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Differential cortical activation during voluntary and reflexive saccades in man

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Abstract

A saccade involves both a step in eye position and an obligatory shift in spatial attention. The traditional division of saccades into two types, the "reflexive" saccade made in response to an exogenous stimulus change in the visual periphery and the "voluntary" saccade based on an endogenous judgement to move gaze, is supported by lines of evidence which include the longer onset latency of the latter and the differential effects of lesions in humans and primates on each. It has been supposed that differences between the two types of saccade derive from differences in how the spatial attention shifts involved in each are processed. However, while functional imaging studies have affirmed the close link between saccades and attentional shifts by showing they activate overlapping cortical networks, attempts to contrast exogenous with endogenous ("covert") attentional shifts directly have not revealed separate patterns of cortical activation. We took the "overt" approach, contrasting whole reflexive and voluntary saccades using event-related fMRI. This demonstrated that, relative to reflexive saccades, voluntary saccades produced greater activation within the frontal eye fields and the saccade-related area of the intraparietal sulci. The reverse contrast showed reflexive saccades to be associated with relative activation of the angular gyrus of the inferior parietal lobule, strongest in the right hemisphere. The frequent involvement of the right inferior parietal lobule in lesions causing hemispatial neglect has long implicated this parietal region in an important, though as yet uncertain, role in the awareness and exploration of space. This is the first study to demonstrate preferential activation of an area in its posterior part, the right angular gyrus, during production of exogenously triggered rather than endogenously generated saccades, a finding which we propose is consistent with an important role for the angular gyrus in exogenous saccadic orienting.

Introduction

That three main cortical areas or "eye fields," bilaterally represented in the cerebral hemispheres, are involved in the generation of saccades is well established and draws on converging data from human stimulation and lesion studies (reviewed in Tehovnik et al., 2000; Pierrot-Deseilligny et al., 1995), from functional neuroimaging (e.g., Fox et al., 1985; Anderson et al., 1994), and from studies of primate neurophysiology (reviewed in Tehovnik et al., 2000; Andersen et al., 1987). These are the frontal eye field (FEF),[1] the supplementary eye field (SEF), and the eye-movement related region within the intraparietal sulcus

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[1] Abbreviations used: FEF, frontal eye field; fMRI, functional MRI; SEF, supplementary eye field; PPC, posterior parietal cortex; IPS, intraparietal sulcus.

(IPS) of the posterior parietal cortex (PPC), sometimes referred to as the "parietal eye field."

What is much less understood is the role each plays in the generation and control of eye movements. One aspect of particular interest is the relative contribution the eye fields and other cortical areas make to reflexive and voluntary saccades in humans. These two types of saccade are conceptually defined (Holmes, 1938; Klein et al., 1992). The reflexive saccade is so named because it represents an immediate eye movement toward an unexpected change in the peripheral sensory environment, such as a flash of light. By contrast, the voluntary eye movement is not directly commanded by a peripheral onset, but instead requires a cognitive judgement, such as the interpretation of a directional instruction, in order to determine when and where to move the eyes.

The paradigm for eliciting a reflexive saccade, usually a sudden brightening in the visual periphery, embodies a stimulus-response coupling at its most simple, although the latency of that response varies depending upon whether or not disengagement has been facilitated by a prior or simultaneous visual offset at fixation (the "gap" effect, Saslow, 1967; Reuter-Lorenz et al., 1991; Klein and Kingstone, 1993). By contrast, the term "voluntary" saccade has subsumed a number of types of saccade which share the common distinction of not being made directly toward such a localizing onset—for example, the memory-guided saccade (made to a remembered target location) and the antisaccade (made in the opposite direction to a peripheral onset). However, it is the "arrow-guided saccade," directly cued by the direction of an arrowhead flashed at fixation, which lends itself best to the study of an endogenously generated, voluntary eye movement (Walker et al., 2000), without the concurrent need for spatial working memory processing (required for memory-guided saccades) or response inhibition (a requirement for antisaccades).

Evidence suggests that beyond a purely conceptual dichotomy, the distinction between reflexive and willed oculomotor behavior exists at the level of the pathways for saccade generation in the brain (Walker et al., 2000; Schiller, 1998; Sweeney et al., 1996; Schall, 1995; Guitton et al., 1985; Henik et al., 1994; Deubel, 1995; Doricchi et al., 1997).

First, voluntary saccades have a longer latency of onset than reflexive saccades; on average about 350 ms compared to 250 ms (Walker et al., 2000; Forbes and Klein, 1996; Henik et al., 1994; Rafal et al., 1994). This finding is not surprising given that by their very nature voluntary saccades need a cognitive judgement before the decision to move the eyes can be made, whereas reflexive saccades do not. But recent evidence shows that some of this latency difference, in generating a voluntary saccade compared to a reflexive saccade, persists even after obviating the need to attend to and process direction from the instructive cue (Walker et al., 2000). This suggests that reflexive and voluntary saccades may differ not only because of the cue processing require-

ments of the latter but because of differences in neural processing subserving production of a saccade in the presence, as opposed to absence, of a salient peripheral visual onset.

Secondly, beyond the latency difference, the reflexive-voluntary distinction is supported by data from both the single unit recordings in primates and the study of the effects of cortical lesions in humans and primates. The picture which has emerged assigns a greater role for the FEF in the production of voluntary saccades and more of a reliance on the PPC for production of reflexive saccades, though how much these distinctions within the frontoparietal network are absolute or, as seems more likely, relative is unresolved. Although neurons of both the primate FEF and the SEF fire before and during reflexive saccades (Bizzi, 1968; Bizzi and Schiller, 1970; Mohler, 1973; Goldberg and Bushnell, 1981; Suzuki et al., 1979; Bruce and Goldberg, 1985; Schlag and Schlag-Rey, 1985, 1987; Schall, 1991; Segraves and Park, 1993; Bon and Lucchetti, 1994; Heinen and Liu, 1997; Russo and Bruce, 1996; Schlag-Rey et al., 1997), lesions of these areas delay only minimally their production and the deficit rapidly recovers; a result which suggests that the FEF and SEF are either not dominantly involved in the generation of reflexive saccades or that their damage can be compensated for by functional contributions from other areas (Dias and Segraves, 1999; Lee and Tehovnik, 1995; Schiller and Chou, 1998; Schiller et al., 1980; van der Steen et al., 1986; Sommer and Tehovnik, 1997).

Comparable data on the production of voluntary saccades is largely lacking. Memory-guided saccades have been studied. Reversible FEF lesions impair these (Sommer and Tehovnik, 1997) but since FEF neurons in whose response fields the extinguished target lies remain active during the delay period it is not clear how much this is a measure of a FEF contribution to location memorization rather than volitional production of an eye movement. SEF lesions do not impair single memory-guided saccades but have profound effects of sequences of such saccades (Sommer and Tehovnik, 1997). The FEF contains neurons which respond maximally during visual search when a target, lying in their visual fields, is selected for a saccade (Schall, 1995). This might be seen as an example of voluntary saccade production but, because it was tested in association with search for targets of "pop-out" visual salience, the saccade produced might equally well be thought to have a strong reflexive component.

Drawing conclusions from the human lesion data has not been helped by the fact that most patients have had lesions which extend to a variable extent beyond any one eye field into adjacent and potentially relevant cortical areas. Tehovnik et al. (2000) have recently revisited the literature on the behavioral consequences of lesions of the FEF (Pierrot-Deseilligny et al., 1991; Braun et al., 1992; Rivaud et al., 1994) and SEF (Gaymard et al., 1990; Pierrot-Deseilligny et al., 1991; Braun et al., 1992) by selectively drawing on data from patients in whom the lesion was reasonably discrete.

The evidence suggests that patients with FEF and SEF lesions perform reflexive saccades normally. Again, memory-guided saccades have been the type of "voluntary" saccade most studied. Unilateral FEF lesions, but not SEF lesions, slow the onset of contralesional memory-guided saccades and render them hypometric.

