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Neural control of fast-regular saccades and antisaccades: an investigation using positron emission tomography

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Abstract Regional cerebral blood flow changes related to the performance of two oculomotor tasks and a central fixation task were compared in ten healthy human subjects. The tasks were: (a) performance of fast-regular saccades; (b) performance of voluntary antisaccades away from a peripheral cue; (c) passive maintenance of central visual fixation in the presence of irrelevant peripheral stimulation. The saccadic task was associated with a relative increase in activity in a number of occipitotemporal areas. Compared with both the fixation and the saccadic task, the performance of antisaccades activated a set of areas including: the superior and inferior parietal lobules, the precentral and prefrontal cortex, the cingulate cortex, and the supplementary motor area.

The results of the present study suggest that: (a) compared with self-determined saccadic responses the performance of fast regular, reflexive saccades produces a limited activation of the frontal eye fields; (b) in the antisaccadic task the inferior parietal lobes subserve operations of sensory-motor integration dealing with attentional disengagement from the initial peripheral cue (appearing at an invalid spatial location) and with the recomputation of the antisaccadic vector on the basis of the wrong (e.g., spatially opposite) information provided by the same cue.

Key words Saccades · PET · Attentional disengagement · Parietal lobe · Frontal eye fields

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Introduction

In primates, evolutionary pressures have brought the suprapontine control of fast eye movements to a high degree of complexity: the final saccade-generating mechanisms in the brainstem can be triggered by different cortical and subcortical structures, depending on environmental conditions and the needs of the organism. Neurophysiological, clinical, and positron emission tomography (PET) studies (review, Pierrot-Desseilligny et al. 1995) have identified the anatomical localization of some of the attentional, sensory, and motor components of the networks involved in saccadic control. Anterior areas of the forebrain, such as the frontal eye fields (FEFs; Fox et al. 1984; Bruce and Goldberg 1985; Petit et al. 1993), supplementary eye fields (Schlag and Schlag-Rey 1987; Gaymard et al. 1990, 1993), the prefrontal cortex (Funahashi et al. 1990, 1993a, b; Paus et al. 1991; Anderson et al. 1994), and the anterior cingulate (Paus et al. 1993) mediate oculomotor functions, together with subcortical structures such as the caudate, the substantia nigra (Hikosaka and Wurtz 1989), and the putamen (Petit et al. 1993). The parietal lobes (Pierrot-Desseilligny et al. 1991), together with the superior colliculi (Schiller et al. 1987), are considered to play an important role in triggering visually cued reflexive saccades.

The present PET study had the following aims. First, we evaluated the role of the FEFs in the production of short-latency saccades. Oculomotor research (Fischer and Weber 1993) has documented the existence of different populations of saccades that are characterized by different onset latencies and that are probably produced by non completely overlapping neural networks (Fischer

and Weber 1993). At least three different types of saccades can be psychophysically defined: express saccades (mean latency 100 ms), fast-regular saccades (mean latency 150 ms), and regular saccades (mean latency 200 ms or more). The production of these different types of saccades can be induced by manipulating factors such as the temporal overlapping or nonoverlapping (gap interval) of the initial fixation point and the saccadic target, the duration of the gap interval, the predictability of target location, and the training of experimental subjects (Fischer and Weber 1993). Clinical and experimental investigations (Schiller et al. 1987; Pierrot-Desseilligny et al. 1991; Braun et al. 1992; Priori et al. 1993; Rivaud et al. 1994) have indicated a limited role of FEFs in the generation of saccades produced in oculomotor tasks characterized by the removal of the initial fixation point 100–200 ms before target presentation (gap paradigm). At variance with these findings, two recent PET studies (Anderson et al. 1994; Sweeney et al. 1996) found FEF activation during the performance of visually guided reflexive saccades. The discrepancy between the results of PET and clinical studies might arise from critical differences in the oculomotor tasks. Anderson and coworkers used a saccadic task in which initial fixation had to be sustained on an empty background with no fixation point. In the task of Sweeney and coworkers, a null (0 ms) gap interval was used. In the present PET study we used a saccadic task with a gap interval of 200 ms, similar to those employed in previous clinical studies (Pierrot-Desseilligny et al. 1991; Braun et al. 1992; Rivaud et al. 1994). We also measured saccadic latencies on a sample of control subjects in order to psychophysically define the saccades elicited by our experimental tasks. This allows a precise comparison of the PET results with those of investigations in which the critical dependent measure is the latency of saccades. With the exception of a study by O'Driscoll et al. (1995), previous PET investigations did not report the latency of saccades performed in the experimental tasks (Melamed and Larsen 1979; Fox et al. 1984; Paus et al. 1993; Petit et al. 1993; Anderson et al. 1994; Sweeney et al. 1996).

The second aim of the study was to define the neural basis of antisaccades, i.e., a condition in which the subject has to inhibit reflexive saccades toward unwilled peripheral stimuli and to voluntarily direct gaze toward opposite spatial locations. These two related options allow the efficient selection and performance of oculomotor programs, providing the organism with independence from the potentially distracting demands of the environment (Butter et al. 1988). The comparison of regional cerebral blood flow (rCBF) changes between the antisaccadic and saccadic tasks may also be considered to provide information about the neural basis of the operation of attentional disengagement (Posner and Petersen 1990). Compared with saccadic tasks, the antisaccadic task requires the subject to covertly attend an initial peripheral cue and to successively displace attention and gaze toward a symmetrical and opposite spatial location. The programming of an antisaccade thus requires the intentional disengagement from a peripheral cue determining an automatic capture of attention at an invalid spatial location. Corbetta et al. (1993) found no activation of the inferior parietal lobule in a PET study of covert attention in which 95% of the cues were valid. These authors hypothesized that the inferior parietal lobule could be activated by attentional disengagement from invalid locations. In the present study, we wished to explore this hypothesis by comparing the PET activations found in the saccadic and in the antisaccadic tasks.

The rCBF changes produced by the saccadic and antisaccadic task were also compared with those produced by a task of passive fixation, with irrelevant peripheral cues appearing at the same retinal locations stimulated during the two oculomotor tasks (Corbetta et al. 1993). The results of this study were presented at the Annual Meeting of the Society for Neuroscience 1994 (Perani et al. 1994).

