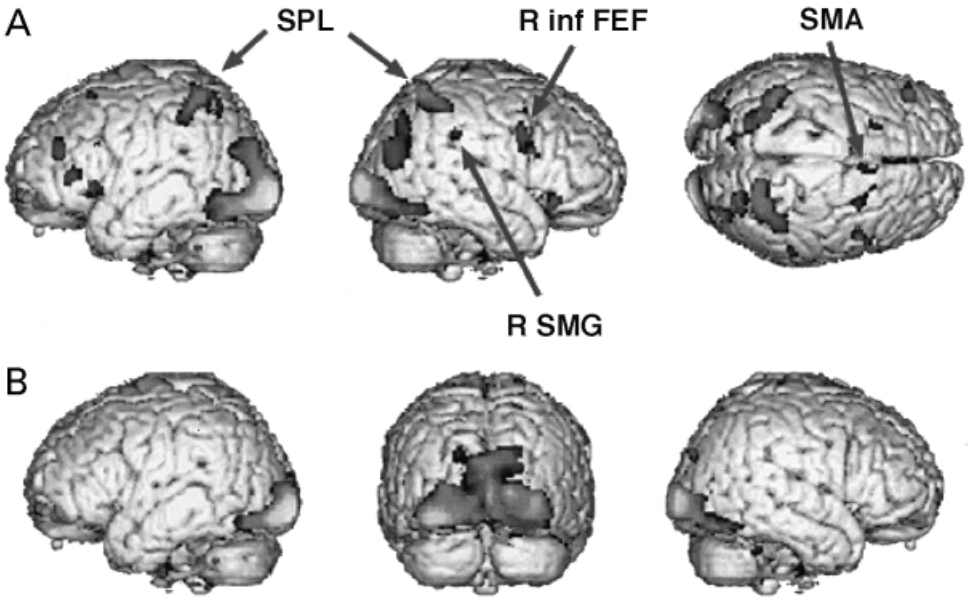

Fig. 3 (**A**) Contrast of targets versus null trials. (**B**) Contrast of targets versus non-targets. Statistical parametric maps from group data (seven subjects), rendered onto 'standard' brain corresponding closely to Talairach space. Height threshold at $P < 0.001$ uncorrected to demonstrate extents of each activated cluster; extent threshold five voxels. Degree of significance of suprathreshold voxels coded on a grey scale, with least significant voxels in black through to most significant voxels in light grey. Actual P values of each peak are given in Table 2. SPL = superior parietal lobule; SMG = supramarginal gyrus; inf = inferior locus; FEF = frontal eye field; SMA = supplementary motor area.

Table 2 *Main peaks of statistical significance in occipital and parietal lobules*

Contrast	Striate/prestriate (BA 17/18)		Dorsal prestriate (BA19)		Superior parietal lobule (BA 7)			Intraparietal sulcus (BA 40)		SMG (BA 40)
	L	R	L	R	L ant	L post	R	L	R	R
Target versus null	–16 –100 –8 0.001 (8.6)	18 –96 2 0.001 (8.1)	–30 –76 24 0.01 (5.0)	38 –74 22 0.02 (4.9)	–36 –48 56 0.001 (5.7)	–22 –62 46 0.001 (5.8)	30 –52 54 0.001 (5.8)	–38 –48 56 0.001 (5.7)	40 –44 48 0.001 (5.4)	60 –36 36 nscl (3.4)
Non-target versus null	–16 –100 –6 0.001 (5.7)	16 –96 0 0.1 (4.5)	–30 –78 24 0.001 (7.0)	40 –76 18 nscl (3.8)	–36 –48 56 0.002 (5.3)	–20 –64 50 0.001 (7.1)	24 –58 62 0.001 (6.9)	–36 –48 56 0.002 (5.3)	36 –40 42 0.001 (5.7)	66 –34 32 0.001 (6.5)
R non-target versus null	–12 –88 –4 0.001 (6.8)		–28 –84 22 0.001 (7.3)		–30 –52 56 0.013 (5.0)	–18 –66 52 0.001 (6.8)	30 –58 60 nscl (4.1)	–40 –44 52 0.03 (4.8)	38 –36 40 0.04 (4.7)	58 –40 36 0.002 (5.3)
L non-target versus null	14 –90 2 0.001 (6.5)	–30 –76 24 nscl (3.4)	34 –82 26 nscl (3.5)	–26 –54 58 0.001 (5.5)	–20 –64 46 0.02 (4.9)	22 –56 60 0.001 (6.8)	–38 –38 44 nscl (3.8)	36 –42 44 0.1 (4.4)	66 –34 32 0.007 (5.1)	

Locations given in coordinate system based on that of Talairach and Tournoux (1988). Below these are the corrected P values (at up to three decimal places) with the z score in parentheses; 'nscl' indicates not significant at the corrected level, but still exceeding $P \leqslant 0.001$ uncorrected. Blank cells indicate $P > 0.001$ uncorrected. BA = Brodmann area.

present study. As will become apparent, these areas can be shown with greater clarity and at much higher levels of significance in some of our other contrasts.

The striate and prestriate areas of both hemispheres showed a highly significant difference in the target versus null trials comparison ($P < 0.001$ corrected, Fig. 3A), which was so widespread within the occipital lobes that it was impossible to identify any visual areas that were specifically not shown in this comparison. Our study design required that the peripheral stimulus remained lit during the saccade, and therefore we cannot directly assess the extent to which the occipital lobe activation is dependent upon differences in the visual input. Previous studies in fMRI (Bodis-Wollner *et al*., 1997) and PET (O'Sullivan *et al*., 1995; Law *et al*., 1998) have demonstrated that the prestriate activation cannot be entirely explained by the visual input, since some activation remains even when saccades are performed in the dark.