By contrast, the PPC and its parietotectal projections have been proposed to be crucial to the generation of reflexive saccades (Gaymard et al., 1998). PPC lesions delay reflexive saccades in humans (Pierrot-Deseilligny et al., 1987, 1991; Heide and Kompf, 1998) and primates (Lynch and Mclaren, 1989). The contribution of PPC to voluntary saccade production has, however, not been extensively evaluated.

Germane to the attempt to distinguish between reflexive and voluntary saccades at the behavioral and neurophysiological level is a consideration of the saccade as combined shift in spatial allocation of attention and physical shift in the position of the eye (e.g., Posner, 1980; Sheliga et al., 1997; Rizzolatti et al., 1987). Evidence suggests that such a shift in attention is prerequisite for any saccade. For example, it is known that subjects cannot simultaneously move their eyes to one location and attend to a different one (Hoffman and Subramaniam, 1995). Moreover, a number of functional imaging studies setting attentional shifts without eye movements ("covert" shifts of attention) against complete eye movements (sometimes referred to as "overt" shifts of attention) have found them to activate the same network of structures, including the eye fields of the frontal and parietal lobes, without evidence of significant regional segregation (Nobre et al., 1997, 2000; Corbetta et al., 1998; Perry and Zeki, 2000), at least not at the level of resolution available.

One might surmise that reflexive and voluntary saccades differ in the way the associated shift in spatial attention of each is achieved; the former directed from without (or "exogenously") and the latter from within ("endogenously"). Attempts to contrast directly brain activation during exogenous and endogenous shifts of attention without eye movements have been made, but have not identified significant differences in the distribution of frontoparietal cortex active during each (Rosen et al., 1999; Kim et al., 1999). Whether the same is true for overt shifts, i.e., during exogenously triggered (reflexive) and endogenously triggered (voluntary) eye movements has not previously been addressed. Where functional imaging studies have examined reflexive saccades (Anderson et al., 1994; Sweeney et al., 1996; Muri et al., 1996; 1998; Darby et al., 1996; Petit et al., 1997; 1998; Luna et al., 1998; Berman et al., 1999; Nobre et al., 2000) and saccades of the "voluntary" type (Fox et al., 1985; Paus et al., 1993; Petit et al., 1996; Darby et al., 1996; Bodis-Wollner et al., 1997; Law et al., 1998; Corbetta et al., 1998; Perry and Zeki, 2000) activation of the FEF, SEF, and IPS has been shown for both, but no study so far has compared reflexive and voluntary saccades directly.
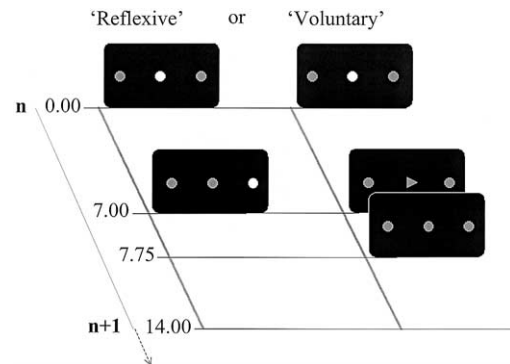
The technique of event-related fMRI offers a powerful

Fig. 1. Timing (s) of the stimulus display sequence of the nth trial ("reflexive" or "voluntary" trial type) of the saccade protocol, trial n finishing with a recentreing saccade triggered by the start of trial $n + 1$.

tool for probing how the brain can produce spatially identical motoric actions, such as two saccades of a given amplitude, under differing behavioral conditions (Perry and Zeki, 2000). We applied this technique to explore differences in cortical activation patterns associated with the production of reflexive and voluntary saccades. For our prototypical voluntary saccade we chose a saccade of a type less confounded by issues of spatial working memory and saccade inhibition than memory-guided and antisaccades, namely the arrow-guided saccade. We find that compared to reflexive saccades, voluntary saccades were associated with relative activation in both the FEF and IPS whereas relative activations associated with reflexive saccades occurred in the angular gyrus of the inferior parietal lobule.

Materials and methods

The oculomotor paradigm and subjects

Twelve young healthy volunteers were studied (ages 21–31, 5 female, 2 left-handed). The experimental protocol was approved by the local hospital ethics committee and written informed consent was obtained prior to the study.

Subjects viewed a horizontal array of 3 spots. There were 2 trial types, named "reflexive" or "voluntary" according to the type of outgoing saccade that each elicited (Fig. 1). At the start of every trial the central spot was kept brightly illuminated and subjects fixated this for 7 s. Then an outgoing saccade to one of the peripheral spots was elicited, subjects holding eccentric fixation until a recentring saccade was triggered by the start of the next trial, 7 s later. In reflexive trials, the outgoing saccade was triggered by the dimming of the central spot simultaneous with the brightening of one of the peripheral spots. In voluntary trials, the outgoing saccade was triggered by the central bright spot turning into a briefly presented dim arrowhead which directed subjects to immediately saccade to one of the peripheral spots. Subjects were instructed to make all saccades

immediately upon the relevant eliciting stimulus change. The trial order was pseudorandomized to ensure a balanced number of left/right and reflexive/voluntary saccades and equal number of switches and nonswitches between the different trial types. All subjects underwent the same trial sequence.

Behavioral study

Subjects first underwent the saccade protocol outside the scanner during which saccades were recorded by infrared oculography (250 Hz; Eyelink, SMI, Germany) and analyzed off-line. For the behavioral session stimuli display spots subtended 2° of visual angle and saccades were 12° in size, and the intersaccade interval within trials was 3 s.

Functional study

Functional imaging data were then acquired while each subject performed the same saccade protocol in the MRI scanner (Siemens Vision 1.5 T) over 2 sessions, the second stimulus sequence reversing the order of the first. T2*-weighted gradient-echo echoplanar (EPI) images, sensitive to blood-oxygen-level-dependent (BOLD) contrast, were acquired with the following parameters: repetition time (TR) 3 s, acquisition time (TA) 2.4 s, echo time (TE) 50 ms, flip angle 90°. Each functional acquisition consisted of 24 planes (voxel size: $3.75 \times 3.75 \times 4.0$ mm), aligned to the anteroposterior commisural (AC-PC) line and covering the whole brain down to midcerebellum. There were 240 acquisitions per session, the first 6 being discarded to permit time for magnetic saturation effects to reach steady state. For the functional imaging session the display was presented on a 21 inch LCD panel (NEC 2010) situated on the floor behind the scanner and viewed through a series of two mirrors. Display spots subtended 1° of visual angle to the subject and saccades were 6° in amplitude. DICOM image files were converted to Analyze format using freeware software (MRIcro; http://www.psychology.nottingham.ac.uk/ staff/cr1/mritut.html). Functional data were then analyzed in SPM-99 (Wellcome Department of Cognitive Neurology, London, UK, see http://www.fil.ion.ucl.ac.uk/spm; Friston et al., 1999) which is written for MATLAB (Maths Works Inc., MA). First, images of each time series were spatially realigned to the first image of the series by sinc interpolation and realignment parameters where checked to confirm that none of the subjects had moved more than 4 mm during the scan run. Then a temporal realignment was performed, using sinc interpolation, of each slice to the most dorsal and first-acquired slice of each acquisition, to counter temporal misalignment inherent in acquiring slices progressively over 2.4 s (Schanze, 1995). After this, all functional data were spatially normalized by bilinear interpolation to the EPI template within SPM-99, bringing it into the coordinate frame of the Montreal Neurological Institute (MNI) average brain which equates approximately with Talairach space

(Talairach and Tournoux, 1988; Friston et al., 1999). Normalized images were then spatially smoothed with a Gaussian kernal of $7 \times 7 \times 8$ mm full width, half-maximum and high-pass filtered (1/62 Hz) prior to statistical analysis. High-resolution T1-weighted structural MRIs were also acquired on all subjects and, after normalization into MNI space, used to derive a group mean brain volume for 2D and 3D rendering of results.