Materials and methods

Experimental tasks

The three tasks used in the present study are shown in Fig. 1. In both the Fast-regular and the Antisaccadic task, targets appeared randomly at one of the four vertices of a virtual diamond. Each side of the diamond occupied 10° of the visual field. The saccadic target was a white spot (1° in diameter) appearing on an empty dark gray background. In the Fixation task the spatial structure of the pattern of stimulation was obtained by the union of four virtual

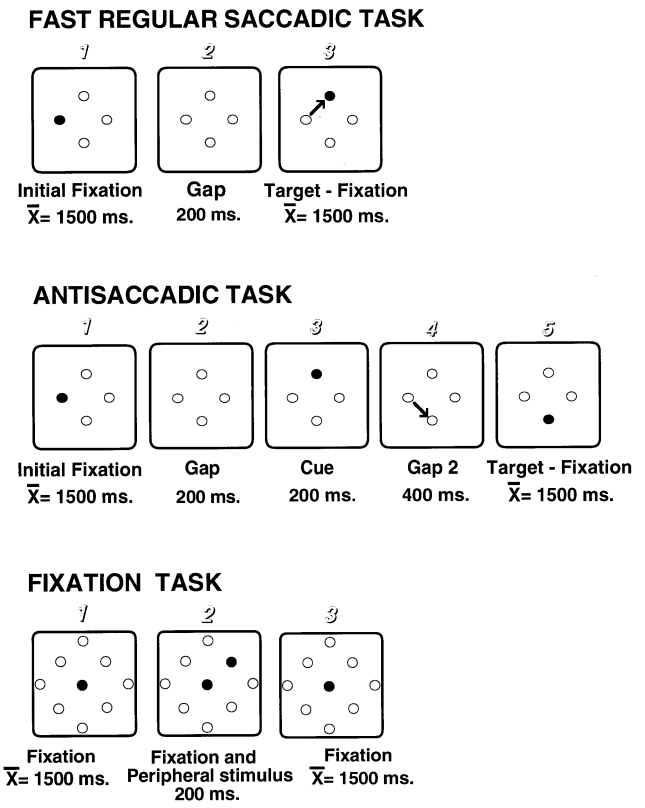


Fig. 1 Structure of the three oculomotor tasks

diamonds. Central fixation was located on the vertex shared by the four diamonds and irrelevant peripheral stimuli were presented at locations coinciding with the same retinal locations stimulated during the Fast-regular and the Antisaccadic tasks. On each trial of the Fast-regular task, subjects had to move their eyes from the initial fixation point to the target. At the beginning of the task the subjects fixated the target, positioned on one of the vertices of the virtual diamond, for a variable interval (phase 1; duration 1000 ms, 1500 ms, or 2000 ms; mean duration 1500 ms). After this interval the target disappeared for 200 ms (phase 2, "gap") and reappeared randomly at one of the remaining three vertices (phase 3), where it persisted for a variable interval (duration 1000 ms, 1500 ms, or 2000 ms; mean duration 1500 ms), constituting the initial fixation point for the following trial. In the Fast-regular task, two-thirds of the saccades were oblique and one-third horizontal or vertical.

In the Antisaccadic task, subjects had to fixate as quickly as possible, the vertex of the virtual diamond opposite to the one in which an initial cue appeared. Phases 1 and 2 were identical to the Fast-regular task. In phase 3 a cue appeared for 200 ms on the left or the right vertex (when initial fixation was on the upper or the lower vertex), or on the upper or the lower vertex (when initial fixation was on the left or the right vertex). After a successive blank interval of 400 ms (phase 4), during which the antisaccade was performed away from the cue, the antisaccadic target reappeared on the opposite vertex (phase 5), where it persisted for a random interval (duration 1000 ms, 1500 ms, or 2000 ms; mean duration 1500 ms), constituting the initial fixation point for the following trial. In the Antisaccadic task all saccades were oblique.

In the Fixation task a central target was always visible and served as central fixation point. Peripheral targets appeared for 200 ms at variable intervals (duration 1000 ms, 1500 ms, or 2000 ms; mean duration 1500 ms) at the same peripheral locations stimulated during the Fast-regular and the Antisaccadic tasks. Subjects were instructed to pay attention and keep their gaze on the central fixation point, disregarding peripheral targets. No gap of central fixation preceded the appearance of peripheral targets. The gap of central fixation releases oculomotor mechanisms from inhibitory influences linked to active fixation, making possible the automatic production of short-latency express and fast-regular saccades. On the contrary, in the human adult, short-latency saccades toward peripheral targets cannot be spontaneously produced when the central fixation point is maintained ("overlap" condition), and extensive training (200 saccades per day for 10 days) is needed to learn rapid disengagement from fixation and reach production of a consistent number of short-latency saccades (Fischer and Breitmeyer 1987). Therefore, in our Fixation task the maintenance of the central fixation point prevented the possibility of producing unwilled fast-regular saccades and, as a consequence, the elicitation of inhibitory activity specifically addressed at preventing the production of the same saccades. In the Fast-regular task, the interposition of the gap between initial fixation and target appearance allowed for the automatic ocular disengagement from central fixation and the triggering of reflexive saccadic responses probably mediated at a collicular level (Fischer and Weber 1993). The gap interval was also present in the Antisaccadic task. In this task peripheral targets were cues appearing at invalid spatial locations and defining, by spatial opposition, the locations toward which the voluntary antisaccades had to be performed. In all three tasks, spatial position and time of appearance of the peripheral targets were unpredictable.

Task validation

The three oculomotor tasks were psychophysically validated in a sample of six subjects matched for sex, age, and educational level with those participating in the PET study. Saccadic latencies and amplitudes were recorded with an infrared system (Permobil, Ober 2 system). Prior to experimental recordings, subjects received training for each of the three tasks. Four consecutive training blocks of trials were administered for each task. As in the PET recordings, each training and experimental block of trials lasted 3 min. The results of the psychophysical study showed that in the saccadic and antisaccadic tasks frequency peaks and mean saccadic latencies were in agreement with existing data (see Figs. 2, 3). In the saccadic task the mean latency was 140 ms (SD 64.9 ms; modal latency 125 ms) corresponding to the latency of fast-regular saccades (Fischer and Weber 1993). In the antisaccadic task, mean latency was 321 ms (SD 111 ms; bimodal distribution of latencies with peaks at 250 ms and 310 ms), which is comparable with data collected in normal subjects by Guitton et al. (1985) in a task with horizontal antisaccades (e.g., 312 ms). Recordings of the fixation task documented that subjects were able to maintain central fixation with virtually perfect accuracy.

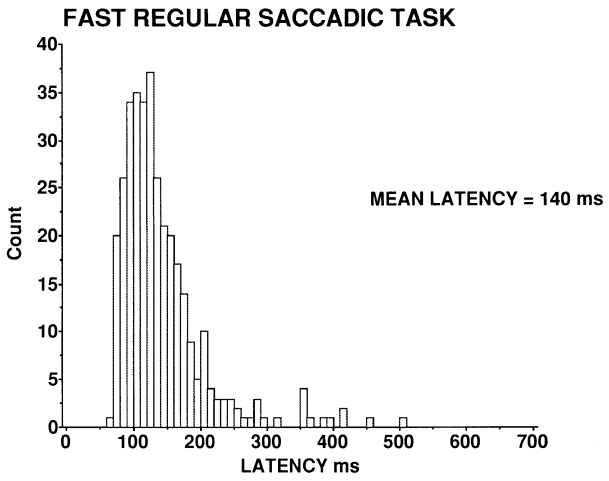


Fig. 2 Frequency distributions and mean values of the saccadic latencies recorded during the psychophysical validation of the Fast-regular saccadic task