Targets versus non-targets

Among the ensemble of brain areas demonstrated in the targets versus null trials contrast (see above), one might expect there to have been a sub-set which were only active when a saccade was actually executed. In Table 1, this is the only type of response (second row) we expect to see in the

Table 3 *Main peaks of statistical significance in the frontal lobes and basal ganglia*

Contrast	Superior FEF (BA6)		Inferior FEF (BA 6/44)		SMA (BA 6)	MFG (BA 46)	Anterior insula (BA 47)		Putamen	
	L	R	L	R	R	L	L	R	L	R
Target versus null	–22 6 50 nscl (3.1)	28 8 48 nscl (4.3)	0.02 (4.9)	50 8 32 nscl (3.35)	8 18 50 0.08 (4.53)	–40 40 26 0.01 (4.9)	–40 32 6 nscl (3.9)	(36 26 –12)		
Non-target versus null	–22 14 60 0.001 (6.4)	26 8 50 0.001 (6.8)	–34 4 46 0.001 (5.6)	38 2 42 0.001 (6.9)	6 16 50 0.001 (6.9)	–38 38 24 0.002 (5.4)	–38 20 –2 0.01 (5.0)	22 22 –6 0.001 (5.6)	–18 4 14 0.001 (6.3)	12 2 8 0.04 (4.7)
R non-target versus null	–28 6 54 0.002 (5.4)	26 8 50 0.01 (5.0)	–34 4 44 0.001 (5.6)	38 2 42 0.002 (5.4)	6 14 52 0.003 (5.3)	–40 36 24 0.001 (5.7)	–34 18 4 nscl (4.0)	22 24 –8 0.003 (5.3)	–20 8 0 0.001 (5.6)	10 14 2 nscl (4.1)
L non-target versus null	–22 16 60 0.03 (4.8)	26 6 50 0.001 (5.6)	–32 2 50 nscl (3.7)	38 4 42 0.001 (5.8)	6 16 50 0.001 (5.7)	–38 42 30 nscl (3.7)	–42 18 0 0.01 (5.0)	24 22 4 nscl (4.1)	–24 14 –4 0.04 (4.7)	10 4 8 0.06 (4.6)
Non-target versus targets	–22 12 60 nscl (3.6)	24 8 52 nscl (3.5)	–34 2 42 nscl (4.2)	40 4 42 0.03 (4.8)	4 14 52 0.1 (4.5)			24 22 4 0.001 (5.5)	–22 8 0 0.001 (5.4)	(24 14 –4) nscl (4.0)

FEF = frontal eye fields (as defined by imaging studies); SMA = supplementary motor area; MFG = middle frontal gyrus. Other details as in Table 2.

targets versus non-targets comparison, which should exclude any areas that are also engaged by covert attention shifts.

The contrast targets versus non-targets is shown in Fig. 3B. The extensive activation of striate and prestriate areas was very similar in extent and statistical significance to that in Fig. 3A, as would be expected if most of this activation was related to saccades (see above). However, the activation hardly spreads outside the borders of the occipital lobe, and there were no areas of significant saccade-specific activity in parietal cortex, the frontal eye fields or in supplementary motor cortex.

As will become apparent, the present technique is capable of detecting task-related differences in BOLD signal in all of these areas, at high levels of statistical significance. Our results are therefore not readily compatible with the conclusion that any of the frontoparietal areas shown in previous functional imaging studies of saccades are directly related to the execution of saccades, as has previously been suggested (Corbetta, 1998).

Non-targets versus null trials

Previous studies of covert shifts in attention have asked 'what is the complete ensemble of areas involved in planning and executing covert shifts in spatial attention?'; in our study these areas are shown in the non-targets versus null trials comparison (first, third and fourth rows of Table 1). The results of this contrast (for all non-targets) are listed in the second rows of Tables 2 and 3, and the individual contrasts for right non-targets and left non-targets are shown in Fig. 4A and B, respectively. The areas traditionally assigned to the generation of saccades were demonstrated with unusual clarity, and at very high significance levels, although the subjects did not make saccades in either of these conditions. The next few paragraphs are devoted to these contrasts since they are the most useful for demonstrating the functional anatomy of the system.

There were three completely separate clusters of activity in parietal cortex, in the right superior lobule, the left superior lobule (labelled 'SPL' in Fig. 4A, both extending down into the intraparietal sulcus), and in the right SMG ($P < 0.001$ in each case). Note that no significant responses were seen in the left SMG. Highly significant activations ($P < 0.001$) were also seen in both precentral gyri in or near the expected locations of the FEFs, with separate superior and inferior peaks, at least in the left hemisphere, as in some previous studies (e.g. Luna *et al*., 1998). Other highly significant clusters appeared in prestriate cortex (see Table 2), the SMA, the left middle frontal gyrus, the anterior part of the insula bilaterally, and in both putamina (see Fig. 5 and Table 3).

For the first time, we have been able to show the pattern of laterality in these areas in the human brain. The most obvious differences between the responses to right and left non-targets (in Fig. 4A and B, respectively) were in prestriate cortex, where the vast majority of the response was contralateral to the stimulus, as expected (see also Fig. 6). The superior parietal lobules also showed a contralateral bias; the views from above the brain in Fig. 4 show that the area of highest significance (in the lightest grey) appears in the left SPL for right non-targets (Fig. 4A) and the right SPL for left non-targets (Fig. 4B).

Direct comparisons of right non-targets with left non-targets confirmed this contralateral bias. The peak voxel in the right SPL (i.e. the most significant voxel in this region in the contrast all non-targets versus null trials) showed a significantly greater response to left non-targets than to right non-targets ($P < 0.008$ uncorrected). The posterior part of the left SPL, on the other hand, showed a significantly greater response to right non-targets than to left non-targets ($P < 0.004$ uncorrected). Uncorrected statistics are quoted for these right versus left comparisons since only one voxel is examined in each contrast. Perhaps the most important finding in these contrasts, however, is that the responses of the right SMG to left- and right-sided non-targets were almost identical, both in extent and significance (compare Fig. 4A and B; see Table 2).

