Dorsal Cortical Regions Subserving Visually Guided Saccades in Humans: An fMRI Study

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Neurophysiological studies in non-human primates have identified saccade-related neuronal activity in cortical regions including frontal (FEF), supplementary (SEF) and parietal eye fields. Lesion and neuroimaging studies suggest a generally homologous mapping of the oculomotor system in humans; however, a detailed mapping of the precise anatomical location of these functional regions has not yet been achieved. We investigated dorsal frontal and parietal cortex during a saccade task vs. central fixation in 10 adult subjects using functional magnetic resonance imaging (fMRI). The FEF were restricted to the precentral sulcus, and did not extend anteriorly into Brodmann area 8, which has traditionally been viewed as their location in humans. The SEF were located in cortex along the interhemispheric fissure and extended minimally onto the dorsal cortical surface. Parietal activation was seen in precuneus and along the intraparietal sulcus, extending into both superior and inferior parietal lobules. These findings localize areas in frontal and parietal cortex involved in saccade generation in humans, and indicate significant differences from the macaque monkey in both frontal and parietal cortex. These differences may have functional implications for the roles these areas play in visuomotor processes.

Introduction

Saccades are rapid eye movements made in order to foveate visual stimuli of interest. They are the primary mechanism by which primates explore their visual environment. Single-cell recording studies of non-human primates have demonstrated that several subcortical regions are involved in saccade generation, including cerebellum (Keller, 1989), brainstem (Hepp *et al.*, 1989), striatum (Hikosaka *et al.*, 1989) and thalamus (Schlag-Rey and Schlag, 1984). Studies of dorsal cortical regions in monkeys have provided evidence that the frontal eye fields (FEF) (Bruce *et al.*, 1985; Goldberg and Bruce, 1990), supplementary eye fields (SEF) (Schall, 1991) and posterior parietal cortex (PPC) (Andersen, 1987; Colby *et al.*, 1993) also subserve saccade generation. Clinical studies of lobectomy and stroke effects on FEF, SEF and PPC (Guitton *et al.*, 1985; Paus *et al.*, 1991; Henik *et al.*, 1994; Pierrot-Deseilligny *et al.*, 1995), and positron emission tomography (PET) studies of healthy individuals (Fox *et al.*, 1985; Paus *et al.*, 1993; Anderson *et al.*, 1994; Petit *et al.*, 1996; Sweeney *et al.*, 1996b), provide evidence that frontal and parietal cortices contribute to saccade generation in humans.

Despite the general homology of saccade control systems in human and non-human primates, there are data suggesting possible differences in their cortical organization. Paus (1996) reviewed PET studies of brain activation during saccade tasks, and concluded that existing data mapped the human FEF to the precentral gyrus and adjacent superior frontal sulcus. He proposed that the saccade-related region of human FEF may be located in Brodmann area 6 rather than area 8, which has traditionally been considered to be their location in humans and is known to be their location in the macaque monkey (Bruce and Goldberg, 1985; Bruce *et al.*, 1985). However, the low spatial resolution of PET imaging, together with the analysis of activation maps averaged across subjects rather than from individual subjects, limits precision of the localization of saccade-related areas of the human brain in PET studies.

The increased spatial resolution and signal-to-noise ratio of functional magnetic resonance imaging (fMRI) permits a more exact mapping of task-related activation in individual subjects (Thulborn *et al.*, 1997). To our knowledge, three published studies have used fMRI to investigate brain regions related to visually guided saccades (Darby *et al.*, 1996; Muri *et al.*, 1996; Petit *et al.*, 1997). Their findings indicate saccade-related activation in Brodmann areas 4 and 6 and parietal areas. However, limitations in these studies included low spatial resolution of imaging methodologies, and image acquisition or analysis strategies that restricted characterization of all cortical regions subserving oculomotor processes. More precise mapping of the regions subserving the oculomotor system is needed to delineate the degree of homology between human and non-human primates. This mapping is also needed to guide future studies using high-resolution neuroimaging to identify the unique sensorimotor functions of oculomotor regions and to direct histologic studies investigating their cytoarchitecture in humans.

In the present study, we used echo-planar fMRI to localize saccade-related activity in dorsal frontal and parietal cortex using a saccade vs. visual fixation comparison. Regions of task-related activation were identified at the level of individual subjects using anatomic landmarks. In addition, in order to summarize results across subjects and to present data in a format directly comparable to previous PET studies, we also averaged image sets across subjects to provide a group activation map.

Materials and Methods

Subjects

Subjects were 10 healthy 19–30 year old volunteers (mean age 25.1 years, SD = 3.8 years). Five subjects were female and all but one were right-handed. Informed consent was obtained from each subject before testing. Experimental procedures complied with the Code of Ethics of the World Medical Association (1964 Declaration of Helsinki) and the standards of the University of Pittsburgh Internal Review Board. A laboratory assessment of visual fixation and saccadic eye movements was conducted to train subjects in oculomotor tasks and to verify the absence of oculomotor abnormalities before imaging studies. Immediately prior to the imaging session, subjects spent ~20 min in a simulation scanner that reproduced the sounds and confinement of an MR scanner to acclimate them to the MR environment (Rosenberg *et al.*, 1997).