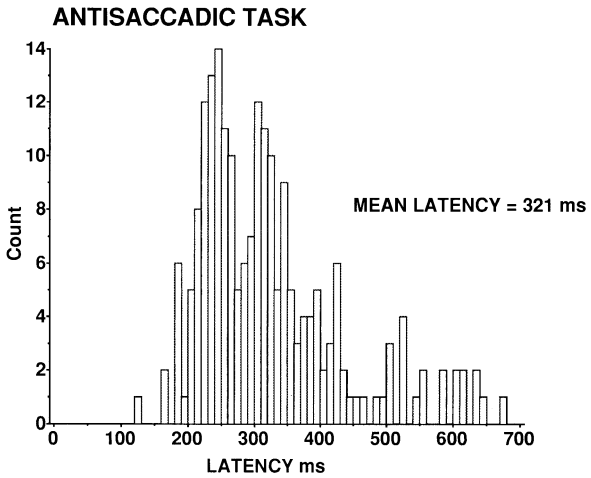


Fig. 3 Frequency distributions and mean values of the saccadic latencies recorded during the psychophysical validation of the Antisaccadic task

Subjects

Ten right-handed men between 20 and 26 years of age participated in the experiment. All subjects provided informed consent. The experimental procedure was approved by the local Ethical Committee. Before the PET study, the subjects received the same training administered for task validation. During the PET study, eye

movements were monitored and videotaped synchronously with the videotaping of the stimulus display for off-line control of directional accuracy in the performance of oculomotor tasks. The video camera was focused on one eye of the subjects. Video recording was sensitive to eye movements of 1° of visual angle.

PET data acquisition and analysis

Changes in rCBF were measured using the intravenous radioactively labeled water [^{15}O]H_2O bolus technique. The positron emission tomograph was a Siemens 931/04–12 (Siemens-CPS Knoxville, Tennessee, USA) whole body scanner. Each scan lasted 2 min; integrated counts were collected for 90 s, starting 30 s after injection. An i.v. bolus injection of 850 MBq (30 mCi) [^{15}O]H_2O was given for each scan. Scans were separated by an interval of about 10 min to allow isotope decay. Two scans for each experimental task were acquired for each subject. Two sets of three scans each were taken to cover the whole brain by moving the bed of the scanner in order to have an overlay of the image sections of the first set of acquisitions with the image sections of the second set. The higher section of the brain was always scanned first, followed by the scanning of the lower part, which included the cerebellum. Once reconstructed, the two images corresponding to the same oculomotor task were combined to form a single image of the brain. Scans 1 and 4 were of the Fixation task, 2 and 5 the Fast-regular saccadic task, and 3 and 6 the Antisaccadic task. A normalization factor was calculated from the integral counts detected in the overlaid plane section. The smoothing filter was 20×20×12. Image transformation into a standard stereotactic anatomical space, as defined in the atlas of Tailarach and Tournoux (1988), was carried out followed by statistical analysis using statistical parametric mapping (SPM-95; Friston et al. 1995). Global differences in rCBF within and between subjects were covaried out for all voxels, and comparisons across conditions were made using *t* statistics. The significance of rCBF differences was assessed in an omnibus sense. Threshold significance was set at $P<0.01$, which corresponds to *Z*-score 2.33. In order to assist in the localization of brain activity, anatomical areas of activation were also defined according to the Brodmann's classification (Brodmann area, BA) reported in the atlas by Tailarach and Tournoux (1988).

The stereotactic coordinates of some activation foci of interest found in the categorical comparisons were used to build "activation profiles" for each of the three experimental conditions (see Fig. 4a, b). These profiles of activity, represented as relative rCBF values in each task (histograms), are used to better demonstrate the differential involvement of a selected brain area in the three experimental conditions.

A principal component analysis of the whole data set (composed of the scans acquired in all conditions) was also performed using the SPM package (Friston et al. 1993). Singular value decomposition (SVD) was used to decompose the original time series into two sets of orthogonal vectors (patterns in space and patterns in time). The original data set is projected on a series of orthogonal vectors (i.e., the spatial modes) with a decreasing amount on the contribution to the variance of the voxel values. For each spatial mode, the SVD supplies three parameters: an eigenimage, a pattern of covariation structures that can be displayed as a brain image; an eigenvalue, which is the 2-norm of the eigenimage and also gives proportional contribution to the global variance; and an eigenvector, a time-dependent profile that represents the influences of the pattern on the different conditions of activation. This decomposition leads to the principal component analysis (PCA). On the basis that the spatial modes are independent, they can be viewed as independent factors of variance. The profile of the eigenvector of the components is the most relevant indication for the functional attribution of the origin of variance. Eigenimages are divided into positive and negative structures for a more readable presentation: conditions in which temporal contribution is positive are modulated by the positive corresponding eigenimage and vice versa (for a complete description of this type of analysis see Friston et al. 1993).

Results

Task performance accuracy

The video recordings documented that during PET scans subjects performed the Fixation and the Fast-regular saccadic task with nearly perfect accuracy. In the Antisaccadic task fewer than 5% of errors were made. These errors consisted almost exclusively of failures in the inhibition of reflexive responses toward the initial peripheral cue.

Categorical comparisons

For each comparison, local maxima of rCBF increases and decreases significant at $P < 0.01$ ($Z > 2.33$) and $P < 0.001$ ($Z > 3.09$) are reported in Tables 1–3.

Fast-regular saccadic task compared with Fixation task (relative increases in rCBF)

This comparison showed significantly greater activity of the extrastriate cortex (cuneus, BA 18) and the right thalamus. See Table 1.

Fixation task compared with Fast-regular saccadic task (or relative decreases in rCBF in the Fast-regular vs Fixation task comparison)

Subcortical foci were found bilaterally in the caudate nucleus and in the left thalamus. There was bilateral superior parietal activation (BA 7) and right-sided parahippocampal and inferior occipital activation. See Table 1.

Table 1 Fast regular saccadic task compared with Fixation task: areas of relative increase and decrease (inverse comparison) in regional cerebral blood flow (*rCBF*). Localization values are given in Talairach and Tournoux (1988) coordinates (*sup* superior, *inf* inferior)

x	*y*	*z*	*Z*-score	Anatomy
Fast-regular vs fixation				
+30	–26	0	2.84*	R thalamus
–16	–86	+8	3.28**	L cuneus (Ba 18)
+12	–98	+8	3.15**	R cuneus (Ba 18)
fixation vs Fast-regular				
–16	+22	+4	4.28**	L caudate
+16	+14	+20	3.19**	R caudate
–18	–22	+16	2.75*	L thalamus
+8	+2	–20	2.71*	R parahippocampal gyrus
–12	–36	+48	2.69*	L sup parietal lobule (Ba 7)
+22	–36	+48	2.50*	R sup parietal lobule (Ba 7)
+34	–82	–4	2.66*	R inf Occipital Gyrus (Ba 19)

* Local maxima of rCBF activity significant at $P<0.01$ ($z>2.33$)
** Local maxima of rCBF activity significant at $P<0.001$ ($z>3.09$)