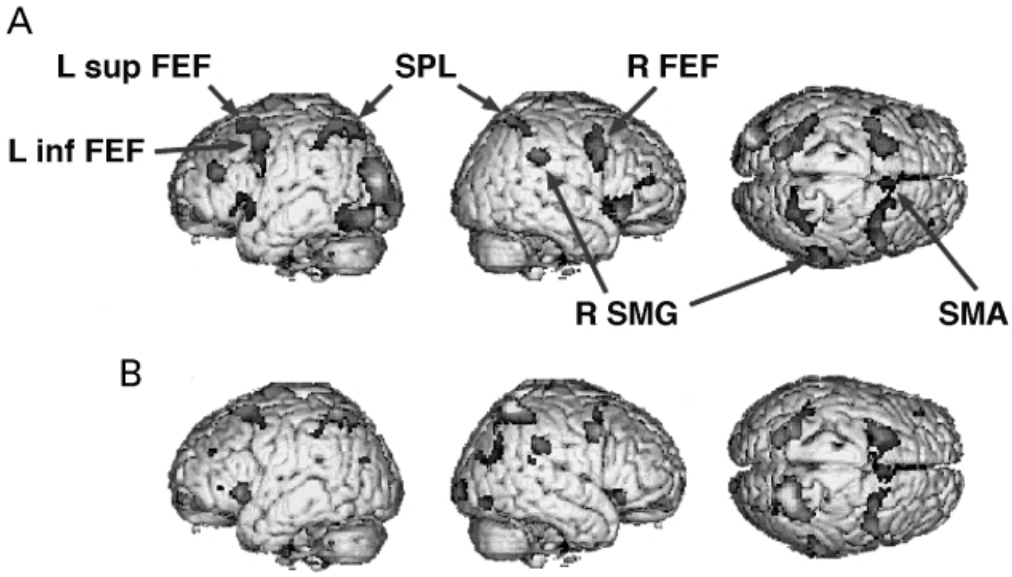

Fig. 4 (**A**) Contrast of right non-targets versus null trials. (**B**) Contrast of left non-targets versus null trials. Format, thresholds and abbreviations as in legend to Fig. 3, *P* values in Tables 2 and 3. sup = superior locus.

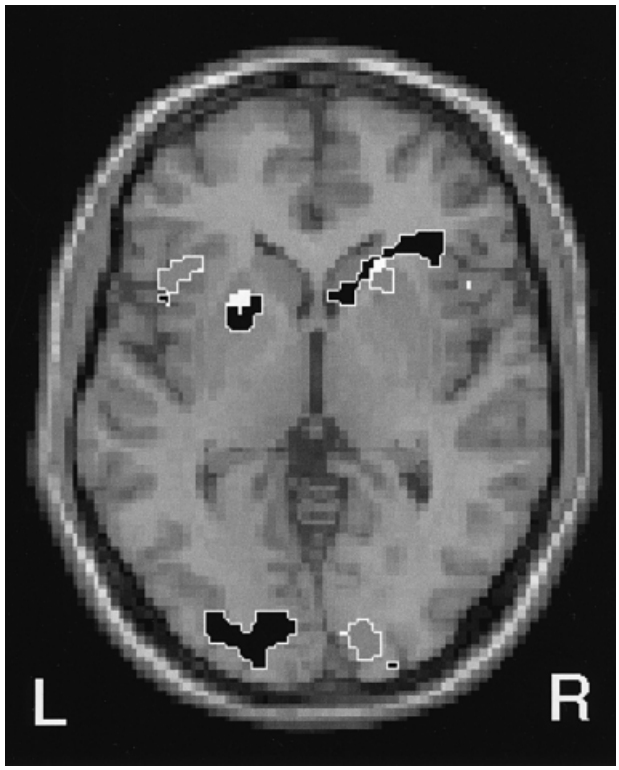

Fig. 5 Ipsilateral activation of anterior insula in contrasts of right non-targets versus null trials (shown in black) and left non-targets versus null trials (shown in grey). Areas activated by both right and by left non-targets appear in white. Statistical parametric maps thresholded at $P < 0.001$ uncorrected, superimposed onto horizontal section through template brain in Talairach space. Note mainly contralateral activations in prestriate cortex and putamina, but mainly ipsilateral activations in anterior insula. Peak *P* values given in Tables 2 and 3.

The next difference between the responses to right and left non-targets, looking at the lateral views of the left hemisphere, is that the inferior part of the left FEF cluster in Fig. 4A (L inf FEF) disappears in Fig. 4B, indicating that this region only responded to right-sided (i.e. contralateral) non-targets. The direct comparison of right non-targets with left non-targets confirmed that this left inferior FEF locus showed significantly greater responses to right-sided stimuli ($P < 0.002$ uncorrected). There were non-significant trends towards a contralateral bias at the other three FEF loci (see Table 3).

Figure 5 shows a horizontal section through the brain at the level of the basal ganglia. Responses to right non-targets (compared with null trials) are now shown in black, with responses to left non-targets in grey. As expected, prestriate areas responded only to contralateral stimuli. The putamen also showed mainly contralateral responses, although the small white clusters (representing overlap of responses) suggest that the most anterior part of the putamen gave bilateral responses. However, the pattern of laterality in the insula was more surprising, in that the responses here were mainly ipsilateral. When responses to right- and left-sided non-targets were compared directly, the right insula gave significantly greater responses to right non-targets ($P < 0.008$ uncorrected), whilst the left insula gave significantly greater responses to left non-targets ($P < 0.02$ uncorrected).