Behavioral Tasks

Subjects performed 6.5 continuous cycles of a paradigm that consisted of 30 s of visually guided saccades alternating with 30 s of central fixation. The paradigm began and ended with the fixation task. The saccade target was a solid white circle and the fixation target was a white cross-hair. Both targets subtended 0.75° of visual angle on a black background.

Table 1
Number of subjects showing different extent of activations in regions of interest in each hemisphere

Number of activated voxels	FEF				SEF		SPL		Precuneus		IPL	
	Superior PCS		Inferior PCS									
	L	R	L	R	L	R	L	R	L	R	L	R
≥4 voxels	7	8	3	5	5	4	9	8	4	5	5	7
1–4 voxels	3	2	3	2	4	4	1	2	1	3	4	3
0 voxels	0	0	4	3	1	2	0	0	5	2	1	0

FEF, frontal eye fields; PCS, precentral sulcus; SEF, supplementary eye fields; SPL, superior parietal lobule; IPL, inferior parietal lobule; L, left hemisphere; R, right hemisphere. Voxels were considered to be activated when comparisons of task conditions yielded a *t*-value >4.0.

Targets for saccades were presented at center fixation and 3°, 6° and 9° of visual angle to the left and right of center along the horizontal plane. The target moved with a 0.5 probability to the left or right every 0.75 s in a 3° step from its previous position, except at the 9° targets when the next step was always back toward the center of the screen. In this manner, the location of upcoming targets for saccades had a minimal level of spatial predictability. Visual stimuli were presented using in-house stimulus presentation software and a Macintosh computer (Thulborn *et al.*, 1996). Stimuli were presented on a rear projection screen placed above the subject's chest that could be viewed in an angled mirror fixed to the head coil. The screen was at a distance of 55–60 cm from subjects' eyes. Head motion was restricted by firm cushions packed around the head. Eye movement activity was not monitored in the scanner, but the previous training and simplicity of this task make it reasonable to assume that the task was performed as instructed by these cooperative volunteers.

Scanning Procedures

fMRI studies were performed on a 1.5 T Signa whole-body MR scanner (General Electric Medical Systems, Milwaukee, WI) with echo-planar imaging (EPI) capability (Advanced NMR Systems, Inc., Wilmington, MA). Gradient-echo echo-planar imaging, sensitive to blood oxygen level dependent (BOLD) effects (Kwong *et al.*, 1992), was performed using a commercial head RF coil. Acquisition parameters were: *TE* = 50 ms; *TR* = 1.5 s; single shot; full *k*-space; 128 × 64 acquisition matrix with a field of view (FOV) = 40 × 20 cm, generating an in-plane resolution of 3.125 mm^2. Since we were interested in investigating the areas in dorsal frontal and parietal cortex controlling saccade generation, seven 5 mm thick axial slices with a 1 mm gap were prescribed, spanning from the vertex of the brain to near the superior aspect of the corpus callosum (see sagittal slice in Fig. 1). For anatomic imaging, we used a T_2-weighted spin-echo echo-planar sequence with six of our subjects, and a three-dimensional volume spoiled gradient-echo pulse sequence with the remaining four subjects. Both image sets were acquired in the axial plane and provided adequate resolution for aligning the images into Talairach space. For the three-dimensional volume spoiled gradient-echo images, 1.5 mm thick slices were obtained. For the *T*2-weighted spin-echo images, two image sets with 3 mm thick slices were obtained with an offset of 1.5 mm between the slice prescriptions. The *T*2 image sets were interleaved, resulting in an apparent slice thickness of 1.5 mm.

Data Analyses

FIASCO software (Functional Imaging Analysis Software — Computational Olio) (Eddy *et al.*, 1996) was used to estimate in-plane rigid head motion (horizontal and vertical translation). Nine of the subjects had a maximum in-plane head movement of <0.15 mm during the study. The other subject had a maximum head movement of 1.2 mm (approximately one-third of in-plane voxel dimension). Motion correction was not applied to the data. Functional data were analyzed using IVANA (Interactive Visualization and Analysis of Neural Activation) software. IVANA is an in-house package comprised of a collection of AVS modules (Application Visualization Systems, Advanced Visualization Systems Inc., Waltham, MA) developed to generate voxel-wise *t*-maps and to interactively visualize image data (Thulborn *et al.*, 1996). The functional activation maps generated by IVANA were overlaid onto coplanar anatomic images using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996), and then transformed into Talairach space (Talairach and Tournoux, 1988) to establish a common coordinate system for the images in order to allow for averaging of results across subjects. The following sequence of steps were used to transfer anatomic images into Talairach space using AFNI (Cox, 1996). First, the anterior and posterior commisure and two mid-hemispheric points were marked. AFNI then rotated the brain such that the AC–PC line was parallel to the axial slice plane and the hemispheric fissure was parallel to the sagittal plane. Then the most extreme dorsal, ventral, left, right, anterior and posterior extents of the brain were marked, partitioning the brain into 12 subvolumes, each of which was then manipulated by AFNI in order to transform the anatomy to conform to the Talairach atlas. Finally, IVANA was also used to examine correlations between the time course of activity in individual voxels (from regions of interest and from the superior sagittal sinus) with that of the remaining voxels in images in order to rule out the presence of vascular artifacts.

