

Cortical control of saccades and fixation in man

A PET study

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Summary

To identify cortical regions activated during saccades and visual fixation, regional cerebral blood flow (rCBF) was measured in eight healthy subjects using $C^{15}O_2$ PET during the performance of three tasks: (i) central fixation; (ii) reflexive saccades to random targets; (iii) remembered saccades to locations of recent target appearance. Significant rCBF increases were identified using analysis of covariance and the *t* statistic ($P < 0.001$). Compared with central fixation there was activation of striate and extra-striate cortex, posterior parietal cortex (PPC) and frontal eye fields (FEF) during both reflexive and remembered saccades. During

remembered saccades there was additional activation of supplementary motor area (SMA), insula, cingulate, thalamus, midbrain, cerebellum and right superior temporal gyrus (Brodmann's area 22). Compared with the individual saccadic tasks, central fixation activated extensive regions of ventromedial (areas 10, 11 and 32) and anterolateral (areas 8, 9, 10, 45 and 46) prefrontal cortex, and foveal visual cortex. We conclude that FEF and PPC are associated with the generation of both reflexive and remembered saccades, with SMA additionally involved during remembered saccades. Sustained voluntary fixation is mediated by prefrontal cortex.

Key words: saccades; PET; oculomotor control; frontal eye field; supplementary motor area

Introduction

Saccades, other than the quick phases of nystagmus, are triggered by structures within the cerebral hemispheres. Animal studies, and observations following cerebral ablations in man, suggest that saccades performed under different behavioural circumstances are controlled by different cortical and subcortical oculomotor regions (for review, see Pierrot-Deseilligny, 1990). Such areas have been located in the frontal lobes, frontal eye field (FEF) (Bruce and Goldberg, 1985; Godoy *et al.*, 1990), supplementary motor area (SMA) (Schlag and Schlag-Rey, 1987; Fried *et al.*, 1991), dorsolateral prefrontal cortex (Funahashi *et al.*, 1989, 1991; Pierrot-Deseilligny *et al.*, 1991*b*), the posterior parietal cortex (PPC), particularly the inferior parietal lobule (Gnadt and Andersen, 1988; Andersen *et al.*, 1990; Barash *et al.*, 1991*a*; Pierrot-Deseilligny *et al.*, 1991*b*), the basal ganglia (Hikosaka and Wurtz, 1985; Lasker *et al.*, 1988; Crawford *et al.*, 1989; Hikosaka *et al.*, 1989*a,b*) and superior colliculus (Schiller *et al.*, 1980; Pierrot-Deseilligny *et al.*, 1991*c*).

Positron emission tomography offers the unique opportunity for examining cerebral function during saccadic performance in the awake, intact human subject, so

contributing to our understanding of the specific roles of these different cortical areas in their generation. There have been a limited number of studies reporting changes in regional cerebral blood flow (rCBF) during various saccadic tasks in man (Melamed and Larsen, 1979; Fox *et al.*, 1985; Petit *et al.*, 1993*a,b*). In none of these studies has a pure reflexive (random) visually guided paradigm been utilized and compared with other volitional saccadic paradigms. The aim of this present study was to identify and contrast the cortical and subcortical regions which participate in the control of reflexive visually guided saccades, single remembered visually guided saccades and central fixation.

Methods

Subjects

Eight right-handed normal male volunteers aged 22–36 years were studied. All gave informed consent and the project had the approval of the Hammersmith Hospital Ethics Committee, and the Administration of Radioactive Substances Advisory Committee of the Department of Health (UK). All subjects,