Figure 6A shows the contrasts of right non-targets versus null trials separately for stimuli at 2.5° and 10° (in grey and black, respectively) confirming the well known topography of the human primary visual cortex, within which central vision is represented posteriorly, and peripheral vision anteriorly (Förster, 1890; Fox *et al.*, 1986). These contrasts did not, however, demonstrate such a topographical

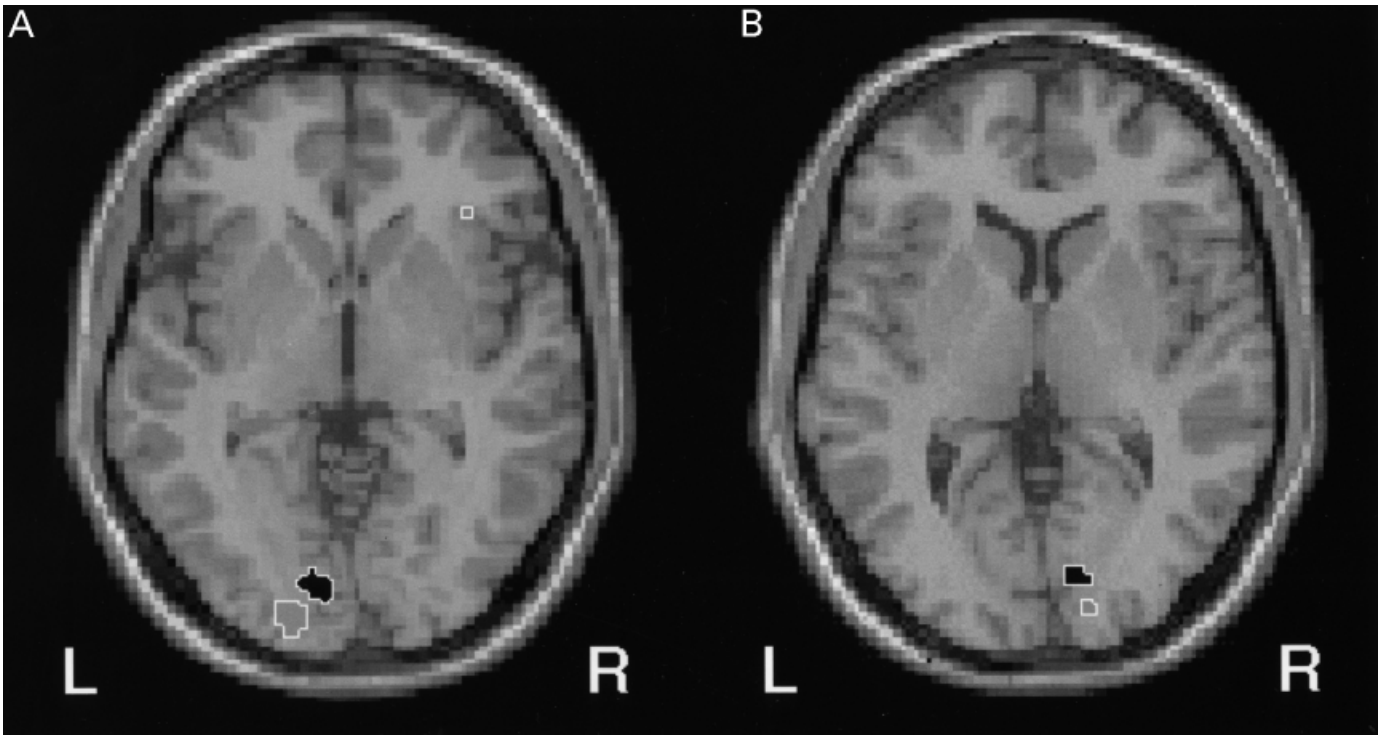

Fig. 6 (**A**) Contrasts of right non-target versus null trials, at eccentricities of 10° (shown in black, peak at –8, –84, –2, $P < 0.001$ corrected, $Z = 7.5$) and 2.5° (shown in grey, peak at –14, –94, –6, $P < 0.001$ corrected, $Z = 7.1$). (**B**) Contrasts of left non-targets versus null trials, at eccentricities of 10° (shown in black, peak at 14, –82, 6, $P < 0.001$ corrected, $Z = 6.8$) and 2.5° (shown in grey, peak at 16, –92, 0, $P < 0.001$ corrected, $Z = 7.2$). Format and thresholding as in legend to Fig. 5.

organization in any of the parietal or frontal areas described in the previous sections.

Null trials versus non-targets: ipsilateral prestriate inhibition

In the contrasts of null trials versus right and left non-targets, shown in Fig. 7, we can see areas of brain which are significantly deactivated by the appearance of a right-sided (in black) or a left-sided (in grey) non-target (thresholded at $P < 0.001$ uncorrected). To be adequately modelled within our design matrix, the deactivation would need to be transient, and of a time-course fairly similar to the canonical haemodynamic response function in SPM97, i.e. a wave of BOLD signal depression. Within the occipital cortex ipsilateral to the stimulus, there was a statistically significant cluster lying just anterior to the striate cortex, within V2 (as mapped by DeYoe *et al*., 1996). These responses were highly significant for right non-targets ($P < 0.001$ corrected at 10, –76, –6) and left non-targets ($P < 0.001$ corrected at –8, –76, –2). Thus, whilst visual stimuli cause the expected striate and prestriate activation in the contralateral hemisphere (as in Figs 6 and 7), they also appear to cause a wave of inhibition in the ipsilateral hemisphere, a phenomenon that has not been observed previously, presumably because it was obscured in epoch-based designs.