Based on the existing human neuroimaging literature and a review of activations in individual subjects in the present study, we defined the anatomical boundaries of regions of interest in order to characterize the extent of task-related activation in predefined regions (the number of voxels showing significant activation during saccades compared to fixation). The region within which we identified FEF activation included the precentral sulcus and immediately adjacent gyral surfaces showing contiguous activation. Since the precentral sulcus in humans is as a rule divided into discrete *superior/medial* and *inferior/lateral* elements divided by a break in the sulcus (Ono *et al.*, 1990), each element was analyzed independently. The region within which we identified SEF lacked clear sulcal landmarks (Paus *et al.*, 1996; Wise *et al.*, 1996); hence, we used a conservative measurement strategy and identified a relatively large region to ensure that SEF activation would be included for all subjects. The SEF region of interest was defined ventrally by the cingulate sulcus, posteriorly by the posterior-most aspect of the precentral sulcus, and anteriorly by the anterior-most aspect of the head of the caudate nucleus. Three regions of interest were defined in parietal cortex. Activation in the superior parietal lobule was defined as including the *medial* bank of the intraparietal sulcus and contiguous activation that extended onto the adjacent gyral surface. Activation in the inferior parietal lobule was defined as including the *lateral* bank of the intraparietal sulcus and the adjacent gyral surface. The base of the intraparietal sulcus separated these regions. Precuneus activation was defined to include mesial posterior parietal cortex posterior to the marginal ramus of the cingulate sulcus and anterior to the parietooccipital sulcus. Typically, activation in the precuneus stopped near the lip of the interhemispheric fissure, but in four cases, in at least one hemisphere, precuneus activation was contiguous with that of the superior parietal lobule. In those cases, only voxels on the medial wall and lip of the interhemispheric fissure were considered to be within the precuneus.

The number of voxels reaching an activation threshold (*t*-value ≥4.0) during saccades versus central fixation in each region was tabulated. The threshold value 4.0 for the *t*-statistic was chosen because it yielded a reasonable empirical error rate over many studies that our group as well as other investigators have performed with the particular scanner, single-shot echo-planar pulse sequence, and stimulus presentation method that we used. This threshold was chosen *a priori* and was used consistently in all analyses of both group and individual data sets. We also