The event-related analysis was performed using the standard hemodynamic response function (canonical HRF) provided within SPM-99, according to methods established by others (Josephs et al., 1997; Friston et al., 1998). The principle underlying the event-related approach is no different from block-design functional imaging; namely that exact knowledge of when behavioral events of interest (in this case, relatively sparse and brief events, such as a leftward outgoing voluntary saccade) occurred during the scan run permits a prediction of how the consequent blood flow transients (represented as a regressor for the specific event onsets convolved with the HRF) will be seen as signal change in the successive "snapshots" taken of the brain which constitute the functional time series. These regressors are then used as covariates in a general linear model to derive, pixelwise, statistical estimates of how well the observed signal change actually correlates with the predicted profiles. The result is a statistical parametric map of the t statistic generated for each voxel (SPM {t}). In our study, the temporal spacing of saccades (7 s) was deliberately chosen to be a nonmultiple of the spacing of whole brain acquisitions (3 s), in order to sample from widely, and therefore maximize the effective temporal resolution of, the event-related signal changes (Josephs et al., 1997).

In this analysis, eight "events" of interest were modeled, corresponding to the various, equally represented, combinations of (i) each of the two saccades of each trial (outgoing/recentring), (ii) the trial type in which they occurred (reflexive/voluntary), and (iii) their direction (leftward/ rightward).

The results presented derive from a fixed-effect analysis (Friston et al., 1999). Contrasts were performed on the whole of the sampled brain and not constrained to a priori regions of interest, except for the tests of laterality preference (see later) which were performed as second-order contrasts based on a small volume of voxels which proved statistically significant for the relevant first-order contrasts (Worsley et al., 1996). Results are presented of the spatial extent (voxels) and peak height (SPM{t} transformed to Z values) of foci which for contrasts of interests achieved a statistical value of activation above the threshold of $P < 0.001$ ($Z > 3.09$), uncorrected for multiple comparisons. We have also indicated whether or not the clusters in which these voxels reside survived a correction for multiple comparisons using the theory of Gaussian fields as instantiated in SPM-99. This correction both adjusts statistical significance for the many voxelwise comparisons made, given the potential for false positives, and takes account of signal
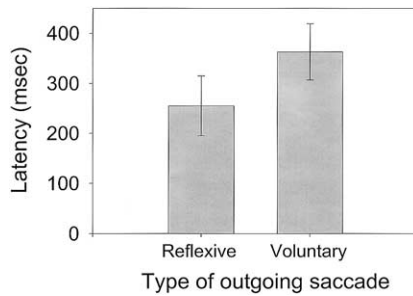
Fig. 2. Mean saccade latencies (ms) and standard deviations for the behavioral saccade protocol, performed outside the MRI scanner and just before the functional imaging session. The onset latency of voluntary saccades was longer than reflexive saccades (voluntary saccades: 363 ± 60, reflexive saccades: 265 ± 56, mean ± SD_{n-1}, $P < 0.005$).

cooperativity between voxels which arises as a result of spatial smoothing. While some voxels reaching significance at the uncorrected value did not survive the correction for multiple comparisons, their validity is nonetheless supported by the observation that they occurred bilaterally within areas known to be relevant to spatial orienting and/or saccade generation. Clusters under 8 voxels in size were excluded from the results.

A separate random effects analysis was performed and the results are included below. It makes more stringent demands for homogenity of response across the subject group but runs the risk of missing small significant effects seen on average within the group. It has therefore to be seen as complimentary to the fixed effects analysis, the results of which, while pertaining to the group of 12 subjects studied, may not generalize to the population as a whole.

Results

Analysis of saccades from the behavioral session outside the scanner showed that subjects did not make mistakes ($<1\%$), a reflection of how easy the task was to perform. On average half (voluntary saccades 54%; reflexive saccades 48%) of the primary outgoing saccades were followed by a small secondary corrective saccade onto the target spot. The onset latency of voluntary saccades was longer than reflexive saccades (voluntary saccades, 363 ± 60; reflexive sac-

cades, 265 ± 56, mean ± SD_{11}, $P < 0.005$), on average 25 ms longer than in Walker et al. (2000), but differing between the two saccade types by a comparable margin (approximately 100 ms) (Fig. 2).

The design of our functional study used only active events (saccades) so our analysis is limited to the assessment of relative activation during one event type compared to another, not absolute activation. Only the outgoing saccades were unpredictable for both saccade type and direction. Our event-related design allowed us to specifically focus on these relevant events by using only outgoing saccade events for contrasts of interest.

Voluntary versus reflexive saccades

Contrasting outgoing voluntary saccades with outgoing reflexive saccades revealed bilateral activations in the FEF, IPS, and a lateral occipital area, each statistically significant at $P < 0.05$, corrected for multiple comparisons, except activation within the right FEF which was only apparent at the uncorrected level ($P < 0.001$). These results are listed in Table 1 and presented as surface-rendered activations (within SPM-99) onto the group mean brain image in Fig. 3.

Thus, for this whole-brain group contrast, two of the three areas, identified as showing relatively greater bilateral activation for voluntary compared to reflexive saccades, are within two of the three established cortical eye fields. The left FEF activation was stronger than the right and situated slightly more lateral and deeper in the precentral sulcus of the group mean brain image. Activations of the IPS were symmetrical in extent along the superior anterolateral portion of the sulcus bilaterally, though weaker and less continuous on the left compared to the right.

Some recent fMRI studies of saccades have provided evidence of two foci of activation within the precentral sulcus, the so-called "superior FEF," lying anteromedially, and the "inferior FEF," lying ventrolaterally (Luna et al., 1998; Heide et al., 2001; Grosbras et al., 2001; Perry and Zeki, 2000) independent of constraints imposed on their functional interpretation by any use of a priori regions of interest. Fig. 5 summarizes the group mean average Talairach-type coordinates of FEF activations in previous fMRI studies where either saccades or covert attention of the voluntary/endogenous or reflexive/exogenous type have

Table 1
Comparison of outgoing voluntary saccades versus outgoing reflexive saccades

	Left hemisphere					Right hemisphere				
	x	y	z	Voxels	Z	x	y	z	Voxels	Z
Precentral sulcus (FEF)	−40	0	44	233	5.46*	28	−6	50	98	4.29
Intraparietal sulcus (IPS)	−30	−54	52	354	4.42*	36	−58	58	662	5.62*
Lateral occipital (LO)	−44	−74	6	302	4.48*	44	−74	−6	493	5.19*

Note. Talairach-equivalent coordinates following normalization to the MNI template, cluster sizes (voxel), and "Z score" of voxels ($P < 0.001$, uncorrected).