Several other areas in the brain show a significant dip ($P < 0.001$ corrected) in BOLD signal in response to non-targets. Peaks of statistical significance are found in both superior temporal gyri (62, 2, 4 and –62, –6, 0 visible in Fig. 7), in the left post-central gyrus (–44, –10, 16), in medial frontal cortex (6, –18, 54 and 0, 52, –8), in the posterior part of the cingulate gyrus (2, –48, 20), and near the parieto-occipital sulcus (0, –74, 24).

Non-targets versus targets

Among the group of areas demonstrated in the non-targets versus null trials contrast, there may be a sub-set whose responses are specific to a 'covert' attention-shifting task, i.e. they are engaged by this task, but not engaged during the generation of saccades (bottom row of Table 1); these may be revealed in the non-targets versus targets contrast. However, this contrast may also show areas specifically involved in suppressing saccades (i.e. maintaining fixation) in the presence of a peripheral visual stimulus, and areas where there is a tonic visual response to a peripheral stimulus which is cut short if a saccade brings this stimulus into the central part of the visual field (third row of Table 1).

As shown in Fig. 8, this contrast shows both FEFs and the left SPL, with a hint of activity in the right SPL, although only the right inferior FEF peak reaches corrected significance ($P < 0.03$) in this relatively insensitive analysis. Since this is a particularly important contrast, we repeated the analysis, omitting the temporal realignment step (which reduces the

statistical sensitivity, see Methods), with the timing of events correctly specified for dorsal regions of the brain. This more sensitive analysis revealed the following dorsal areas at a statistical significance of at least $P < 0.01$ corrected: the left superior frontal eye field (–28, 4, 56), the right and left inferior frontal eye fields (40, 4, 44 and –34, 2, 44), the right supplementary motor area (6, 14, 50) and the left superior parietal lobe (–18, –68, 50). In addition, the right superior parietal lobule (12, –60, 52) exceeded $P < 0.05$ corrected. Thus all of the areas in the dorsal frontoparietal network that respond to targets in fact give a significantly greater response to non-targets.

We needed to know if the difference between non-target and target responses was bilateral, or mainly contralateral to the stimulus, since the pattern of laterality could influence our interpretation (see Discussion). When the contrast non-targets versus targets was made for right-sided stimuli alone (again without temporally realigning the data), the left SPL and the left FEF both exceeded corrected significance (at –16, –68, 48 and –36, 2, 44, both $P < 0.001$ corrected) whilst responses at the equivalent loci in the right hemisphere did not. Similarly, left-sided stimuli elicited a significant response in the right FEF ($P < 0.04$ corrected), with a trend towards corrected significance also in the right SPL ($P < 0.1$ corrected), but much less significant responses on the left. Thus the difference between non-target and target responses is biased towards the hemisphere contralateral to the stimulus.

The contrast non-targets versus targets (with the temporal realignment reinstated) also showed highly significant activation in the left putamen, and a less significant activation in the right putamen (see Table 3). In this study, the putamen was the only brain area which appeared to be entirely specific for covert attention shifts, in that there was no significant response in these nuclei during saccades.

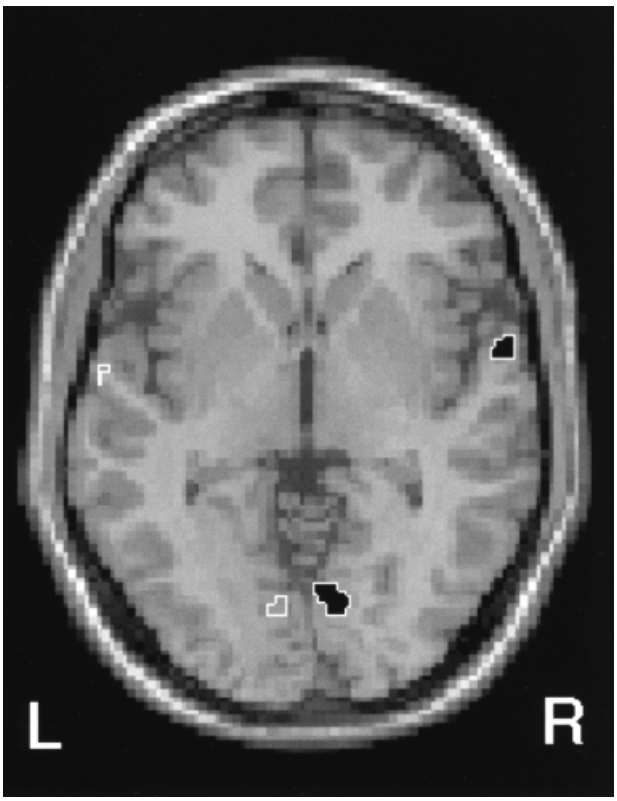

Fig. 7 Prestriate areas deactivated by the appearance of right (shown in black) and left (in grey) non-targets, as shown by the contrasts of null trials versus right and left non-target trials. Format and thresholding as in legend to Fig. 5.

Interaction of sudden onset with target

We were interested to know if saccade-related activity might differ according to whether the stimulus appeared suddenly, or had been visible for some time, since physiological studies in monkeys indicate that these stimuli are treated differently, at least within the parietal lobes (Gottlieb *et al*., 1998). In the context of this study, this question can be rephrased as follows: is the result of the contrast targets versus non-targets significantly affected by whether sudden-onset or stable stimuli are used? To address this question we examined the interaction contrast, which may be summarized as:

[(sudden targets) – (sudden non-targets)]
versus [(stable targets) – (stable non-targets)].