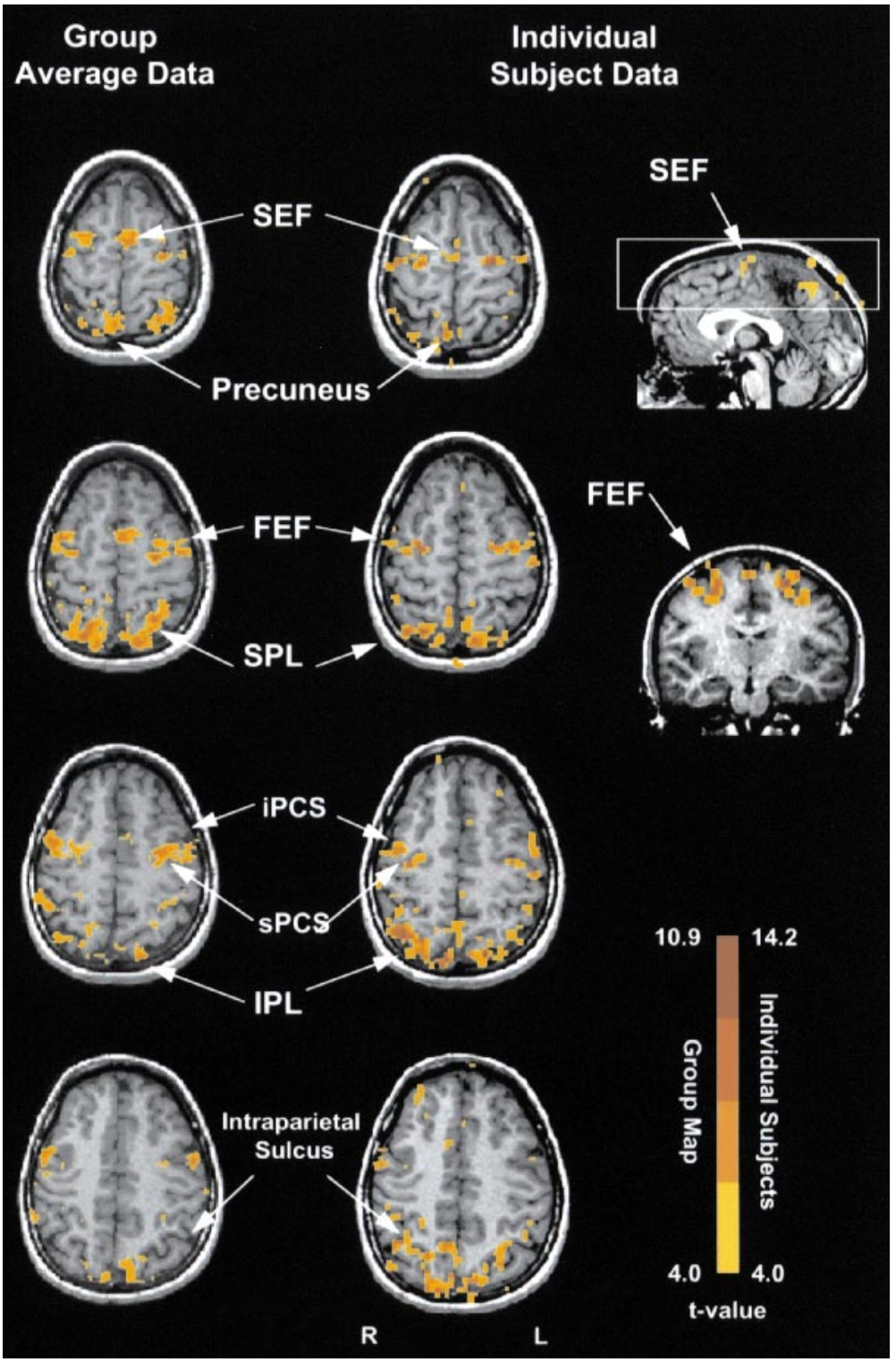

Figure 1. Activation during a visually guided saccade task relative to a visual fixation task superimposed on structural anatomic images. The group average map is overlaid on anatomic images from the same 'representative' subject whose activation map is depicted in this figure. Images are presented in 6 mm intervals, similar to the fMRI image acquisition protocol (5 mm slice thickness with 1 mm interslice gap). The Talairach planes for the axial images are $z = +57$, $+51$, $+45$ and $+39$. The plane of the sagittal image is $y = -15$, and of the coronal image is $x = 2$. The brain region included in our functional slice prescription is represented by the white box surrounding dorsal cortex in the sagittal image. FEF, frontal eye fields; sPCS, superior element of the precentral sulcus; iPCS, inferior element of the precentral sulcus; SEF, supplementary eye fields; IPL, inferior parietal lobule; SPL, superior parietal lobule.

obtained Talairach coordinates for the location of the voxel showing peak activation in regions of interest in each hemisphere for every subject. Planned comparisons using two-tailed paired *t*-tests were performed to investigate differences in the number of activated voxels between hemispheres and to compare the superior and inferior elements of the precentral sulcus. To further characterize activation effects in individual

subjects, we counted the number of subjects that had either >4 activated voxels, 1–4 activated voxels, or no activated voxels in each region of interest. We averaged activations across subjects after transforming image sets into Talairach coordinate space (Talairach and Tournoux, 1988) to generate a group activation map that was overlaid onto the anatomy of a representative subject. In order to investigate the effects of averaging anatomy across subjects, we also examined the group activation map superimposed over the average subject anatomy created by pooling structural image sets across all 10 subjects.

Results

Activation Effects in Individual Subjects

Data at the individual subject level indicated that, except for one subject who did not show SEF activation and another who did not show precuneus activation, all subjects demonstrated significant activations ($t \geq 4.0$) in FEF, SEF and all defined areas of PPC during saccade generation (see Table 1). The activation map from a representative individual subject is depicted in Figure 1. As depicted in Figure 2, the highest number of activated voxels were located in the superior aspect of the FEF and in the superior parietal lobule.

All subjects showed activation of the FEF in the *superior* element of the precentral sulcus. Inspection of each subject's data indicated that activity in the FEF was always located within the depths and on the lip of the precentral sulcus. This area of activation did not extend anteriorly from the lip of the precentral sulcus in any subject. The peak activation in the precentral sulcus was typically located at the level of the posterior-most aspect of the superior frontal sulcus.

Activation in the *inferior* element of the precentral sulcus was present in at least one hemisphere in eight subjects (including the subject depicted in Fig. 1). There were significantly fewer activated voxels in the inferior than superior element of the precentral sulcus across subjects (left: $t_9 = 3.37$, $P < 0.01$; right: $t_9 = 2.88$, $P < 0.05$), and the voxels with peak activation had significantly lower *t*-values in the *inferior* than the *superior* precentral sulcus in both hemispheres (left: $t_9 = 3.11$, $P < 0.05$; right: $t_9 = 11.07$, $P < 0.001$).