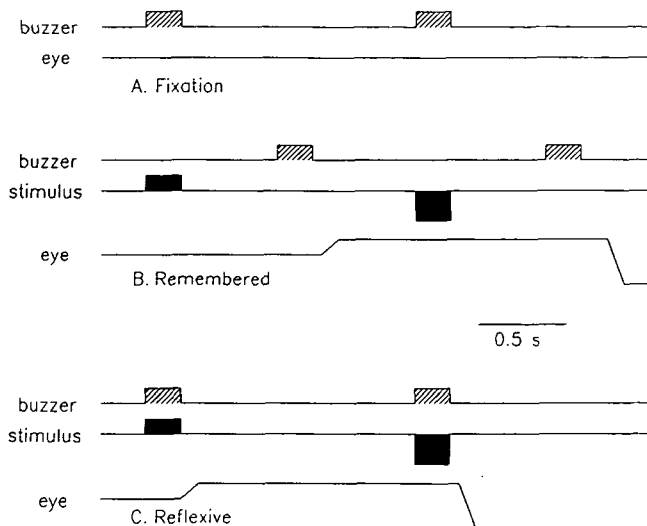


Fig. 1 Schematic representation of the paradigms. **(A)** Fixation: the subject continually fixates a dim central LED stimulus. A buzzer sounds at random intervals between 1400 and 1600 ms (mean, 1500 ms). **(B)** Remembered: the subject withholds making a saccade to a peripheral LED stimulus until the buzzer sounds and then maintains gaze at the new location until the next saccade. **(C)** Reflexive: the subject makes saccades to a peripheral LED stimulus coincident with the buzzer sounding and maintains gaze at the new location (in the dark) until the next stimulus.

excepting one, were naive to oculomotor recordings, and none were exposed to the saccadic paradigms prior to a brief practice session immediately before the procedure.

Tasks

Six sequential rCBF measurements were obtained at 15 min intervals from each subject as they performed saccadic eye movements. Blocks of three different paradigms (Fig. 1), one central fixation (A) and two saccadic-remembered (B) and random (C)-were presented in palindromic order (ABCCBA) to negate fatigue or habituation effects.

A horizontal light bar was mounted 60 cm in front of the subject. Thirteen 3 mm red light-emitting diode (LED) targets were embedded at 5° intervals within the bar. Thus, on either side of a central diode were diodes at 5, 10, 15, 20, 25 and 30° eccentricity to the subject's central gaze position. There was an additional low luminance central diode for fixation. The experiments were carried out in complete darkness. A buzzer was located centrally above the subject's head and was always sounded for 200 ms, at intervals varying from 1.4 to 1.6 s (mean 1.5 s). Stimulus presentation was controlled by microcomputer. Each block was initiated 25 s after the start of each scan, and 5 s before the administration of tracer.

Paradigm A, fixation (Fig. 1)

Subjects were instructed to maintain fixation upon the central dim target (diode) which was constantly illuminated for

3.6 min, and ignore the buzzer. No peripheral LED stimuli were presented.

Paradigm B, remembered saccades (Fig. 1)

Subjects made saccades to a recent, briefly presented peripheral target (duration 200 ms). They were instructed to withhold making a saccade to the target location until the buzzer sounded 400–600 ms (mean 500 ms) after target offset. They then had to make a saccade to the remembered location of the target and hold gaze at this location until the next saccade. This meant that gaze was held during this phase in the absence of the target.

Paradigm C, reflexive saccades (Fig. 1)

Subjects made immediate saccades to a briefly presented peripheral target (duration 200 ms) coincident with the buzzer sounding. They were then instructed to hold gaze at this location in the absence of the target until the next saccade.

Each block of paradigms B and C consisted of a total of 144 sequential trials. The order of peripheral LED illumination, which could be any one of the 13 LEDs, identical in both paradigms, was pseudo-random, eliciting equal numbers of saccades of 5, 15 and 25° amplitude, leftwards and rightwards. The interval between successive saccadic stimuli varied randomly from 1400 to 1600 ms (mean 1500 ms).

Oculomotor recordings

Eye movements were monitored using routine electro-oculography with bitemporal electrode placement and recorded on a chart recorder. The purpose of these recordings was to assess the reliability of task performance rather than analyse saccadic metrics in detail.

Data acquisition

The scans were performed with an ECAT 931-08/12 PET scanner (CTI Inc. Knoxville, Tennessee, USA), the physical characteristics of which have been described elsewhere (Spinks *et al.*, 1988). Fifteen parallel transaxial scan planes of data were collected within a total axial field of view of 10.5 cm. Radiation attenuation by the head and head holder was corrected using a transmission scan obtained during exposure of a ⁶⁸Ge/⁶⁸Ga external ring source. Scans were reconstructed with a Hanning 0.5 filter giving a transaxial image resolution of 8.5 mm full width at half maximum. The reconstructed images contained 128×128 pixels, each of 2.05×2.05 mm. The subject's head was immobilized in a head holder constructed with thermally moulded foam.