The only brain areas that appeared in this contrast at anything approaching corrected statistical significance, were in or near the superior layers of the right cerebellum. Figure 9 shows this interaction for left-sided stimuli (grey cluster) which revealed a crescent within the right superior semilunar lobule ($P < 0.07$ corrected), and for right-sided stimuli (black clusters), which shows an area just anterior to this ($P < 0.003$ corrected), presumably also originating from the cerebellum,

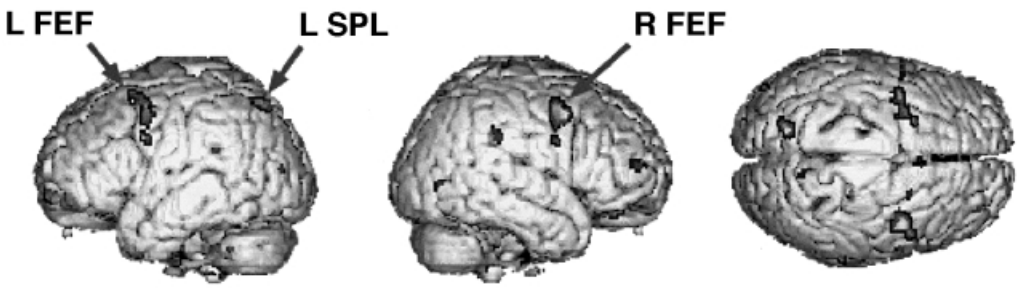

Fig. 8 Contrast of non-targets versus targets. Format and thresholds as in legend to Fig. 3. Peak *P* values in Tables 2 and 3.

although in this case the cluster spreads up into the fusiform gyrus in this (smoothed) data. Both of these areas can be seen, although much less clearly, in the main effect sudden-onset versus stable stimulus (not shown, $P < 0.001$ uncorrected in each case). Thus this area of the cerebellum appears to give a greater saccade-specific response in the context of sudden-onset stimuli than in the context of stable stimuli.

Discussion

Using the new technique of event-related fMRI we have made a direct contrast between strictly comparable saccades and attention shifts within the same experimental paradigm, allowing us to assess the extent to which these two behaviours rely on the same cortical machinery. Shifts to the left could be compared with shifts to the right without contamination of each by the return shifts, allowing us to make a clear assessment of the pattern of laterality of the areas involved, which yields some unexpected new results. Finally, our paradigm has allowed us to demonstrate for the first time that, in normal subjects, the right SMG has a special role in generating saccades and attention shifts, a function which it does not appear to share with the left SMG.

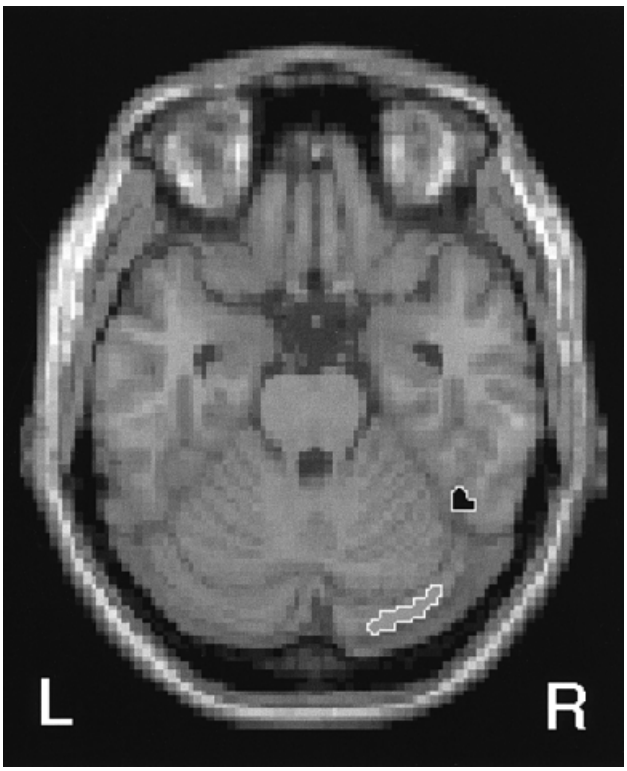

Fig. 9 Interaction between sudden-onset stimuli and targets, shown separately for right-sided stimuli (in black, peak at 48, –48, –22, $P < 0.07$ corrected, $Z = 4.6$) and left-sided stimuli (in grey, peak at 22, –88, –26, $P < 0.07$ corrected, $Z = 4.6$). Format and thresholding as in legend to Fig. 5.

Support for the premotor theory of attention

A combined assessment of previous functional imaging studies of saccades and separate studies of covert attention shifts suggested that the most inferior and anterior parts of the frontal eye fields may be involved specifically in saccades, whilst the most superior and posterior regions may be responsible mainly for covert attention shifts (Corbetta, 1998). However, comparisons across studies are difficult because of differences in the groups of subject, in the experimental paradigms used, and in the processing of the data. Clearly this question is an important test for the premotor theory of attention, which states that covert attention shifts are simply saccades which are planned but never executed (Sheliga *et al*., 1995). According to this hypothesis there should be complete, or at least considerable, overlap between the responses during these two types of behaviour.

The difficulties of making such a direct comparison in epoch-based studies, illustrated in Fig. 1, are further demonstrated in the only other functional imaging study incorporating both saccades and covert attention shifts (Corbetta *et al*., 1998). In this study, a typical covert attention shift was from one stimulus at a (retinotopic) eccentricity of 7° to another at 10°. The saccade that was most nearly comparable (between the same two stimuli) was made to a target with an eccentricity of only 3°, because of the difference in the initial eye position. As discussed in the Introduction, such difficulties inevitably confound epoch-based comparisons.