* Clusters surviving correction for multiple comparisons at the cluster level ($P < 0.05$). Voxel size: 3.75 × 3.75 × 4.0 mm. 1 resel = 211.3 voxels.
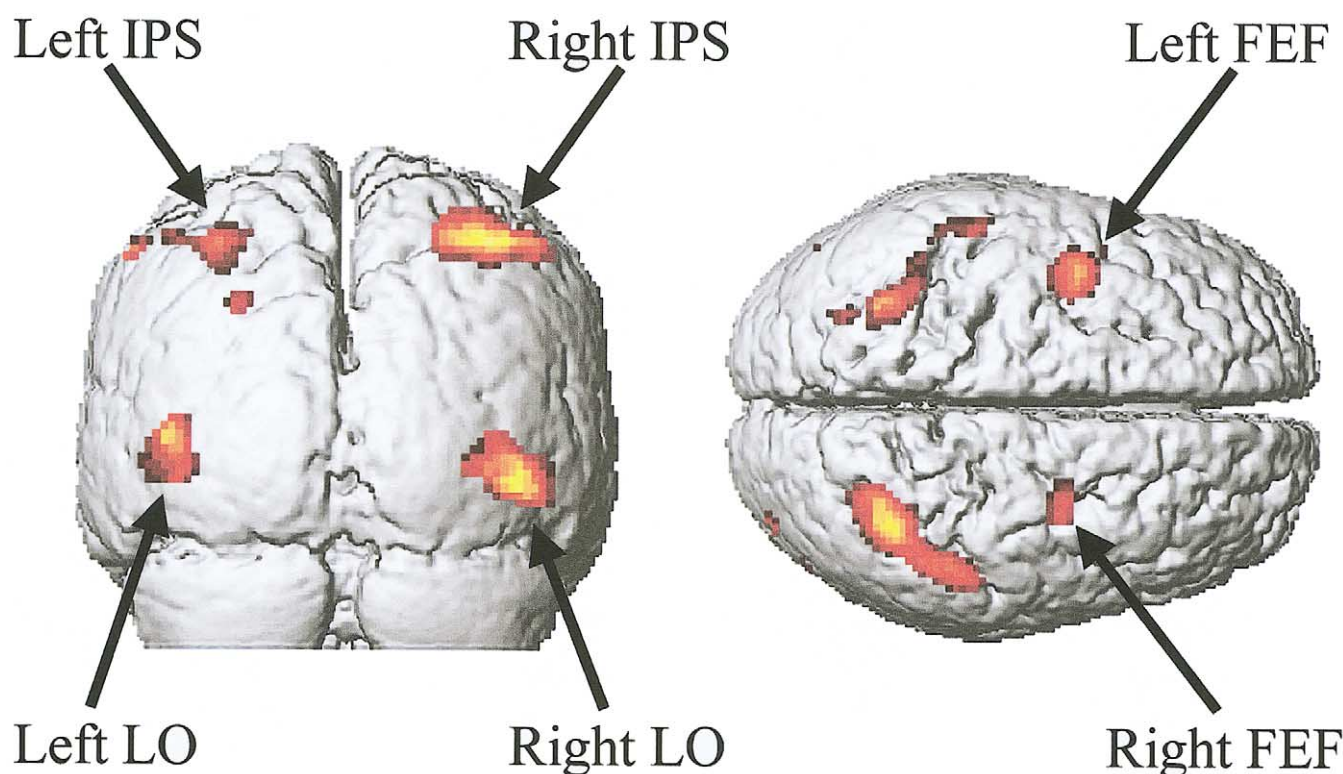
Fig. 3. Voxels showing relative activation for the contrast "outgoing voluntary versus outgoing reflexive saccades" ($P < 0.001$, uncorrected, spatial extent >8 voxels).

been investigated. These coordinates and the studies from which they were reported is provided, as supplementary information, in Table A of the appendix. We make the observation that previous reported activations in relation to reflexive saccades appear to cluster in the region of the superior FEF. However, insufficient data are available from the literature to subject this hypothesis to an effects meta-analysis. The foci of the precentral sulci which have been identified as relatively more active during voluntary as opposed to reflexive saccades both lie inferior to this cluster, more so and more anteriorly in the left hemisphere, suggesting that, where a direct comparison of the two saccades types is made, the inferior FEF is more active during voluntary saccades.

Fig. 6 provides a similar overview of the distribution, from other fMRI studies, of group activations within the superior parietal lobule (SPL) and IPS in relation to saccades or covert attentional shifts (see Table B, appendix material). Activations along the region of its superior anterolateral portion bilaterally have been a consistent feature of all investigations of saccades and attentional shifts. Activations reported in relation to reflexive saccades appear to have been better confined to this section of the intraparietal sulcus. However, the direct comparison, in this study, with voluntary saccades suggests that activation of this area by voluntary saccades is greater and strongest in the right hemisphere.

The other area which showed significant relative activa-

tion for the contrast of voluntary versus reflexive outgoing saccades was a lateral occipital area centred over the middle occipital gyrus. This has the same Talairach coordinates as the lateral occipital (LO) area, identified by Malach et al. (Malach et al., 1995; Grill-Spector et al., 1999) as a cortical area which shows position-invariant preference for objects. This area was also highlighted by Corbetta et al. (2000) in a recent event-related study of precued covert horizontal shifts of attention. Their analysis of the BOLD time course of that activation suggested that it related to the processing of the arrowhead precue because, though time-locked to presentation of the precue, its activation was not sustained for the interval up until the trigger for an attentional shift was given. It seems very likely that this area is differentially activated for the voluntary saccade in our study because only the voluntary saccade trial involved presentation of an arrowhead object.

Reflexive versus voluntary saccades

The results of the reverse contrast, reflexive against voluntary outgoing saccades, identified weaker activations, listed in Table 2 and surface-rendered onto the group mean brain image in Fig. 4. While reviewing group activations from the fMRI literature (Fig. 5, appendix Table A) highlights the superior FEF as the commonest locus of activation in the production of reflexive saccades, our direct contrast provided no evidence that there is any area of the FEF

Table 2
Comparison of outgoing reflexive saccades versus outgoing voluntary saccades

	Left hemisphere					Right hemisphere				
	x	y	z	Voxels	Z	x	y	z	Voxels	Z
Angular gyrus	−46	−76	32	69	5.46	42	−66	30	270	4.37*
Precuneus	−6	−30	64	183	4.10*	20	−30	66	212	4.00
Posterior cingulate						2	−44	34	154	4.33
Superior frontal gyrus						10	38	58	414	4.64*

Note. Data presented as in Table 1.

which is greater activated by reflexive saccades compared to voluntary saccades.

Activations which were present at the uncorrected level of $P < 0.001$ were seen in the precuneus, the posterior cingulate cortex, and the angular gyrus of the inferior parietal lobule. Activations centered, at $P < 0.05$ corrected for multiple comparisons, in the right superior frontal gyrus (SFG) were seen extending into the adjacent gyrus. They lay anterior to the area of cortex containing the supplementary eye fields and could correspond to what some authors have called "preSEF" but the functional significance of these frontal activations for this contrast is not clear.
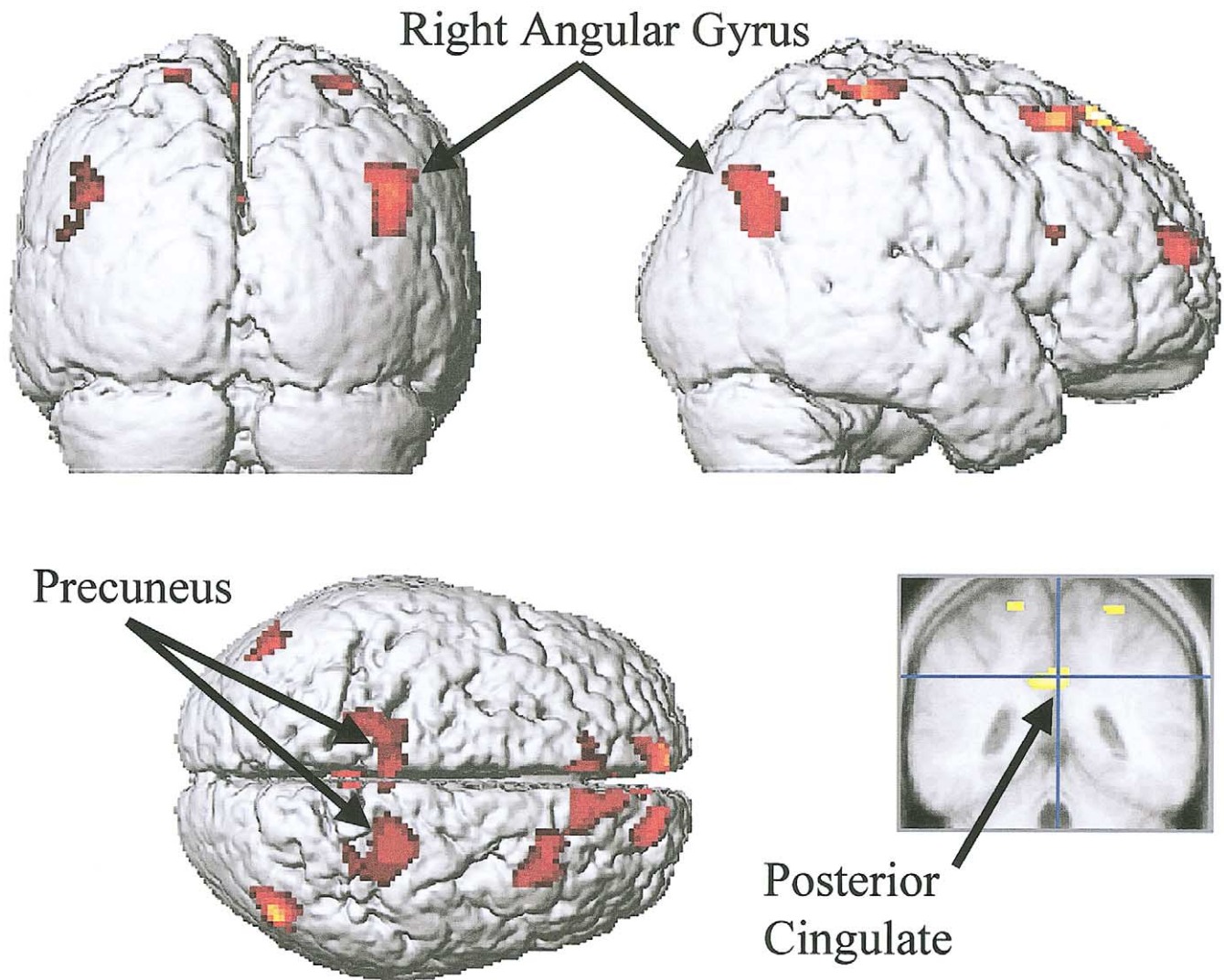