Table 2 Antisaccadic task compared with Fixation task: areas of relative increase and decrease (inverse comparison) in rCBF

x	*y*	*z*	*Z*-score	Anatomy
Antisaccades vs Fixation				
+4	+32	+20	3.05*	R ant cingulate gyrus (Ba 32)
–2	+26	+16	4.12**	L ant cingulate gyrus (Ba 24/32)
–30	–6	+48	3.21**	L sup frontal sulcus (Ba 6) (FEFs)
–40	–4	+40	3.14**	L precentral sulcus (Ba 6) (FEFs)
+18	–4	+40	2.52*	R precentral sulcus (Ba 6) (FEFs)
–24	–54	+44	2.50*	L sup parietal lobule (Ba 7)
+16	–76	+44	2.71*	R sup parietal lobule (Ba 7)
+4	–66	+48	3.09*	R precuneus (Ba 7)
–36	–62	+32	2.64*	L inf parietal lobule (Ba 39/40)
+50	–50	+32	2.77*	R inf parietal lobule (Ba 39/40)
0	–46	+40	2.62*	L/R post cingulate gyrus (Ba 31)
+12	–2	+48	2.61*	R supplementary motor area (Ba 6)
fixation vs Antisaccades				
–16	+18	0	3.73**	L ant cingulate gyrus (Ba 24/32)
+4	+36	–8	2.79*	R ant cingulate gyrus (Ba 32)
–38	–82	+4	2.61*	L middle occipital gyrus (Ba 19)
+38	–78	0	3.80**	R middle occipital gyrus (Ba 19)
–46	–20	–20	3.28**	L fusiform gyrus (Ba 37)
+42	–38	–20	2.85*	R fusiform gyrus (Ba 37)
–60	–44	+4	3.41**	L middle temporal gyrus (Ba 21)
+56	–24	+8	3.73**	R middle temporal gyrus (Ba 21)
+10	+4	–20	2.50*	R parahippocampal gyrus
–14	–26	+8	2.88*	L thalamus

* Local maxima of rCBF activity significant at $P<0.01$ ($z>2.33$); ** local maxima of rCBF activity significant at $P<0.001$ ($z>3.09$)

Table 3 Antisaccadic task compared with Fast-regular saccadic task: areas of relative increase and decrease (inverse comparison) in rCBF

x	*y*	*z*	*Z*-score	Anatomy
Antisaccades vs Fast-regular				
–6	+26	+12	4.40**	L ant cingulate gyrus (Ba 24)
+2	+26	+16	3.80**	R ant cingulate gyrus (Ba 24)
–32	0	+48	3.42**	L sup frontal sulcus (Ba 6) (FEFs)
+22	0	+48	2.50*	R sup frontal sulcus (Ba 6) (FEFs)
–38	–4	+44	3.51**	L precentral sulcus (Ba 6) (FEFs)
–32	+8	+40	3.08*	L middle frontal gyrus (Ba 6/8)
+30	+2	+40	2.75*	R middle frontal gyrus (Ba 6/8)
–38	+28	+32	3.78**	L middle frontal gyrus (Ba 8/9)
+36	+10	+36	2.57*	R middle frontal gyrus (Ba 8/9)
–4	+54	+36	2.50*	L medical frontal gyrus (Ba 8/9)
+6	+34	+44	2.67*	R medial frontal gyrus (Ba 8)
–12	–36	+48	3.41**	L sup parietal lobule (Ba 7)
+28	–36	+48	3.01*	R sup parietal lobule (Ba 7)
–36	–54	+32	2.88*	L inf parietal lobule (Ba 39)
+30	–48	+28	2.83*	R inf parietal lobule (Ba 39)
+18	+2	+48	2.50*	R supplementary motor area (Ba 6)
Fast-regular vs Antisaccades				
+44	–38	–20	3.44**	R fusiform gyrus (Ba 37)
–30	–34	–16	2.95*	L fusiform gyrus (Ba 37)
–38	–78	–4	3.15**	L inf occipital gyrus (Ba 19)
+44	–68	0	2.70*	R inf occipital gyrus (Ba 19)
–60	–44	+4	3.04*	L middle temporal gyrus (Ba 21)
+54	–26	+8	3.23**	R middle temporal gyrus (Ba 21)
–26	–76	+8	3.02*	L middle occipital gyrus (Ba 19)
+36	–74	+4	2.78*	R middle occipital gyrus (Ba 19)
+32	–20	0	2.71*	R lenticular nucleus

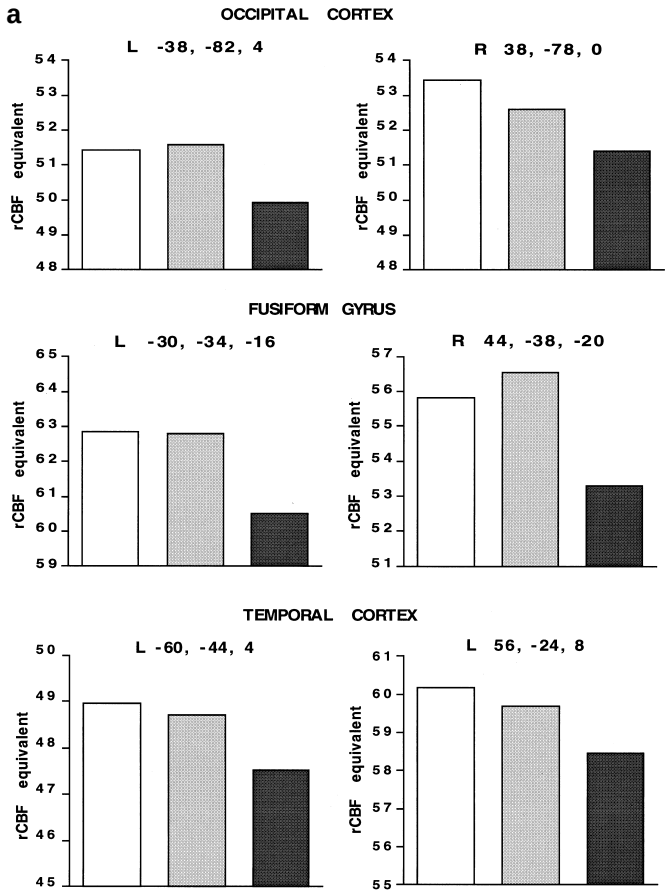
* Local maxima of rCBF activity significant at $P<0.01$ ($z>2.33$); ** local maxima of rCBF activity significant at $P<0.001$ ($z>3.09$)

Antisaccadic task compared with Fixation task (relative increases in rCBF)

Task comparison showed bilateral activations in the superior parietal lobule (BA 7), inferior parietal cortex (BA 39/40), and anterior (BA 32) and posterior (BA 31) cingulate cortex. Activation foci were shown in the FEF regions: precentral sulcus (BA 6) bilaterally and superior frontal sulcus (BA 6) on the left. Activation of the supplementary motor area (SMA; BA 6) was found only in the right hemisphere. See Table 2.