Event-related fMRI has allowed us to examine only the first (outward) saccade or attention shift, giving us a valid direct comparison between these two behaviours. This technique did not demonstrate any area within the parietal or frontal lobes which was significantly more active in target trials (where a saccade is made) than in non-target trials (with no saccade; see Fig. 3B). It therefore seems highly unlikely that there is a sizeable area of cortex within the frontal eye fields whose neurones fire only when a saccade is made. We conclude that if there are neurones in the human frontal eye fields that respond specifically to the execution of saccades, as in the monkey (Bruce and Goldberg, 1985), then these neurones are dispersed among others which give mainly visual, attentional or saccade-planning responses. Thus our results are broadly consistent with the premotor theory of attention (see above), but an alternative hypothesis, that saccades and covert attention shifts are subserved by separate but spatially overlapping mechanisms, cannot be ruled out by functional imaging alone.

Larger responses to covert attention shifts than to saccades

Surprisingly, BOLD responses to covert attention shifts were significantly larger throughout the frontoparietal network than responses to saccades, a finding which is not predicted by the premotor theory of attention. The most likely explanation

is that there may be neurones in the human frontoparietal network that respond tonically in the presence of the peripheral visual stimulus in our study, as in the frontoparietal network in primates (Bushnell *et al*., 1981; Goldberg and Bushnell, 1981; Bruce and Goldberg, 1985; Snyder *et al*., 1997; Gottlieb *et al*., 1998). The responses of these neurones are presumably cut short when a saccade brings the peripheral stimulus to the centre of vision, so the total response to a target will be much shorter than that to a non-target, resulting in a smaller BOLD signal. It is likely that much of this response is related to a sustained deflection of visual attention, rather than a purely visual response. Although we did not aim to dissociate these two types of response in the present study, parietal neurones in monkeys often give attention-dependent responses (Bushnell *et al*., 1981; Snyder *et al*., 1997; Gottlieb *et al*., 1998). Furthermore, Corbetta *et al.* have previously demonstrated, using PET imaging in the human brain, that there is a greater response in the superior parietal cortex and the frontal eye fields when subjects attend to peripheral stimuli than when they attend to central stimuli, the peripheral stimuli being identical in both cases (Corbetta *et al.*, 1993).

A less likely alternative explanation for the extra activity in non-target trials would be to attribute it to 'fixation neurones'. In primate frontal eye fields, these are neurones which have central receptive fields, and whose activity diminishes prior to the onset of the saccade, regardless of the direction of this saccade (Bruce and Goldberg, 1985). Although some of their response is visual, they also respond during fixation of a remembered position in space, in the absence of a visual stimulus (Hanes *et al*., 1998). However, fixation neurones should give the same response regardless of the position of the peripheral non-target, since these neurones have small, central receptive fields. In contrast, the excess activity in non-target trials in our study was only significant in the hemisphere contralateral to the stimulus.

In conclusion, then, most of the difference in activity in the frontoparietal network between non-target and target trials can probably be attributed to tonic responses to the sustained presence of a peripheral stimulus. These responses are unlikely to be purely visual, and may largely reflect a sustained displacement of visuospatial attention away from the centre of vision during non-target trials.

Our results indicate that in future functional imaging experiments using visual stimuli, it would be unwise to require subjects to maintain central fixation purely with the aim of minimizing 'eye-movement' related activity. In such circumstances, subjects are likely to assess the stimulus using covert attention shifts, leading to more rather than less activity in the frontoparietal network.

Pattern of laterality

When responses to right and left non-targets were independently assessed, the frontal eye fields, the putamina and the posterior parts of the superior parietal lobules responded to stimuli on either side, although there was a contralateral bias in all of these areas. These results are expected from electrophysiological recordings of visually responsive neurones in the parietal lobes and frontal eye fields of monkeys; these tend to show large receptive fields that are centred in the contralateral visual field, but often extend into the ipsilateral field as well (Yin and Mountcastle, 1977; Motter and Mountcastle, 1981; Bruce and Goldberg, 1985). Our results suggest that many of the cells in equivalent areas of the human brain may also have bilateral receptive fields. The bilateral nature of the BOLD responses is also broadly consistent with clinical evidence which suggests that both hemispheres are involved in responses right across the visual field, but with a graded bias towards the contralateral side (Kinsbourne, 1977). However, we have only examined shifts which are either leftwards into the left visual field or rightwards into the right visual field, so further studies will be needed to test specifically for a graded bias across the whole visual field.

Most of the frontoparietal network for spatial attention appears to be distributed reasonably symmetrically between the two hemispheres. One of the most obvious asymmetries in the system is that there is a highly significant response in the right SMG, with no response at all in the left SMG (Fig. 4). The same asymmetrical pattern was seen, at a lower significance level, in the response to saccades (Fig. 3A). The involvement of the right SMG shown in Fig. 4 is very much clearer than the weak, non-significant activation in the right SMG in the study of Corbetta *et al.* (1993), or the hint of a slightly broader cluster of activation in the right SPL/IPS than in the left in some other studies (Nobre *et al*., 1997; Kim *et al*., 1999). Moreover, we provide evidence for a functional dissociation between the right SMG and the SPLs. Whereas the responses in the SPLs are largely biased towards contralateral stimuli, the right SMG gives equally significant responses to right and left stimuli. This observation is of particular interest with respect to the syndrome of left hemi-neglect.

Right SMG and neglect

Visual neglect occurs most frequently and persistently after right hemisphere lesions which include precisely that area in the right SMG which was identified in the present study (compare Fig. 4 in the present study with Fig. 1 in Driver and Mattingley, 1998). Our study shows that this area gives identical responses to stimuli on the right and on the left. One interpretation is that the right SMG may contain a representation of the whole of visual space, a conclusion that would be broadly consistent with previous hypotheses suggesting that the right hemisphere is involved in directing attention in either direction whilst the left hemisphere is only involved in directing attention to the right (Heilman and Valenstein, 1979; Weintraub and Mesulam, 1987; see Introduction).