Fig. 4. Voxels showing relative activation for the contrast "outgoing reflexive versus outgoing voluntary saccades" ($P < 0.001$, uncorrected, spatial extent >8 voxels). Note, activation in the rostral aspect of right dorsomedial prefrontal cortex appears to have breached the midline because of the effect of image smoothing during analysis.

Both the precuneus (Anderson et al., 1994; Darby et al., 1996; Muri et al., 1996; Luna et al., 1998; Berman et al., 1999) and the posterior cingulate (Berman et al., 1999) have been reported to be active during saccades by previous functional imaging studies. However, the area of precuneus activation highlighted here is more anterior and medial than the foci of group activations seen is other fMRI studies of reflexive saccades (e.g., Luna et al. (1998), -8, -83 38, left; 11, -56, 60, right; Berman et al. (1999), -6.8, -66.5, 54, left; 8.3, -68, 51.5, right; Heide et al. (2001), 8, -68, 44, right). The posterior cingulate activation is comparable to that found in relation to reflexive saccades by Berman et al. (1999) (-12, -25, 40, left; 10, -26, 43, right).

The finding of relative activation, strongest in the right hemisphere, of the angular gyrus of the inferior parietal lobule for reflexive saccades compared to voluntary saccades is a particularly intriguing one, given that damage to this area in the right hemisphere is commonly associated with the attentional deficits which comprise the clinical condition of left hemispatial neglect (Holmes, 1918a; Bisiach et al., 1979; Hier et al., 1983; Vallar and Perani, 1987; Karnath, 1997). Activations within the IPL, usually in the right hemisphere, have been an infrequent finding of previous fMRI studies of saccades and/or covert attention (Luna et al., 1998; Corbetta et al., 2000; Perry and Zeki, 2000; Grosbras et al., 2001; Vandenberghe et al., 2001a,b). However, with the exception of IPL activation in association with sustained eccentric attention in the study of Vandenberghe et al. (2001b), all these activations have been in the supramarginal gyrus. Ours in almost 2 cm more posterior, located in the angular gyrus. Ours is the first study to indentify activation of the angular gyrus of the IPL in relation to reflexive saccades and suggests that this important differential activation is only revealed by the direct comparison of the two saccade types.

Laterality preferences

Direct contrasts, left versus right and vice versa, for outgoing saccades of each type did not produce any statistically significant evidence of regional preference for saccade direction. This may reflect loss of statistical power in only considering events of both one saccade type and one direction. However, we went on to perform secondary contrasts for preference of direction (left versus right outgoing saccades and vice versa), using a search volume of 10-mm radius ("small volume correction") centered on each of the major areas identified in the primary contrasts (Worsley et al., 1996). This revealed that the left FEF showed a stronger activation for right than left voluntary outgoing saccades (FEF; -40, 0, 44, left, Z 3.18). None of the other areas identified by the primary contrasts showed laterality preferences that reached statistical significance.

Random effects analysis

Contrasts were also performed with a random effects analysis. This confirmed activations of the IPS bilaterally (-34, -58, 48, left, Z 4.35, cluster 169 voxels; 34, -58, 46, right, Z 3.72, cluster 187 voxels) and left FEF (-32, 0, 52, left, Z 3.97, cluster 73 voxels) for the contrast of voluntary versus reflexive saccades, statistically significant at the $P <$ 0.05 level, corrected for multiple comparisons. Other activations identified in the fixed effects analysis did not survive at this level.

Discussion

Ours is the first study to use event-related fMRI to make a direct comparison of cerebral cortical activation associated with individual reflexive (exogenously triggered) and voluntary (endogenously triggered) saccades. This comparison has revealed preferential cortical activations associated with each of the two saccade types: within the FEF and IPS for voluntary saccades, and areas including the angular gyrus of the inferior parietal lobule for reflexive saccades.

Our eye-movement paradigm was designed so that stimulus conditions would be identical in each type of trial, reflexive and voluntary, until the point when the outgoing saccade was commanded. Differences between regional activation associated with outgoing saccades from each trial type therefore may be presumed to encompass all the processing components which distinguish these two types of saccades in real life, both contextual (sensory) and motoric.

Though the "reflexivity" of outgoing saccades elicited by our reflexive saccade condition could not include a complete unpredictability of the timing of saccade events per se, or their required amplitude, it did encompass (i) an equal chance of occurrence of the outgoing saccade being reflexive (and elicited by a peripheral onset) as opposed to being voluntary (and instructed by a central arrowhead) and (ii) an unpredictability for saccade direction.

Relative activation in superior FEF and IPS for voluntary saccades

Previous functional imaging investigations of reflexive saccades (Darby et al., 1996; Petit et al., 1997; Muri et al., 1998; Luna et al., 1998; Berman et al., 1999; Nobre et al., 2000) and of voluntary saccades (Fox et al., 1985; Paus et al., 1993; Paus, 1996; Darby et al., 1996; Bodis-Wollner et al., 1997; Law et al., 1998; Corbetta et al., 1998) have all shown activation of the FEF. In this context, our finding of greater activation of the FEF during production of a voluntary compared to an reflexive saccade is in agreement with a general tenet that the FEF is more involved in the programming and execution of voluntary saccades. Moreover, this activation, strongest on the left, occurred within a region of the FEF which has previously been referred to as

"inferior" FEF, suggesting that this cortical area may be most important for the internal generation of voluntary saccades.

By contrast, our finding that the IPS of the PPC was more active for voluntary saccades might appear to be at odds with the belief from that the "parietal eye fields," located within the IPS, are more important for reflexive saccades, a belief derived from evidence in humans (Gaymard et al., 1998) and primates (Lynch and Mclaren, 1989). The contribution of PPC to voluntary saccade production has, however, not been extensively evaluated. From previous functional imaging studies of voluntary saccades, self-paced voluntary saccades in the dark (Law et al., 1998) and centrally cued saccades into the left hemifield (Corbetta et al., 1998), it is known that the IPS is extensively activated. So while our findings underscore a greater functional activation of the IPS for voluntary saccades they do not contest the evidence from lesion evidence, suggesting that intact function of the PPC in general is more essential to the correct performance of reflexive saccades.

While evidence suggests that cue processing does not explain all of the longer latency of the voluntary saccade compared to the reflexive saccade (Walker et al., 2000), it is an interesting finding that, beyond relative activation of LO, which is likely to be the neural correlate of cue processing in our experiment, the voluntary saccade condition also produced relative activation in two of the three frontoparietal eye fields. It is possible that this finding provides insight into previous suggestions (e.g., Walker et al., 2000) that neural processing demands may be greater for generation of a saccade in the absence of a salient peripheral onset compared to its presence.