During each scan, subjects continuously inhaled ¹⁵O-labelled CO₂ at a concentration of 6 MBq/ml and a flow rate of 500 ml/min through a standard oxygen face mask for a period of 2 min. Dynamic PET scans were collected over

3.5 min starting 0.5 min before $C^{15}O_2$ delivery (to obtain background radiation levels). Each activation task started 5 s before administration of the isotope. During scanning the arterial blood activity was measured continuously at 1 s intervals via a cannula sited in the left radial artery. Blood time–activity curves were corrected for delay and dispersion (Lammertsma *et al.*, 1990).

Data analysis

Calculations and image matrix manipulations were performed in PROMATLAB (Mathworks Inc., Sherborn, Massachusetts, USA) on SUN 3/60 and Sparc2 computers with software for image analysis (statistical parametric map; MRC Cyclotron Unit, UK: ANALYZE; Biodynamic Research Unit, Mayo Clinic, Minnesota, USA).

The 15 original axial planes (interplanar distance 6.75 mm) were linearly interpolated to 43 planes to render voxels approximately cubic (2 mm diameter). All scans were converted to rCBF images, by a dynamic/integral method using the corrected blood time–activity curves, to calculate rCBF from the activity recorded during the 2 min of administration of the isotope (Lammertsma *et al.*, 1990).

The intercommissural line was identified directly on each PET rCBF image, which was then reoriented and rescaled to fit a standard stereotactic space as defined in the brain atlas of Talairach and Tournoux (1988) resulting in 26 planes of data parallel to the AC–PC line (effective interplanar distance 4 mm; Friston *et al.*, 1989). These slices were resampled in a non-linear fashion to account for non-linear differences in brain shape (Friston *et al.*, 1991a). Each image was then smoothed with a Gaussian filter of 2 cm diameter to compensate for intersubject gyral variability and to attenuate high frequency noise, thus increasing the signal to noise ratio.

Differences in global blood flow between subjects and conditions were removed by an analysis of covariance with global flow as the confounding variable (Friston *et al.*, 1990). This process resulted in the generation of a map of group mean blood flow for each condition. The pixel values of rCBF in these maps, together with the associated adjusted error variances were used for further statistical analysis. Pixel means across conditions were compared using the *t* statistic. The resulting set of values constitutes a statistical parametric map [SPM(*t*)] (Friston *et al.*, 1991b).

The significance of these statistical parametric maps in a statistical sense was assessed by comparing the expected and observed distribution of the *t* statistic under the null hypothesis of no activation effect on rCBF. Only comparisons which were significant in this omnibus sense at $P < 0.001$ or better are reported. These significant areas were displayed on coronal, sagittal and transverse views of the brain. This statistical threshold has been validated by applying the same methodology to scans obtained from ‘phantoms’ containing pockets of radioactivity, correctly identifying changes in

activity of 2.5% or more with no false positives (Bailey *et al.*, 1991).

The following comparisons were made between conditions: reflexive saccades (C) versus fixation (A); remembered saccades (B) versus fixation (A); remembered saccades (B) versus reflexive saccades (C). The inverse comparisons were made to detect areas of significant activation, i.e. reflexive saccades (C) versus remembered saccades (B); fixation (A) versus reflexive saccades (C); fixation (A) versus remembered saccades (B).

Percentage rCBF increases, which were measured from the normalized condition specific maps, were calculated for the pixel with greatest significance of change for each separate activation peak. These values represent the mean activation from a spherical region, of 2 cm in diameter, centred on that pixel. The location of such maxima was identified with reference to the atlas of Talairach and Tournoux (1988). These were measured from the normalized condition specific maps.

Results

The fixation task was well performed, with fewer than five extraneous saccades off the target per subject. Most subjects volunteered, however, that they found this task difficult, having a frequent ‘urge’ to take the eyes away from the target, requiring ‘an act of will’ to hold fixation. Some reported the occasional illusory motion of the target, particularly towards the end of the paradigm. It was thus apparent that fixation was not a passive activity. During the remembered saccade paradigm the mean error rate (premature reflexive saccades, anticipatory saccades or missed saccades) was 20% (range 1–46%). The mean error rate (anticipatory or missed saccades) was 8% (range 1–19%) during the reflexive paradigm.

The PET results will be presented in sections defined by the task comparisons: (i) *saccadic tasks*, in which fixation is treated as the control condition and (ii) *fixation task*, in which the saccadic tasks are the reference conditions. Numerated brain areas in the text relate to Brodmann’s classification (1909). Those areas delineated in Figs 2–5 are denoted in the text by the same lower case bracketed letters.