Our observation that the responses in the right SMG are

not influenced at all by the location of the stimulus, however, tends to suggest that the right SMG may not carry a topographic representation of visual space. An alternative idea is that this area may be involved in switching from local to global features of a stimulus regardless of its position in space (Halligan and Marshall, 1994), since lesions including right SMG have been shown to disrupt global processing (Robertson *et al*., 1988). Perhaps a more radical interpretation, however, is that the right SMG may have an entirely non-spatial role, such as 'alerting' other sub-systems to the presence of a potentially relevant visual stimulus, regardless of its location (see Posner and Peterson, 1990; Robertson *et al*., 1998). Non-spatial deficits are indeed observed in neglect (Husain *et al*., 1997), and the spatial deficits in this syndrome can be ameliorated by non-spatial alerting (Robertson *et al*., 1998).

Our results lead to a paradox: how can damage to an area which gives similar responses to right- and left-sided stimuli result in left hemi-neglect? A possible resolution of this paradox is suggested by the observation that right and left hemisphere strokes initially cause neglect with fairly similar frequencies, but that neglect from right hemispheric lesions is much more likely to persist chronically (Stone *et al*., 1991). One interpretation of this result is that there may be at least two components of neglect. The first may be an immediate spatial deficit which can be caused by lesions of either hemisphere. The second may be a superadded non-spatial deficit, which severely hampers recovery from the first deficit (Robertson, 1993). If this interpretation is correct, then our data suggest that damage or disconnection of either SPL/IPS may be responsible for the first, immediate contralateral deficit. The second, non-spatial deficit may result from damage to the right SMG, which hampers recovery from the first, spatial deficit. Only the conjunction of the second deficit with the first can result in persistent neglect, and a single lesion can only cause this if it involves both the right SMG and the right SPL/IPS, thus explaining the asymmetry of lesions observed clinically. Our results therefore lead to the prediction that small lesions confined to the right SMG should not cause left hemi-neglect, but should instead result either in a symmetrical spatial deficit or in a non-spatial deficit.

Why have previous functional imaging studies of covert attention shifts not showed the highly significant activation in the right SMG which we have observed? One possibility is that the particular form of the BOLD response in this cortical area may reduce the sensitivity with which it can be detected using epoch-based methods, as might occur if the positive BOLD response is followed by an unusually large negative undershoot. A more interesting possibility, however, is that the right SMG may only be fully engaged when subjects must decide whether or not to make a saccade on a trial-by-trial basis. Therefore our study may, for example, have demanded a stronger alerting response than epoch-based saccade studies, in which the sequence of saccades is often entirely predictable and can be performed relatively automatically.

Attentional effects in early visual areas

When a visual stimulus is presented, we have demonstrated that the expected increase in BOLD signal in the contralateral striate/prestriate cortex is accompanied by a transient decrease in the ipsilateral prestriate cortex, which we interpret as representing a transient fall in the ipsilateral synaptic activity. This may either be a component of the visual response, or may be related to shifts of spatial attention.

Kastner *et al.* have demonstrated using fMRI that there are local inhibitory interactions in V4 (and probably also V1 and V2) between the responses to neighbouring visual stimuli presented simultaneously, and that these inhibitory effects can be reversed by attention (Kastner *et al.*, 1998). The present experiment, however, demonstrates for the first time that there are more distant inhibitory effects, extending even as far as the opposite cerebral hemisphere. A recent fMRI experiment by Brefczynski and DeYoe shows that attention to a given visual stimulus not only increases the responses in the corresponding regions of striate and extrastriate cortex, but also appears to cause inhibition in neighbouring regions, although statistical evidence is not yet available (Brefczynski and DeYoe, 1999). These results suggest that inhibitory interactions in early visual areas may contribute to the phenomenon of spatial attention.

Another effect which we observe in the hemisphere ipsilateral to the visual stimulus is a positive BOLD response in the insula. Could this be related to the decrease in BOLD in ipsilateral prestriate areas? Patients with frontal lobe lesions often find it difficult to suppress reflexive responses to visual stimuli (Guitton *et al*., 1985), and it is possible that the insula may be the gateway through which the frontal lobes can suppress prestriate responses to irrelevant visual stimuli in the normal brain.

Role of the lateral cerebellum

We have demonstrated that the response in the lateral cerebellum at the time of a saccade depends upon the preceding sensory context: if the stimulus appears at the very moment when the saccade is required (sudden-onset trials), the BOLD response is larger than if the stimulus has already been present for some time (stable trials). Mushiake and Strick have made an analogous observation in a study of visually guided reaching in the macaque monkey (Mushiake and Strick, 1993). They identified a population of neurones in the dentate nucleus (to which the Purkinje cells of the lateral cerebellar cortex project) which they designated 'track' neurones. Their responses were modulated by visual stimuli only when they were immediately used to guide reaching. Although the analogous observation has not yet been made for saccades, the lateral cerebellar cortex and the dentate nuclei do show pre-saccadic activity (Gardner and Fuchs,

1975; Marple-Horvat and Stein, 1990; Marple-Horvat *et al*., 1998). Thus the lateral cerebellum may be involved in generating 'automatic' saccades in particular sensory contexts, in contrast to the well known involvement of the medial part of the cerebellum in saccadic gain control (Noda, 1991).

Conclusion

So far there has been little progress in dissecting out the individual roles of the various components of the system for saccades and attention shifts in the human brain. The present study, by providing new evidence about the pattern of laterality of these areas, has yielded some clues as to the possible functions of the right SMG and the anterior insula. The technique of event-related fMRI will continue to allow more subtle trial-by-trial manipulations of attention than have been possible in epoch-based studies, and may even allow a dissection of the different temporal components of saccade and covert attention tasks (Corbetta *et al*., 1999).

Acknowledgements

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