Nine of the 10 subjects showed activation of the SEF that was localized to cortex along the interhemispheric fissure. In cases where the paracentral sulcal branch of the cingulate sulcus was clearly evident, SEF activation typically was found adjacent to it. SEF activation was detected superior to the cingulate sulcus, and did not extend to the cortical surface except for two cases where activation included a minimal amount of the cortical surface. There was very little task-associated activation in the prefrontal region included in our field of view. When such task-related signal change was present, it was in the form of isolated voxels well anterior to the activity seen in the precentral sulcus.

All subjects showed activation in posterior parietal cortex. Bilateral activation of the superior parietal lobule was present in every subject in the medial bank of the intraparietal sulcus. Similarly, all subjects showed activation of the inferior parietal lobule (bilateral in nine subjects) in the lateral bank of the intraparietal sulcus. Nine subjects showed significant activation in precuneus, in at least one hemisphere, that was localized to the mesial aspect of posterior parietal cortex.

Intersubject variability in the Talairach location and *t*-value of the voxels with peak activation in each region of interest are presented in Table 2. Despite variability in the Talairach location of the voxel with peak activation across subjects, the voxel showing the greatest activation in regions of interest in each subject was always located either on the midline (precuneus and

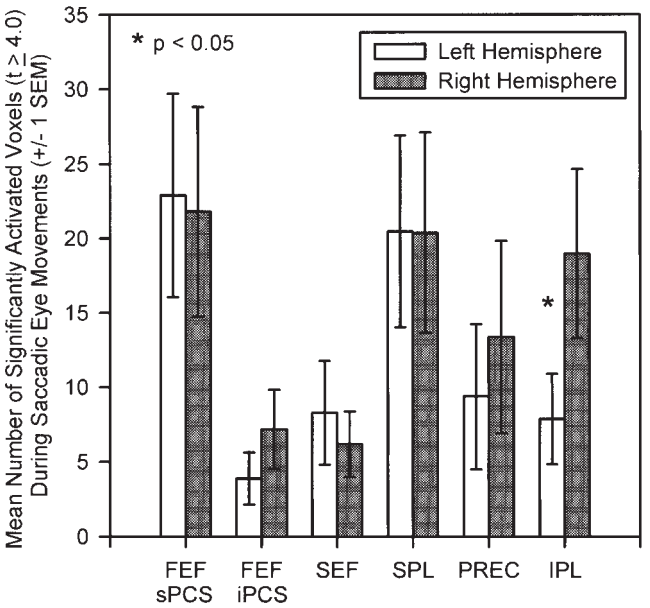

Figure 2. Mean number of voxels (±1 SEM) with significant activation ($t \geq 4.0$) across subjects in each region of interest. FEF, frontal eye fields; sPCS, superior element of the precentral sulcus; iPCS, inferior element of the precentral sulcus; SEF, supplementary eye fields; SPL, superior parietal lobule; PREC, precuneus; IPL, inferior parietal lobule.

SEF) or within the sulcus of interest (precentral or intraparietal sulcus). There was minimal variability in the *t*-value of the voxel with peak activation across subjects and regions of interest. However, the number of voxels with significant activation in regions of interest varied widely across subjects (see Table 1 and Fig. 2).

Significant laterality effects in the number of voxels activated in the two hemispheres were only present the inferior parietal lobule ($t_9 = 2.90$, $P < 0.05$), where activation was greater in the right than left hemisphere. There was no consistent activation in any brain region within our field of view during fixation that was greater than that seen during saccades.

Group Average Data

In the group average map, activations in regions of interest extended further from the sulci or midline onto adjacent gyri than was the case for activations in individual subjects, which were largely restricted to sulci of interest or the inter-hemispheric fissure (see Fig. 1). This effect was most evident for the presumed FEF, where activation in precentral sulcus in the group map was not restricted to the sulcus, as it was in individual subjects, but proceeded anteriorly to include posterior superior and middle frontal gyri. Inspection of differences in individual subject anatomy, and of structural anatomy averaged across all 10 subjects, indicated that there was considerable variability in the anterior/posterior location of the precentral sulcus across subjects. This anatomic variability appeared to account for much of the anterior–posterior spread of activation in FEF seen in the group activation map.

The Talairach location of the voxel with peak activation in the group average map for the different ROIs (see Table 3), although in close proximity, differed somewhat from those obtained by averaging the Talairach coordinates of each individual subject's voxel with peak activation. This is the result of calculating peak activation in the group map based on all data from all subjects

Table 2
Mean (±SD) location in Talairach space across 10 subjects in the voxel showing peak activation in regions of interest in each hemisphere