Fixation task compared with antisaccadic task (or relative decreases in rCBF in the Antisaccadic vs Fixation task comparison)

Significant bilateral activations were found in anterior cingulate cortex (BA 24/32), the middle occipital gyrus



(BA 19), the fusiform gyrus (BA 37), and in the middle temporal gyrus (BA 21). Other foci of activation were found in the left thalamus and in the right parahippocampal gyrus. See Table 2.

Antisaccadic task compared with Fast-regular saccadic task (relative increases in rCBF)

In this comparison activity was found in the right and left superior frontal sulcus (BA 6), in the left precentral sulcus (BA 6; FEF regions), and in the right SMA (supplementary eye field, BA 6). Bilateral foci of activation were found in the dorsolateral and medial frontal cortex (BA 8 and 9), the superior parietal lobule (BA 7), the inferior parietal lobule (BA 39/40), and in the anterior cingulate cortex (BA 24). See Table 3.

Fast-regular saccadic task compared with Antisaccadic task (or relative decreases in rCBF in the Antisaccadic vs Fast-regular task comparison)

In this comparison the significant areas, bilaterally activated, were the fusiform gyrus (BA 37), the middle temporal gyrus (BA 21), and the inferior and medial occipital cortex (BA 19). See Table 3.

Activation profiles

The results of the categorical comparison showed a complex pattern of relative increases, which can be attributed

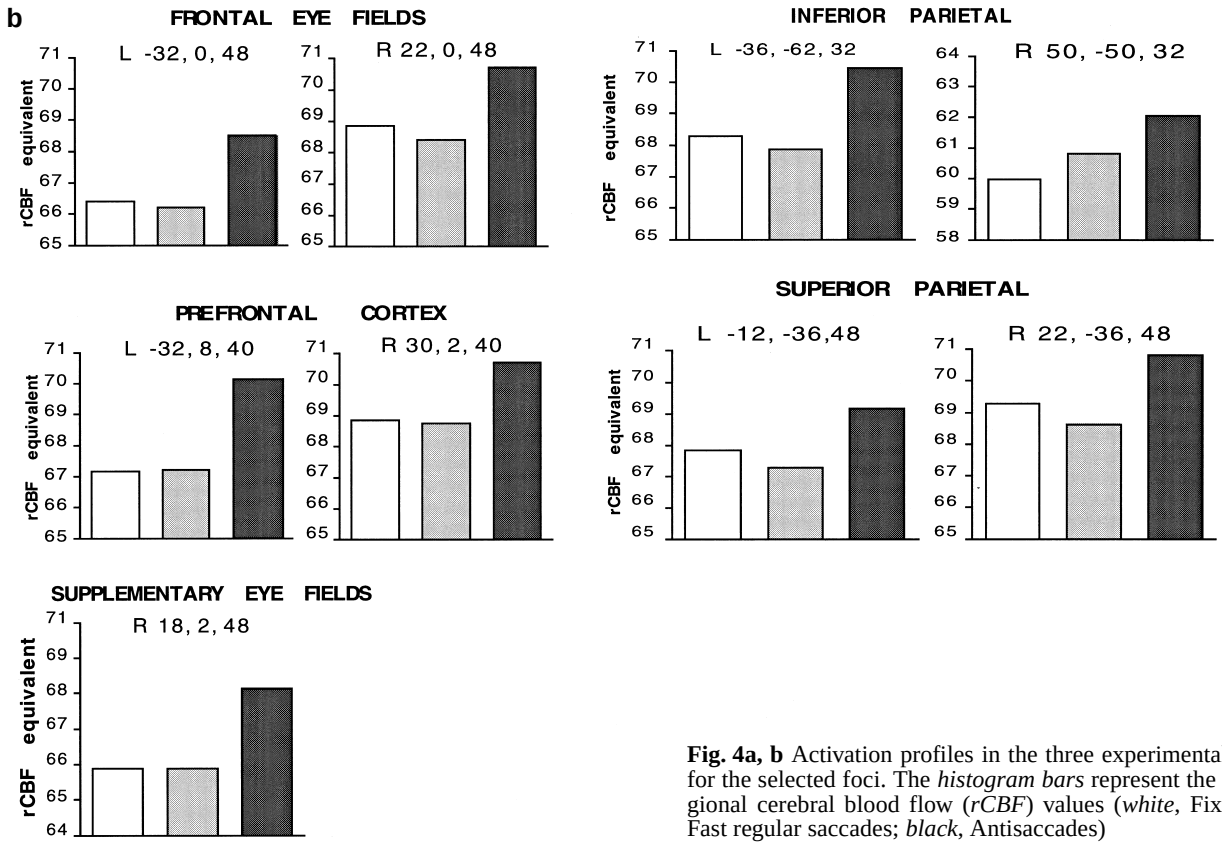


Fig. 4a, b Activation profiles in the three experimental conditions for the selected foci. The *histogram bars* represent the adjusted regional cerebral blood flow (*rCBF*) values (*white*, Fixation; *gray*, Fast regular saccades; *black*, Antisaccades)

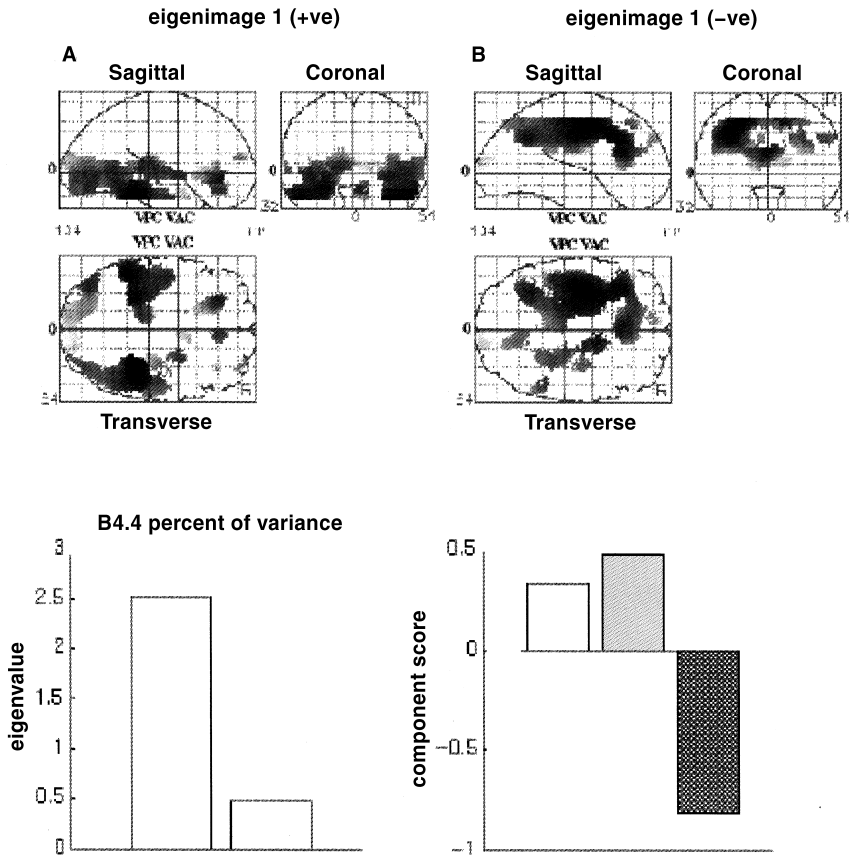


Fig. 5A, B Cortical rendering showing the task-related brain structures that better explain the experimental variance, as revealed by principal component analysis. **A** Fixation and Fast-regular saccades; **B** Anti-saccades. The *histogram bars* represent the task conditions (*white*, Fixation; *gray*, Fast-regular saccades; *black*, Anti-saccades)