Relative activation, in our study, of the IPS for the production of a voluntary saccade also consorts well with the hypothesis that it is the (endogenous) attentional shift component of the voluntary saccade that distinguishes it from the reflexive saccade. Bilateral IPS activation accompanied the arrow-cued covert (endogenous) shift in a previous event-related study (Hopfinger et al., 2000). And block-design fMRI studies which have attempted to contrast endogenous and exogenous covert attentional shifts have reported modestly greater activations within IPS for the endogenous shift condition (Kim et al., 1999; Rosen et al., 1999; Vandenberghe et al., 2001a). However, since activation along the IPS of the PPC is also one of the most consistent findings in functional imaging studies where the application of visuospatial attention is required (for example, Corbetta et al., 1998; Gitelman et al., 1999; Vandenberghe et al., 2001b; Beauchamp et al., 2001), it remains possible that relative activations of IPS for voluntary saccades, in our case, and for endogenous shifts of covert attention in previous studies, stem from greater attentional demands of processing the initiating cue.

Although SEF activation has been demonstrated for both reflexive (Anderson et al., 1994; Sweeney et al., 1996; Muri et al., 1996, 1998; Darby et al., 1996; Petit et al., 1997; Berman et al., 1999; Nobre et al., 2000) and voluntary saccades (Fox et al., 1985; Darby et al., 1996; Bodis-Wollner et al., 1997; Corbetta et al., 1998), we found no evidence for its differential activation in one saccade type compared to the other.

Relative activation of precuneus, posterior cingulate cortex, and angular gyrus for reflexive saccades

Those areas which showed relative activation for reflexive saccades included the precuneus, the posterior cingulate cortex, and the angular gyrus of the inferior parietal lobule. Both the precuneus (Anderson et al., 1994; Darby et al., 1996; Muri et al., 1996; Luna et al., 1998; Berman et al., 1999) and the posterior cingulate (Berman et al., 1999) have been reported to be active during saccades by previous functional imaging studies.

The area of the precuneus is likely to include by homology the primate areas PO/POd (Colby et al., 1988) and 7m (Cavada and Goldman-Rakic, 1989). PO/POd contains neurons which fire in relation to saccades and also show direction-selective responses to moving stimuli. Since the suddenly salient target of many reflexive saccades made in the real world is a moving one, the finding that the precuneus is relatively activated for reflexive saccades is in keeping with a role for this area in the programming of saccades in relation to sudden target appearance or indeed sudden apparent displacement, an illusion which our subjects did not report but which in theory could be created by any study which, like us, used a "step" (zero-gap) reflexive saccade paradigm.

In primate posterior cingulate cortex, neurons have been identified that fire just after a saccade in relation to its size and direction (Olson et al., 1996) and may serve to provide eye position signals which, when integrated with visual input, permit monitoring of either eye or self motion. In our study we have found the human posterior cingulate to be activated by the reflexive saccade relative to the voluntary saccade. The difference could arise from differences in certainty about eye position in each case. The new eye position produced by a voluntary saccade, where saccade direction is voluntarily selected, would be known with greater internal certainty than that produced by a reflexive saccade, with its parameters commanded externally. The posterior cingulate activation might then reflect a greater role in confirming new eye position after reflexive saccades than after voluntary saccades.

The finding that the angular gyrus of the inferior parietal lobule is relatively activated by reflexive compared to voluntary saccades is a most important one, as it argues a direct role for this region in reflexive orienting to a saccadic target. It has been known for some time that an inability to reflexively orient to stimuli at peripheral locations is found in patients with the clinical syndrome of left hemispatial neglect and can be partly overcome when those locations are precued (Posner et al., 1984; Bartolomeo et al., 2001; Bartolomeo and Chokron,
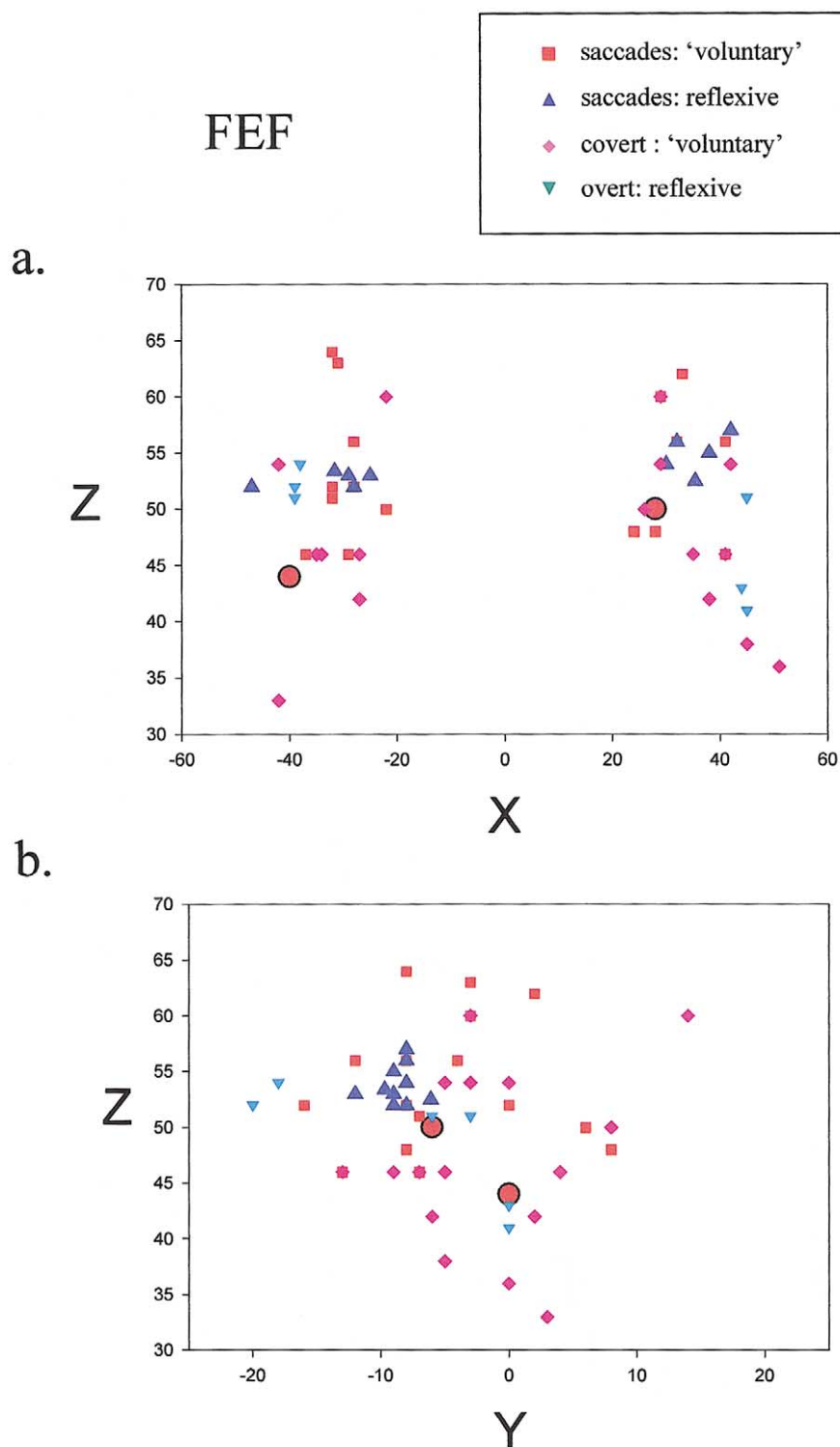
Fig. 5. Activations from other studies, listed in appendix Table A, plotted in the coronal (a) and saggital (b) planes. Methods of spatial normalization will have differed between studies, including their target reference space (e.g., Talairach, MNI, and others) and may be considered approximate but not identical in their anatomical frames. The large red circle represents the focus of FEF activation in this study resulting from the contrast of all outgoing voluntary saccades with reflexive saccades (Table 1).