Region of interest	Left hemisphere				Right hemisphere			
	x	*y*	*z*	*t*-value	*x*	*y*	*z*	*t*-value
FEF: superior PCS	–30.2 (7.4)	–4.1 (7.2)	49.1 (6.5)	7.8 (3.0)	34.2 (9.1)	–3.4 (5.0)	46.9 (4.8)	7.4 (1.9)
FEF: inferior PCS	–42.6 (8.2)	7.3 (5.9)	40.6 (8.7)	5.1 (1.4)	43.7 (9.3)	7.5 (6.6)	38.3 (6.4)	5.0 (1.8)
SEF	–2.3 (3.8)	–1.1 (6.6)	56.3 (5.4)	5.8 (2.2)	4.6 (2.0)	0.6 (10.8)	55.4 (8.8)	5.1 (1.7)
SPL	–19.3 (6.9)	–59.7 (7.5)	56.2 (4.9)	6.8 (1.7)	21.0 (6.3)	–61.0 (7.3)	54.0 (3.9)	7.3 (3.4)
Precuneus	–4.7 (4.3)	–61.0 (11.9)	47.8 (4.9)	5.2 (1.5)	5.4 (3.9)	–58.7 (15.4)	52.4 (7.7)	5.3 (2.3)
IPL	–39.8 (8.6)	–45.5 (7.7)	43.3 (6.6)	5.8 (1.5)	42.4 (14.2)	–44.6 (9.8)	44.7 (9.5)	7.8 (3.3)

FEF, frontal eye fields; PCS, precentral sulcus; SEF, supplementary eye fields; SPL, superior parietal lobule; IPL, inferior parietal lobule. The *x*, *y* and *z* represent the location of voxels in Talairach coordinates in millimeters. The *t*-values reflect the degree of increase in MR signal intensity for that voxel during the saccade condition relative to visual fixation.

Table 3
Location in Talairach space of the voxel showing peak activation in the regions of interest in the group average data

Region of interest	Left hemisphere				Right hemisphere			
	x	*y*	*z*	*t*-value	*x*	*y*	*z*	*t*-value
FEF: superior PCS	–25	–12	53	10.93	38	–9	55	6.88
FEF: inferior PCS	–52	0	37	7.86	48	5	44	8.29
SEF	0	0	54	8.84	0	0	48	5.02
SPL	–25	–57	52	8.73	24	–67	51	9.17
Precuneus	–8	–83	38	5.67	11	–56	60	8.29
IPL	–31	–41	40	5.78	50	–42	46	6.44

FEF, frontal eye fields; PCS, precentral sulcus; SEF, supplementary eye fields, SPL, superior parietal lobule; IPL, inferior parietal lobule. The *x*, *y* and *z* represent the location of voxels in Talairach coordinates in millimeters. The *t*-values reflect the degree of increase in MR signal intensity for that voxel during the saccade condition relative to visual fixation.

versus averaging the location of each individual subject's voxel with peak activation.

Discussion

Our results localize cortical oculomotor regions with higher spatial resolution and comprehensiveness than was achieved in previous human lesion (Guitton *et al.*, 1985; Paus *et al.*, 1991; Henik *et al.*, 1994; Pierrot-Deseilligny *et al.*, 1995), PET (Fox *et al.*, 1985; Paus *et al.*, 1993; Anderson *et al.*, 1994; Petit *et al.*, 1996; Sweeney *et al.*, 1996b) and fMRI (Darby *et al.*, 1996; Muri *et al.*, 1996; Petit *et al.*, 1997) studies. They indicate that saccades in humans are subserved by a dorsal cortical network including the FEF localized to the precentral sulcus, the SEF mapped to mesial frontal cortex, and specific regions of posterior parietal cortex. Using gradient-echo echo-planar fMRI, we characterized the functional anatomy of each of these regions at the level of individual subjects. The results indicated broad similarities between the cortical nodes subserving oculomotor control in human and non-human primates, while delineating significant cross-species differences in functional anatomy.

Frontal Eye Fields

Our observations indicate that the FEF are located within the precentral sulcus and continue minimally onto the anterior and posterior gyral surfaces. This provides considerably improved anatomic detail to localization of human FEF in comparison to those provided by previous xenon inhalation (Melamed and Larsen, 1979), PET (Paus *et al.*, 1993; Petit *et al.*, 1993, 1996; Paus, 1996; Sweeney *et al.*, 1996b) and fMRI studies with human subjects (Darby *et al.*, 1996; Muri *et al.*, 1996; Petit *et al.*, 1997). We also extend prior work by documenting the consistency of this localization at the level of single subjects. The lower resolution, spatial filtering and across-subject averaging of previous PET studies made it difficult to determine whether saccade-related activation in FEF occurred anterior or posterior to the precentral sulcus. As in previous PET studies, when we averaged our fMRI data across subjects, we observed what appeared to be a considerable spread of activation beyond the precentral sulcus. The high signal-to-noise ratio and spatial resolution provided by fMRI allowed us to demonstrate in individual subjects that task-related activation was restricted to the precentral sulcus. The apparent activation anterior to the precentral sulcus, evident in group average maps including our own, appears to be a result of transforming brains with divergent precentral sulcus location into a common coordinate space with a resultant spatial blurring of FEF activation. Inspection of the region anterior to the precentral sulcus in individual subjects with less conservative thresholding offered no indication of subthreshold activation. This result further confirms the view that the FEF do not extend anteriorly from the precentral sulcus.