both to activation and deactivation of cerebral areas in each task. We obtained also activation profiles for the left and right precentral and prefrontal regions (BA 6), the extrastriate cortex (cuneus, BA 18, and fusiform gyrus, BA 37), the middle temporal cortex (BA 21), the precuneus (medial and lateral BA 7), the inferior parietal cortex (BA 39/40), the anterior cingulate cortex (BA 24/32), and the right SMA (BA 6; see Fig. 4a, b). This type of analysis showed the predominant activation of the frontal cortex (precentral and prefrontal regions) and the inferior parietal cortex in the Antisaccadic task in comparison with the Fast-regular saccadic and Fixation condition; conversely, activation in the occipital and temporal areas was prevalent in the Fast-regular saccadic and Fixation tasks.

Principal component analysis

A further analysis was performed in order to confirm the distinction of an occipito-temporal and frontoparietal network suggested by the previous results. Principal component analysis of the whole data set revealed that the first component accounted for 84.4% of the variance. The antisaccade condition accounted for a large part of the variance. Fixation and fast-regular conditions have the same influence (positive vectors), in contrast to the condition involving antisaccades (negative vectors). Positive components of the eigenvectors engage bilateral posterior brain regions (occipital and temporal). Conversely, negative components of the eigenvectors are related to parietal and frontal regions (see Fig. 5). This confirms that different patterns of activation, involving complex corticosubcortical networks, are associated with the experimental tasks (Fig. 5).

Discussion

The present PET study shows the activation of many cortical areas and subcortical structures, with a main separation between a occipitotemporal network, associated with the Fast-regular saccadic task, and a frontoparietal network more involved in the Antisaccadic task. The visual Fixation task was associated with a pattern of activation partially overlapping the previous two (in particular, with the Fast-regular saccadic task; see Principal component analysis).

Fast-regular saccades

The performance of fast-regular saccades was associated with activation of a stream of *occipitotemporal areas*. In humans, activation of the striate and extra-striate visual cortex was documented by previous PET studies during the performance of reflexive saccades (Melamed and Larsen 1979; Fox et al. 1984; Anderson et al. 1995) and

was related to the visual processing of peripheral saccadic targets. While animal studies showed that extrastriate visual areas have an attentional- and saccadic-independent enhancement of activity upon presentation of potential saccadic targets (Goldberg and Segraves 1989), Petit et al. (1993) found a significant rCBF increase in the fusiform and lingual gyri during the performance of voluntary saccades in the dark, suggesting a genuine oculomotor role for these areas.

In the Fast-regular and Antisaccadic comparison, a focus of activation was found bilaterally in *BA 19*, with peak coordinates in good correspondence to those of the area V5 described by Zeki et al. (1991), in the adjacent fusiform gyrus (BA 37) and middle temporal area (BA 21). Human V5, located at the junction between BA19 and BA37, has been shown by clinical and activation studies to be relevant for motion processing (Corbetta et al. 1991; De Jong et al. 1994; Shipp et al. 1994; Tootell et al. 1995). In patients with neglect, unilateral lesions centered over the same area reduce the amplitude of the quick phases of optokinetic nystagmus directed contralesionally (Incoccia et al. 1995). A recent PET activation study (O'Sullivan et al. 1995) suggests a relevant anatomical overlap between the motion-processing pathway and the pathway mediating visually guided reflexive saccades in humans. In the monkey, motion processing is subserved by the middle (MT) and middle-superior temporal (MST) areas (Boussaud et al. 1990). These areas send efferents to parietal and frontal areas involved in attentional and oculomotor control (Boussaud et al. 1990). Recent evidence demonstrated that unilateral lesions of MT and MST areas significantly increase the latency of reflexive saccades directed to contralesional stimuli (O'Scalaidhe et al. 1995). On the basis of these data, the relative increase in activation of the occipitotemporal visual pathway during the performance of the Fast-regular saccadic task could be attributed both to the monitoring of target displacements and to the performance of reflexive oculomotor responses.

It is noteworthy that the same occipitotemporal areas were not found to be active in the Antisaccadic task, even though the initial three phases of the oculomotor task (e.g., initial fixation, gap, appearance of a peripheral cue) were spatially and temporally equivalent to those of the Fast-regular saccadic task. This finding could be tentatively explained by hypothesizing that, since the direction of the antisaccade was incongruent and opposite to the direction of cue displacement, the extensive attentional processing of the initial cue in the occipitotemporal pathway could have been potentially disturbing for the programming of the antisaccades and so it was inhibited, resulting in a deactivation in the antisaccadic task. This hypothesis could find support in a recent experimental report documenting a significant reduction of the fMRI signal in human MT and MST areas when subjects shift visual attention from moving dots to intermixed stationary ones (O'Craven et al. 1995). This finding provides further evidence for the inhibitory effects of selective attention on the activity of the occipitotemporal visual pathway (Heinze et al. 1994).

No *FEF* activation was found in the Fast-regular saccadic and Fixation comparison (as well as in the inverse comparison), and FEFs were significantly active both in the Antisaccadic and Fast regular saccadic and in the Antisaccadic and Fixation comparisons. These results suggest that, compared with intentional saccades, the contribution of FEFs to the production of short-latency reflexive saccades is limited. Different results have been reported in other PET studies. Anderson and coworkers (1994) found no quantitative differences in FEF activation between reflexive and memory-delayed saccades. Sweeney and co-workers (1996) found that in a reflexive saccadic task FEFs were more activated than in a fixation task but less activated than in an antisaccadic task. Differences in the oculomotor task used to trigger reflexive saccades could at least in part account for these differences. Anderson and coworkers used a saccadic task in which initial fixation had to be maintained without a fixation point. Petit et al. (1995) found that maintenance of fixation on an empty background induces a significant enhancement of rCBF in the FEFs, probably linked to the activity of both fixation and working memory neurons. Therefore, in Anderson and coworkers' study, the maintenance of fixation required by their saccadic task might have contributed to FEF activation. Sweeney et al. (1996) found FEF activation when subtracting rCBF changes found during a central fixation task from those observed during the performance of reflexive saccades toward peripheral targets. However, in their study subjects had to voluntarily move their eyes back to central fixation after each saccade. This means that during the performance of the task half of the saccades were reflexively directed toward unpredictable locations and the other half were intentionally directed toward a fixed spatial location. Therefore, the activation of FEFs could be, at least in part, ascribed to voluntary central refixation.