2002). The lesion most commonly underlying this clinical syndrome involves the right inferior parietal lobule (Holmes, 1918, 1919; Bisiach et al., 1979; Hier et al., 1983; Vallar and Perani, 1987; Karnath, 1997; Vallar, 1993, 2001). Our findings therefore provide strong support for the theory that damage to the inferior parietal lobule is found to commonly underlie hemispatial neglect because it disrupts neural processing necessary for normal reflexive exploration of the visual world.

SPL/IPS
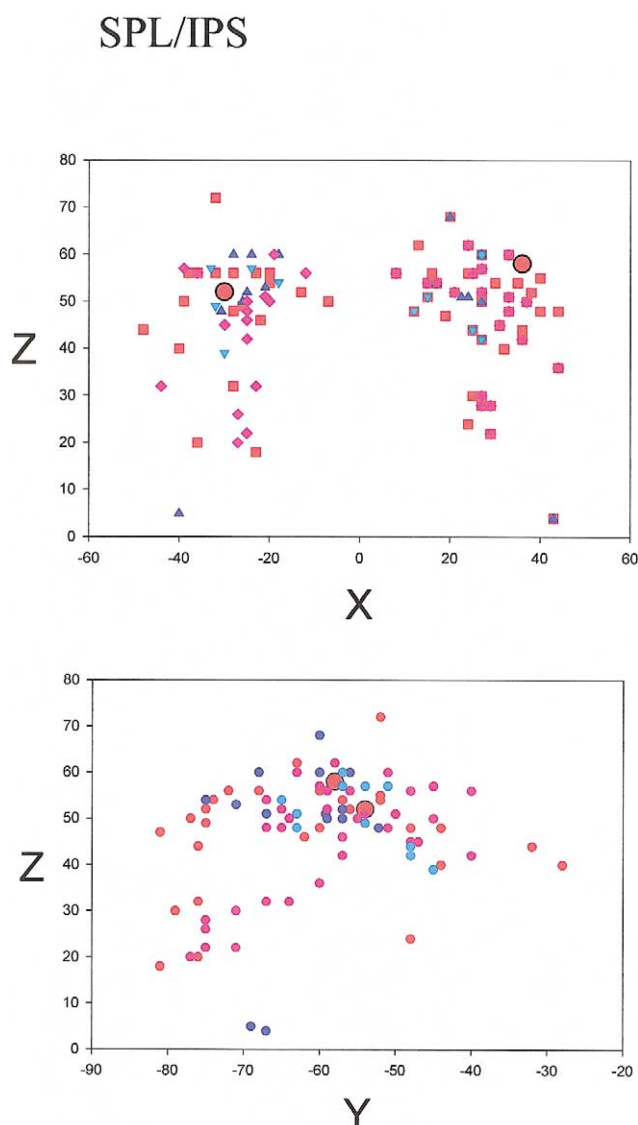

Fig. 6. SPL/IPS activations from other studies, listed in appendix Table B, plotted as in Fig. 5. Methods of spatial normalization will have differed between studies, including their target reference space (e.g., Talairach, MNI, and others) and may be considered approximate but not identical in their anatomical frames. The large red circle represents the focus of IPS activation in this study resulting from the contrast of all outgoing voluntary saccades with reflexive saccades (Table 1).

Hemispheric lateralization

For the principal contrasts, considering outgoing saccades in both directions equally, all areas identified, except the posterior cingulate which appeared centered to the right of midline, showed bilateral activation. But it was noticeable that those activations were stronger in the right hemisphere for both the IPS and the lateral occipital area (voluntary versus reflexive saccades), and the angular gyrus of the inferior parietal lobule (reflexive versus voluntary saccades). These findings ally with the strong body of evidence

that the right hemisphere usually plays a dominant role for spatial function.

The issue of cortical hemispheric specialization in relation to saccade direction in humans remains unresolved. Most of the epoch-based functional imaging studies of saccades have, by definition, only been able to consider activation across blocks, thereby collapsing direction as a putative factor of interest. Interestingly, two fMRI studies which compared covert attentional shifts and saccades, one epoch-based and consisting of sequential shifts into the left hemifield (Corbetta et al., 1998) and the other event-related, looking at shifts to the right and left (Perry and Zeki, 2000), managed to show significant contralaterality in the fronto-parietal network, but only for their covert attentional conditions, not the saccade conditions.

Though the response fields of most cells recorded in primate FEF (Bruce and Goldberg, 1985), SEF (e.g., Schall, 1991) and PPC (Yin and Mountcastle, 1977) are located in the contralateral hemifield, many show extension into or preference for the ipsilateral hemifield (for review, see Tehovnik et al., 2000). It is possible that attempts to distinguish regional preferences for saccade laterality in humans have been hampered by a number of factors, including a spatial resolution insufficient to resolve the topographical proximity of neurons with contralateral and/or ipsilateral response fields, and limits to temporally resolving overlapping event-related BOLD signal transients. Utilizing the event-related approach, this study demonstrated that the left inferior FEF was not only preferentially activated by voluntary saccades, but that its activity was greatest for rightward voluntary saccades compared to leftward. Otherwise, evidence of laterality preferences was lacking. It may be that combining the temporal resolution of EEG and the spatial resolution of fMRI will better address these issues in the future.

Conclusion

With functional imaging having already shown at least three cortical areas (FEF, SEF, IPS) to be involved in generating both reflexive and voluntary saccades we have used event-related fMRI to directly contrast regional activation between these two saccade types. Applying this approach, we find evidence of greater neural activation within two of these areas (FEF and IPS) by arrow-cued voluntary saccades compared to reflexive saccades, a finding which may have bearing on why voluntary saccades have been consistently found to take longer to initiate, even with saccade direction known in advance. We also find the angular gyrus of the inferior parietal lobule, damage to which has long been associated with hemispatial neglect in patients, to be relatively activated during reflexive saccades production, a finding we propose argues strongly for a role for this area in exogenous saccadic orienting.

Appendix

Table A
Previous fMRI studies of saccades or attention

	S/A	V/R	Loc	L hemisphere				R hemisphere				Note
				x	*y*	*z*	*Z'*	*x*	*y*	*z*	*Z'*	
Corbetta et al. (1998)	S	V	SFS	−29	−13	46	5.03	29	−3	60	5.34	1
			s	−37	−7	46	6.75	41	−7	46	7.09	
Perry and Zeki (2000)	S	V	s	−22	6	50	[3.1]³	28	8	48	[4.3]³	
Heide et al. (2001)	S	V	s	−32	−8	52	6.26	32	−4	56	7.14	2
Grozbas et al. (2001)	S	V	s	−28	−12	56	12	24	−8	48	9.6	2
				−32	−8	64	10.53					
				−32	0	52	10.13					
Grozbas et al. (2001)	S	V	s	−28	−16	52	8.82	24	−8	48	5.97	3
Luna et al. (1998)	S	R	s	−25	−12	53	10.93	38	−9	55	6.88	
Berman et al. (1999)	S	R	s	−32	−9.7	53.4	13.4	35.4	−6	53	13.4	
Heide et al. (2001)	S	R	s	−28	−8	52	4.36	32	−8	56	6.69	
Beauchamp et al. (2001)	S + A	R	s	−29	−9	53	[4320]¹	30	−8	54	[3015]¹	4
Corbetta et al. (1998)	S	V	i					35	−1	30	5.82	1
Perry and Zeki (2000)	S	V	i					50	8	32	[3.35]	
Heide et al. (2001)	S	V	i	−48	−4	40	7.39	44	−8	48	7.11	2
Grozbas et al. (2001)	S	V	i	−48	−12	52	7	36	−4	44	6.45	2
				−52	−8	48	7					
Grozbas et al. (2001)	S	V	i	−48	−12	52	4.79					3
Luna et al. (1998)	S	R	i	−52	0	37	7.86	48	5	44	8.29	
Berman et al. (1999)	S	R	i	−50	−3.2	41.4	10.1	50.1	−1	37	10.8	
Heide et al. (2001)	S	R	i	−44	−8	44	5.59	48	−8	44	6.44	
Beauchamp et al. (2001)	S + A	R	i	−41	−2	35	[1259]¹	40	−2	37	[889]¹	4
Merriam et al. (2001)	S	V		−32	−7	51		41	−8	56		
				−31	−3	63		33	2		62	5
Merriam et al. (2001)	S	R		−47	−9	52		42	−8	57		
Corbetta et al. (1998)	A	V	SFS	−27	−13	46	5.67	29	−3	60	6.43	1
	A − S	V	SFS					29	−5	54	7.11	1
	A	V	s	−35	−9	46	6.59	41	−7	46	9.4	1
Perry and Zeki (2000)	A	V	s	−22	14	60	6.4	26	8	50	6.8	
Corbetta et al. (1998)	A − S	V	s					35	−5	46	5.81	1
	A	V	i					45	−5	38	4.89	1
Perry and Zeki (2000)	A	V	i	−34	4	46	5.6	38	2	42	6.9	
Rosen et al. (1999)	A	R		−38	−18	54	[3.1]²	45	0	41	[2.1]²	
				−39	−20	52	[3.3]²	44	0	43	[2.1]²	
Kim et al. (1999)	A	R		−39	−6	51	7.07	45	−3	51	7.69	
		V		−42	0	54	7.84	42	−3	54	7.84	
		R + V		−42	3	33	7.44	42	−3	54	10.86	4
Gitelman et al. (1999)	A	V		−27	−6	42	6.26	51	0	36	5.65	