Based on evidence from cortical stimulation studies (Foerster, 1931; Penfield and Boldrey, 1937; Godoy *et al.*, 1990; Sakamoto *et al.*, 1991) and from a presumed homology with the well-characterized FEF location in macaque monkey (Bruce and Goldberg, 1985; Bruce *et al.*, 1985), the human FEF has traditionally been presumed to be located in Brodmann area 8 (Kandel *et al.*, 1991). However, classic human cytoarchitectural maps position area 8 well anterior to our placement of the FEF, and classify the region of the precentral sulcus where we localized FEF activation as agranular area 6 (Braak, 1980).

Although evidence from the cortical stimulation studies has been traditionally interpreted to localize the human FEF to area 8, these studies in fact found evidence for eye movement related activity in an area comprising both prefrontal and premotor cortical regions (Foerster, 1931; Penfield and Boldrey, 1937; Godoy *et al.*, 1990; Sakamoto *et al.*, 1991). Our fMRI studies point to a more restricted localization for FEF in the human brain. The differences in the extent of human FEF delineated by cortical stimulation and fMRI may be related to the inherent differences in imaging and stimulation methodologies. For example, cortical stimulation studies may have elicited saccades from more anterior and posterior areas by virtue of stimulating white matter pathways connecting FEF to prefrontal and premotor cortex. Alternatively, cortical stimulation methods may be more sensitive for detecting regions with saccade-related neurons that are sparsely distributed in prefrontal cortex to a degree that functional imaging may lack the sensitivity to identify.

There are several possible implications to our placement of the human FEF posterior to the presumptive location of area 8.

One possibility is that the human FEF are in area 6, and if so, they would be comprised of agranular cortex. This would represent a significant lack of homology in the cytoarchitecture of saccade-related FEF in human and non-human primates, and would suggest an altered pattern of thalomocortical connectivity. A shift in FEF from dysgranular to agranular cortex, i.e. from prefrontal to premotor cortex, would raise the possibility that FEF function in humans might be relatively restricted to motor control, with a reduced contribution to the cognitive control of saccadic eye movements relative to that seen in non-human primates (Paus, 1996). However, neuroimaging data available to date provide evidence that the FEF are involved in the cognitive control of saccades in humans (Anderson *et al.*, 1994; O'Driscoll *et al.*, 1995; Sweeney *et al.*, 1996a,b) as they are in the macaque monkey (Segraves and Goldberg, 1987; Funahashi *et al.*, 1989).

A second possibility is that the human FEF are not in area 6, but that the border between areas 6 and 8, and thus the posterior-most aspect of granular/dysgranular cortex, is more posterior than was appreciated in classic human cyto-architectural maps (Brodmann, 1909; Braak, 1980). These maps place the border between premotor (area 6) and prefrontal (area 8) cortex far anterior to the dorsomedial aspect of the precentral sulcus, where we found the most robust saccade-related FEF activation.

The fact that thalamic, cortico-cortical and subcortical connectivity of oculomotor regions have a very robust consistency across New and Old World monkeys (Huerta *et al.*, 1986) seems to suggest that the more likely alternative is that there is an imprecision in the mapping of the boundary of areas 6 and 8 in classic cytoarchitectural maps rather than a major reorganization of the oculomotor system in humans. If FEF were still to demarcate the border zone of areas 6 and 8 in human, as it does in macaque monkey, it would imply that human prefrontal cortex proceeds far more posteriorly than is traditionally appreciated.

Another possibility is that the cytoarchitecture crucial for the saccade-related area of FEF is not the granularity of Layer IV, but rather the increased density of large pyramidal cells in Layer V that has been demonstrated in macaque FEF (Stanton *et al.*, 1989). Notwithstanding the potential significance of cytoarchitectural differences in FEF between humans and the macaque monkey, our findings suggest that the precentral sulcus is a homologue of the arcuate sulcus in the macaque brain in terms of gross anatomical organization (i.e. position relative to SEF and premotor cortex) and function (i.e. involvement in saccade generation).

Supplementary Eye Fields

Reliable activation of mesial frontal cortex was identified in the region believed to comprise the human SEF. This observation is similar to the findings of previous human cerebral blood flow (Melamed and Larsen, 1979; Fox *et al.*, 1985; Anderson *et al.*, 1994; Petit *et al.*, 1996; Sweeney *et al.*, 1996b) and fMRI studies (Darby *et al.*, 1996). It is noteworthy that our findings localize the SEF primarily to the medial wall of the interhemispheric fissure, minimally extending onto the dorsal cortical surface. This localization represents another difference from Old World monkeys in which the larger aspect of SEF is located on the dorsal cortical surface (Schall, 1991).