Saccadic tasks

Reflexive versus fixation (Table 1)

Significant activation was seen in striate and extra-striate cortex (Fig. 2A). The striate activity (c) was bilateral and involved medial area 17, in the region which contains the peripheral visual field representation in the primary visual cortex. Medial extra-striate (areas 18 and 19) were also activated (c), particularly above (dorsal) but also below (ventral) the striate focus. There was also bilateral activation of the parietal lobes in the region of area 7 (e), and of areas in the frontal lobes which lie in the posterior bank of the precentral gyrus and which we attribute to FEF activation (a).

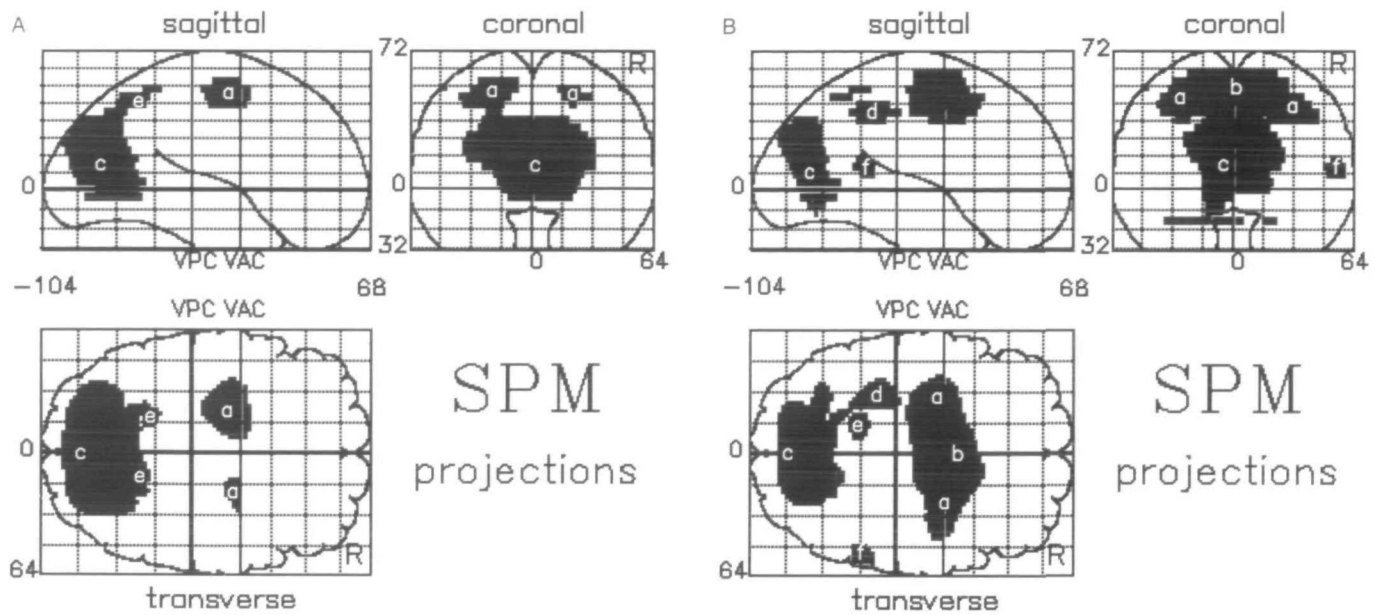


Fig. 2 Comparison of adjusted mean rCBF in eight subjects between reflexive saccades and fixation (A) and remembered saccades and fixation (B). The results are displayed as statistical parametric maps in three projections, sagittal, coronal and transverse. The grid is the stereotactic grid of Talairach and Tournoux (1988) into which all subjects' brains have been scaled. The horizontal intercommissural line (AC–PC line) is set at zero, as is the vertical projection through the anterior commissure (VAC line). An additional vertical line through the posterior commissure (VPC line) is depicted on the transverse and sagittal projections. Distances are in millimetres above (+) and below (–) the AC–PC line, anterior (+) and posterior (–) to the VAC line, and to the right (+) and left (–) of the midline. The pixels show levels of significance above a threshold of $P < 0.001$ (omnibus). Striate and extra-striate (mostly dorsal) cortical activation is seen in both comparisons. Reflexive saccades in comparison with fixation (A) showed significant activation of area 7 and FEF bilaterally. Remembered saccades compared with fixation (B) were associated with significant activation of left area 7, left area 40, right area 22, cerebellum, bilateral FEF and SEF. The lower case letters in this and subsequent figures refer to the following cerebral structures: a, FEF; b, SEF; c, peripheral striate and extra-striate cortex; d, area 40; e, area 7, PPC; f, area 22; g, cerebellum; h, mediodorsal thalamus and midbrain; i, insula/area 47; j, foveal striate and extra-striate cortex; k, hippocampus; m, anterior frontal lobe areas 9, 10, 45 and 46; n, areas 24 and 32 (cingulate); o, area 47, orbitofrontal.