Note. Comparison of Talairach coordinates (*x,y,z,* L/R hemisphere) of group activations in the region of FEF. Abbreviations: S/A, saccades/attention; V/R, voluntary/reflexive; i, inferior FEF; s, superior FEF; SFS, superior frontal sulcus; *Z, Z* score of activation (except, [ ]¹, volume; [ ]², maximal *t* value; [ ]³, nonsignificant determined *P* level). Notes: 1, left hemifield only; 2, novel memory-guided saccade sequences; 3, familiar memory-guided saccades sequences; 4, conjunction analysis; 5, including incompatible cue response trials.

Table B
Previous fMRI studies of saccades or attention

	S/A	V/R	Description	L hemisphere				R hemisphere				Note
				x	*y*	*z*	*Z'*	*x*	*y*	*z*	*Z'*	
Corbetta et al. (1998)	S	V	IPSant	−23	−59	56	9.8	35	−57	54	7.47	1
			IPSpost	−7	−77	50	5.78	13	−63	62	5.78	
			IPS/TOS	−23	−81	18	7.33	25	−79	30	5.45	
	S − A	V	IPSpost	−13	−75	52	5.13					1
Perry and Zeki (2000)	S	V	SPLant	−36	−48	56	5.7	30	−52	54	5.8	
			SPLpost	−22	−62	46	5.8					
			IPS	−38	−48	56	5.7	40	−44	48	5.4	

Table B (*continued*)

	S/A	V/R	Description	L hemisphere				R hemisphere				Note
				x	y	z	Z'	x	y	z	Z'	
Heide et al. (2001)	S	V	midIPS	−40	−44	40	3.88	44	−48	48	4.78	2
			IPS/SPL	−32	−56	56	6.99	38	−56	52	4.03	
			SPL					16	−68	56	6.53	
			SPL					20	−60	68	5.85	
			SPL/MedP	−20	−72	56	6.58					
			postIPS					36	−76	44	5.28	
Merriam et al. (2001)	S	V	"PEF"	−20	−74	54		17	−75	54		
			"PEF"	−26	−75	49		19	−81	47		5
			rostrolatPPC	−39	−57	50		40	−52	55		
Grozbas et al. (2001)	S	V	dorsSPL	−32	−52	72	5.4					2
			postSPL/IPS	−28	−76	32	4.99					
			ant IPS	−28	−60	56	13.53	24	−56	56	11.21	
			antIPS/PoCS	−48	−32	44	6.95	32	−28	40	5.67	
			TOS/IPS	−36	−76	20	5.75					
Grozbas et al. (2001)	S	V	antIPS/SPL	−28	−60	48	6.42					3
			antIPS					24	−48	24	5.58	
Luna et al. (1998)	S	R	SPL	−25	−57	52	8.73	24	−67	51	9.17	
Berman et al. (1999)	S	R	IPS	−31	−52	48	13.7	22.5	−59	51	13.4	
Heide et al. (2001)	S	R	SPL	−28	−56	60	5.44	20	−60	68	5.82	
				−24	−68	60	4.85					
Merriam et al. (2001)	S	R	"PEF"	−21	−71	53		17	−75	54		
Vandenberghe et al. (2001a)	S	R	SPL	−18	−60	60	6.82	27	−57	60	4.68	
Nobre et al. (2000)	S+A	R	"PPC"									4
Beauchamp et al. (2001)	S+A	R	IPS	−26	−57	50	[9253][1]	27	−59	50	[7490][1]	4
			IPS/LOS	−40	−69	5	[3645][1]	43	−67	4	[3525][1]	
Corbetta et al. (1998)	A	V	antIPS	−25	−55	50	8.85	25	−59	56	11.2	1
			postIPS	−19	−63	60	7.12	17	−65	54	9.38	
			ips/TOS	−25	−75	22	4.37	27	−75	28	7.11	
Perry and Zeki (2000)	A	V	antSPL	−36	−48	56	5.3	24	−58	62	6.9	
			postSPL	−20	−64	50	7.1					
			IPS	−36	−48	56	5.3	36	−40	42	5.7	
Rosen et al. (1999)	A	V	"PPC"					31	−47	45	[1.9][3]	
Kim et al. (1999)	A	V	"PPC"	−39	−45	57	7.14	33	−51	60	6.78	
Gitelman et al. (1999)	A	V	IPS/SPL	−21	−50	51	6.59	27	−60	57	7.66	
Corbetta et al. (2000)	A	V	ventIPS	−23	−67	32	7.42	29	−71	22	6.01	6
			ventIPS	−27	−75	26	7.23					
			antIPS	−25	−57	46	7.55	27	−59	52	6.75	
			postIPS	−25	−67	48	7.58	21	−65	52	6.62	
Corbetta et al. (2000)	A	V	ventIPS	−27	−77	20	7.16	27	−71	30	6.63	7
			antIPS	−25	−57	42	7.27	33	−51	48	7.84	
			postIPS	−25	−65	48	6.94					
Hopfinger et al. (2000)	A	V	SPL	−12	−56	56	4.41	8	−40	56	4.27	6
			IPS	−44	−64	32	7.01	44	−60	36	6.63	
Corbetta et al. (1998)	A − S	V	antIPS					37	−45	50	6.77	1
			postIPS					15	−67	54	7.21	
			IPS/TOS					29	−75	28	4.91	
Kim et al. (1999)	A	R+V	"PPC"	−30	−48	45	7.07	33	−54	51	8.44	4
Vandenberghe et al. (2001a)	A	R	SPL	−33	−51	57	5.12	12	−63	48	5.49	
								27	−57	60	4.68	
Rosen et al. (1999)	A	R	"PPC"	−32	−54	49	[1.6][2]	25	−48	44	[1.7][2]	
				−18	−65	54						
Kim et al. (1999)	A	R	"PPC"	−30	−45	39	5.19	27	−48	42	5.56	
Vandenberghe et al. (2001a)	A+ S	R	SPL	−24	−57	57	7.35	15	−63	51	7.21	
				−33	−54	57	6.61	27	−57	60	6.91	

Note. Comparison of Talairach coordinates (*x,y,z*, L/R hemisphere) of group activations in the region of SPL including IPS. Studies have used a number of differing descriptions of which parietal area activations were found. Parietal activations attributed to the precuneus/medial parietal cortex have not been included in this list. Abbreviations: As in Table A; ant/post/vent/dors/mid/med, anterior/posterior/ventral/dorsal/middle/medial; LOS, lateral occipital sulcus; TOS, temporo-occipital sulcus; "PEF," parietal eye field. Notes: 6, at cue presentation; 7, at target presentation.

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