Posterior Parietal Cortex

Performing visually guided saccades resulted in widespread activation of posterior parietal cortex within the intraparietal sulcus that often extended onto the gyral surfaces of both the superior and inferior parietal lobules. Activation of precuneus, primarily within the interhemispheric fissure in posterior parietal cortex, was also seen. In the non-human primate, the superior parietal cortex and precuneus are considered the somaesthetic association cortex (Andersen, 1987), and hence the robust activation of these areas during oculomotor tasks indicates another difference in the functional organization of the eye movement system in humans. Our observations are consistent with previous PET (Paus *et al.*, 1993; Anderson *et al.*, 1994; Petit *et al.*, 1996), human lesion (Pierrot-Deseilligny *et al.*, 1991) and fMRI (Darby *et al.*, 1996) studies demonstrating that the superior parietal lobule plays an important role in generating saccadic eye movements. Some of these neuroimaging studies have also reported precuneus activation during saccade execution (Anderson *et al.*, 1994; Darby *et al.*, 1996; Petit *et al.*, 1996). The activation we observed in inferior parietal lobule, including the lateral bank of the intraparietal sulcus, occurred in an area that in non-human primates is known to contain a dense representation of neurons with both visual and saccade-related activity (Andersen, 1987; Colby *et al.*, 1996). The pattern of activation observed in posterior parietal cortex suggests that there may be a considerably broader organization of parietal regions controlling eye movements in humans than in non-human primates.

With respect to hemispheric specialization, we found that there were significantly more activated voxels in the right than left hemisphere in the inferior parietal lobule, which is consistent with the well-documented right-hemisphere specialization for visuospatial attention in humans (Mesulam, 1981). We did not find laterality effects in any of the other ROIs, indicating an apparent absence of hemispheric specialization in the control of visually guided saccades in other cortical regions.

Methodological Considerations

There are several methodological issues to be considered with respect to our localization of saccade-related areas of the human brain. One consideration is that the BOLD gradient-echo echo-planar fMRI technique is sensitive to changes in the microvasculature and also to its venous drainage with a bias towards larger vessels. Hence, the location of areas of highest MR signal change may not coincide precisely with the voxels having the greatest increase in neuronal activity, and there is some overestimation of the extent of activation and the magnitude of peak activation. Mapping errors are believed to be in the order of millimeters, so that gradient-echo fMRI still provides the spatial resolution needed to delineate the gross anatomy of the cortical control of saccades in humans. As new fMRI techniques are developed that provide greater spatial resolution with reduced sensitivity to venous drainage effects, more precise localization of functional anatomy for saccades and other brain functions will be possible (Thulborn *et al.*, 1997).

A second methodological issue concerns the subtractive nature of standard fMRI image analysis, in which activation is calculated as the relative difference between task and comparison conditions rather than in terms of absolute measurements of task-related activity. As a result of this aspect of image analysis, we may have underestimated or missed regions of activation common to visually guided saccades and fixation (our rest condition) since voxels comprising neurons with increased activity during fixation may show less or no additional activation during saccades. Single-cell studies in behaving non-human primates have demonstrated fixation-related activity

in FEF (Bruce and Goldberg, 1985), SEF (Bon and Lucchetti, 1990), prefrontal cortex (Suzuki and Azuma, 1977) and parietal cortex (Robinson *et al.*, 1978). Most brain imaging studies (Anderson *et al.*, 1994; Luna *et al.*, 1996; Muri *et al.*, 1996) have not detected activation in FEF or SEF during visual fixation tasks, suggesting that in humans activation during fixation is not large relative to that associated with generating saccades. However, Petit *et al.* (1995) did observe FEF and SEF activation during fixation, but not in regions anterior to the precentral sulcus that could have masked saccade-related activation in that region. In a different study, we observed activation during fixation within the intraparietal sulcus in an area overlapping those activated during the saccade task in the present study (Luna *et al.*, 1996), but others have not (Anderson *et al.*, 1994; Petit *et al.*, 1995; Muri *et al.*, 1996). Therefore, we may have underestimated the magnitude of activations associated with saccades in regions of interest in the present study.

Thirdly, our study presented visual stimuli in 'near space' (within the subject's reach). There is evidence from monkey studies that processing of visuospatial information in 'near space' occurs in premotor cortex, as opposed to processing of 'far space' (outside the subject's reach) which has been observed in the prearcuate region (Brodmann area 8) of macaque monkey (Pigarev *et al.*, 1979; Rizzolatti *et al.*, 1983). Hence, we may have restricted our range of cortical activation related to saccades by testing in a restricted focal plane close to the subjects' eyes. Further work is needed to determine whether saccades to targets in extrapersonal space are associated with activation in different areas of frontal and parietal cortex than regions associated with stimulus presentation in near space.

Finally, it is important to note that our study focused on regions of interest in dorsal frontal and parietal cortex. Future neuroimaging studies are needed to clarify the roles played by ventral extrastriate cortex and subcortical areas in the human oculomotor system.

Notes

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