It could be argued that, compared with baseline Fixation tasks with no peripheral stimuli, the Fixation task used in the present study might have caused a higher activation of the FEFs, linked to the attentive selection of the peripheral stimuli and the inhibition of reflexive oculomotor response toward the same stimuli (Schall and Hanes 1993). As a consequence, this activation could have cancelled any activation of the FEFs in the Fast-regular and fixation comparison. We consider this hypothesis unlikely, since Corbetta et al. (1993) did not find any relative increase in rCBF in the section of BA6 corresponding to FEFs when comparing a task of passive fixation using peripheral stimuli similar to the one adopted in the present study with a fixation task using no peripheral stimulation. These authors suggested that, in tasks causing automatic shifts of covert attention, the activation of frontal motor areas is observed only when the selection of a motor response (whether manual or oculomotor) is overtly required. Another possible explanation of the scarce FEF activation is that in our saccadic gap task active disengagement from the initial fixation point was not required. In humans, FEF lesions cause a signifi-

cant increase in saccadic latencies in overlap tasks, but not in gap tasks, where ocular disengagement from initial fixation is provided exogenously by the disappearance of the fixation point (Rivaud et al. 1995), suggesting a role for FEFs in active ocular disengagement.

Finally, the *right thalamic-lenticular* activation could be linked to the activation of part of the cortico-striatal-thalamic-cortical loop for the execution of simple movements, proposed by Alexander et al. (1986), or to shifts of visuospatial attention coupled with saccades (Robinson and Petersen 1992). This network may subserve both the visuoattentional and the motor components of the task.

Antisaccades

The Antisaccadic task activated an extensive network of anterior and posterior cortical areas, as well as subcortical structures.

The *FEFs*, located in the precentral sulcus (BA 6) at the level of the superior frontal sulcus (Paus 1996) were selectively activated by this task. The role of FEFs in the production of voluntary saccades, both targeted or untargeted, has been well documented (Fox et al. 1985; Petit et al. 1993); our study provides further evidence of this functional link, with antisaccades being a particular type of voluntary saccade. In keeping with the studies of O'Driscoll et al. (1995) and Sweeney et al. (1996), activation of FEFs was higher in the Antisaccadic than in the saccadic task. Paus et al. (1993; experiment 2) reported equal activation of FEFs between a reflexive saccadic task with a gap of 200 ms and an antisaccadic task. A possible interpretation of this discrepancy is that, in the saccadic task used by Paus and co-workers, target location was known in advance by the subjects, since the target alternated regularly between two fixed positions, one in the left and the other in the right visual field. Since in this condition the saccadic vectors (direction and amplitude) are voluntarily computed before target appearance, rather than triggered by the target itself, the saccades produced in this paradigm may not be considered as truly reflexive, and the FEFs activation could reflect intentional rather than reflexive saccadic control.

A predominant left-sided activation of FEFs was observed (see Table 2): although not explicitly commented upon, a similar finding was present in several previous PET studies of reflexive and voluntary saccades (Petit et al. 1993; Anderson et al. 1994; Paus et al. 1993).

The *prefrontal cortex* was also bilaterally activated both in its medial (BA 8) and dorsolateral (BA 9) sections in the comparison with the saccadic task, but not with fixation. This activation might thus be related to maintenance of fixation itself. Compared with the Fast-regular saccadic task, the Antisaccadic task required the inhibition of reflexive oculomotor responses toward invalid cues and the effortful maintenance of fixation in the momentary absence of the central fixation point (gap). Deficits of fixation have been related by several authors to anterolateral lesions of the prefrontal cortex (Pierrot-Desseilligny 1994). Paus et al. (1991) described deficits of central-gaze fixation in patients with lesions localized in the medial surface of the frontal lobe and in frontal dorsolateral areas, immediately anterior to BA 45 and centered on BAs 46, 9, and 10 (see Paus et al. 1991; Fig. 1).

Another possibility is that dorsolateral frontal cortex activation might be related to working memory. Funahashi et al. (1990, 1993a, b) described an increase in cellular discharge in the dorsolateral prefrontal cortex of the monkey both before the onset of delayed remembered saccades and the performance of antisaccades. Although it is unclear whether a working memory component is involved in the Antisaccadic task (since antisaccades must be performed as soon as possible after the appearance of the peripheral cue) the results of our investigation suggest that the prefrontal cortex is active whenever the location of appearance of a saccadic target is spatially (as in the antisaccadic task) or temporally uncoupled (as in a remembered task) from the direction or the initiation of the related saccade. As suggested by Funahashi et al. (1993b), in the former case the prefrontal cortex could maintain "on-line" instructional information; in the latter case the prefrontal cortex could sustain the activation of the sensorimotor representation of the target during the delay preceding the oculomotor response.

The Antisaccadic task produced a significant rCBF increase in two other functionally related anterior structures (Luppino et al. 1990): the *anterior cingulate cortex* and the *SMA*. Several researchers have suggested that the anterior cingulate cortex (BAs 24–32) plays a role in the control of response selection (Paus et al. 1993; Devinsky et al. 1995), such as in the antisaccadic task, in which subjects have to select a voluntary motor response at the expense of a stimulus-driven one. The SMA was significantly activated in the right hemisphere: a similar right SMA activation was also reported by Sweeney et al. (1996), whereas O'Driscoll et al. (1995) found bilateral SMA activation. The SMA receives relevant input both from the prefrontal and posterior cerebral cortex (Cavada and Goldman-Rakic 1989; Goldman-Rakic 1988) and projects to the FEF, the superior colliculi, and the reticular formation (Jeffers et al. 1987; Shook et al. 1990). Paus et al. (1991) found that among frontal brain-damaged patients, those with lesions affecting both the SMA, the anterior cingulate, and medial frontal areas suffered the strongest deficit in the inhibition of unwilled reflexive saccades. The SMA might therefore constitute an important component of an anterior circuit coordinating the sequence of inhibitory and excitatory events leading to the selection of the appropriate oculomotor response. A planning function of the SMA is also suggested by its involvement in the memorization and initiation of sequences of saccades (Gaymard et al. 1990, 1993; Petit et al. 1996).

Both the *superior (BA 7)* and the *inferior (BA 39/40) parietal lobule* were significantly more active in the Antisaccadic task. Corbetta et al. (1993) have suggested

that superior parietal activation can be accounted for by covert shifts of attention uncoupled from eye movements. This hypothesis is compatible with the difference between the Fast-regular saccadic task and the Antisaccadic task since in the former shifts of attention were always coupled with saccades, whereas they were uncoupled from eye movements in the latter.

The activation of the *inferior parietal lobule (BA 40)* was not found both for the Fixation and the Fast-regular saccadic tasks and thus cannot be related either to automatic covert shifts of attention or to covert shifts of attention coupled with reflexive oculomotor responses toward peripheral stimuli. Sweeney et al. (1996) tentatively related the activation of the inferior parietal lobule in the antisaccadic task to the computation of the antisaccadic vector toward an untargeted spatial location. However, Fox et al. (1984) found no activation of the inferior parietal lobule when subjects had to alternate voluntary saccades between two untargeted locations. We propose that the activation of the inferior parietal lobule could be explained by hypothesizing a functional link of this area with operations of sensory-motor integration dealing both with attentional disengagement from the initial peripheral cue and with the recomputation of the antisaccadic vector on the basis of the wrong (e.g., spatially opposite) information provided by the same cue. The task used in the present study is different from Posner's classical test of covert attentional shifting, in which the disengagement-movement-engagement sequence is triggered exogenously by the appearance of the target at the unexpected location. However, on each trial of the Antisaccadic task, subjects had to inhibit overt orienting toward the initial peripheral cue and voluntarily reorient their covert attentional and overt oculomotor response in the opposite direction. In terms of Posner's model (Posner and Petersen 1990), the spatial-attentional components of this operation could correspond to attentional disengagement. Rizzolatti and co-workers (1994) have suggested that in covert attentional tasks the appearance of a peripheral spatial cue determines the selection of a corresponding central oculomotor program that is inhibited at a more peripheral level. According to this hypothesis, cues appearing at invalid locations produce attentional costs, because the appearance of the target at a different location triggers the time-consuming recomputation of the direction and/or the amplitude of the previously selected central oculomotor program. Our data from the Antisaccadic task suggest that the cortical structures that could be critically involved in this latter operation are the inferior parietal lobes. In antisaccadic tasks, the attentional disengagement might be functionally coincident with the recomputation of the antisaccadic vector on the basis of the spatial information provided by the initial peripheral cue.

To summarize, the inferior parietal lobule could subserve basic operations of sensorimotor integration (Andersen et al. 1993), which are shared by attentional and oculomotor tasks characterized by a spatial dissonance between the retinotopic location of an attentional or oculomotor spatially informative cue and the location of the final attentional or saccadic target (e.g., invalid trials in Posner's task and antisaccadic trials). Indeed, in a double-step saccadic task, in which the retinotopic position of the second target is spatially noncoincident with the final spatial position of the fovea, patients with lesion of the inferior parietal lobule show deficits in the correct computation of the trajectory of the second saccade (Heide et al. 1995).

An alternative explanation of the inferoparietal activation could be related to a spatial working memory component (Andersen and Gnadt 1989; Jonides et al. 1993), owing to the need to remember that antisaccades had to be performed away from the cue. However, Muri et al. (1995) showed that magnetic transcranial stimulations of the parietal areas perturb the performance of memory-guided saccades only if they are applied about 260 ms after target presentation. This finding shows that the posterior parietal cortex plays a relevant role only in the very early phase of preparation of memory-guided saccades.

Posterior cingulate activation was also observed, in agreement with the suggestion of a role of this area in spatial-oculomotor integration (Olson and Musil 1992; Olson et al. 1992). Mesulam and co-workers (Mesulam 1981; Morecraft et al. 1993) described extensive neural connectivity within an attentional cingulo-fronto-parietal network. The finding of a bilateral activation of the posterior cingulus in the antisaccadic task suggests that this area conveys spatial information elaborated by the parietal lobes to anterior motor areas triggering antisaccades.

Fixation task

The Fixation task, when compared with both oculomotor conditions, was associated with activation of multiple cortical and subcortical regions. This could reflect a genuine activation during fixation or a deactivation during the oculomotor task and is thus difficult to interpret.

Petit et al. (1995) recently documented activation of the *FEFs* during fixation of an imagined visual target and hypothesized that this activation is the consequence of the activity of both fixation neurons (Suzuki and Azuma 1977; Bruce and Goldberg 1985; Bon and Lucchetti 1992; Schlag et al. 1992; Lee and Tehovnik 1995) and working memory neurons located in BA 6 near the FEFs (Jonides et al. 1993). The absence of a detectable activation of the FEFs in the comparisons between the Fixation task and each of the other two tasks in the present study could be due to comparable levels of activation of the fixation-related areas during the three tasks. The fact that the central fixation point was always visible might have facilitated maintenance of fixation, activating a significantly smaller set of frontal working memory neurons compared, for example, with the more difficult imaginative condition studied by Petit and coworkers. Furthermore, as also noted by Petit et al. (1995), fixation neurons might not be the largest group of neurons in the

FEFs. In the monkey, Bruce and Goldberg (1985) found that less than 10% of the neurons had fixation-related activity, whereas more than 70% had saccadic-related activity. If similar proportions are maintained in the neuronal composition of human FEFs, the larger activation of neurons involved in the motor programming of antisaccades could have obscured the activation of the smaller set of fixation neurons in the Antisaccadic and Fixation comparison. For a similar reason, it could be hypothesized that in the Fast-regular task only a limited number of frontal motor neurons were active (see activation profiles, Fig. 3b). The smaller frontal activations found in the Fixation and Fast-regular task, respectively, linked to the maintenance of fixation and the production of saccades, cancelled out each other in the Fast-regular saccadic and Fixation comparison and Fixation and Fast-regular saccadic comparison.

The finding of a strong activation of the *caudate* during the Fixation task seems quite paradoxical. The caudate nucleus inhibits the substantia nigra, which, in turn, exerts an inhibitory influence on the superior colliculi (Hikosaka and Wurtz 1989). The final effect of caudate activity is thus the increase (and not a fixation-related inhibition) of the presaccadic collicular responses. However, it has been recently documented that a population of "fixation" neurons in the rostral pole of the superior colliculi increase their firing during maintenance of fixation (Wurtz and Optican 1994) and that collicular cells with foveal receptive fields engaged at central fixation increase their discharge when peripheral cues are presented (Robinson and Kertzman 1995). It could be hypothesized that caudate activation is functionally related to the activity of fixation collicular neurons.

Conclusions

The results of this PET study provide in vivo evidence for two separate networks of cerebral structures engaged in different oculomotor tasks. Fast-regular saccades are associated with a predominant activation of the posterior occipitotemporal cortex, whereas the performance of voluntary antisaccades engages prefrontal and parietal areas. These findings provide indirect support for a predominant subcortical (probably collicular) regulation of fast reflexive oculomotor responses and further direct evidence for the involvement and the coactivation of parietal and prefrontal areas (Goldman-Rakic 1988) in tasks requiring spatial and/or instructional working memory. Importantly, the results of the present study suggest that the operation of attentional disengagement (whether coupled or coincident with the transformation and recomputation of a previously selected saccadic vector) is localized in the inferior parietal lobes, supporting the hypothesis advanced by Corbetta and coworkers (1993). This evidence should provide a useful clue for future research aimed at clarifying the neural mechanisms subserving covert attentional orienting in humans.

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