Table 1 Comparison of reflexive saccades with fixation: foci of significant rCBF increases

Area activated	Extent of area activated (relative to AC–PC line)	Talairach coordinates of peak activation (x, y, z)	Z-score of peak activation	Percentage change in rCBF
<i>(a) Relative increases in rCBF</i>				
Anterior 17/18/19 (left)	–4 to +32 mm	–14, –76, +28	6.46	4.4
Anterior 17/18/19 (right)	–4 to +32 mm	+14, –76, +24	7.18	5.8
Area 7 (lateral left)	+32 to +52 mm	–18, –68, +36	3.78	2.6
Area 7 (lateral right)	+36, +44 to +48 mm	+2, –74, +36	4.14	3.5
Frontal eye field (left)	+44 to +56 mm	–24, –6, +52	5.7	5.1
Frontal eye field (right)	+48 to +52 mm	+20, –2, +52	3.53	3.2
<i>(b) Relative decreases in rCBF</i>				
Area 47 (left)	–12, –4 to 0 mm	–34, +18, –12	3.56	3.1
Area 47 (right)	–16 to 0 mm	+38, +20, –8	5.3	3.5
Posterior 17/18/19 (left)	–12 to +4 mm	–26, –92, –4	4.99	5.9
Posterior 17/18/19 (right)	–12 to +8 mm	+26, –92, 0	6.72	7.6
Prefrontal (left)	0 to +40 mm	–22, +44, +36	4.2	4.3
Prefrontal (right)	+16 mm	+18, +52, +16	3.12	2.8
Rostral cingulate 24/32	–4 to 0, +12 to +28 mm	–4, +42, +16	3.68	3.1

Remembered versus fixation (Table 2)

Significant striate and extra-striate activation, similar to that found in the reflexive versus fixation comparison, was

observed (Fig. 2B). Only significant activation in left, as opposed to right, parietal area 7 activation was found (e), although bilaterally increased cerebral blood flow in area 7

Table 2 Comparison of remembered saccades with fixation: foci of significant rCBF increases

Area activated	Extent of area activated (relative to AC-PC line)	Talairach coordinates of peak activation (x, y, z)	Z-score of peak activation	Percentage change in rCBF
<i>(a) Relative increases in rCBF</i>				
Cerebellum (left)	-16 mm	-26, -64, -16	3.47	3.7
Cerebellum (right)	-16 mm	+20, -60, -16	3.35	2.9
Cerebellum (vermis)	-12 to -8 mm	-10, -66, -8	3.39	2.8
Anterior 17/18/19 (left)	-4 to +32 mm	-12, -76, +28	5.45	4.6
Anterior 17/18/19 (right)	0 to +32 mm	+12, -74, +24	5.95	4.9
Area 22 (right)	+8 to +16 mm	+54, -40, +12	3.58	2.5
Area 7 (medial)	+36, +48 to +52 mm	-14, -44, +52	3.81	3.6
Area 7 (lateral left)	+48 mm	-18, -56, +48	3.27	3.1
Area 40 (left)	+36 to +44 mm	-30, -34, +40	3.65	4.4
Caudal cingulate 24/32	+36 to +44 mm	-12, +4, +44	5.77	5.7
Frontal eye field (left)	+40 to +56 mm	-18, -2, +52	7.18	8.7
Frontal eye field (right)	+36 to +56 mm	+22, +2, +48	5.12	5.4
Supplementary motor area	+48 to +60 mm	-10, -2, +60	5.81	5.4
<i>(b) Relative decreases in rCBF</i>				
Hippocampus (left)	-16 to 0 mm	-34, -32, -12	5.3	4.6
Hippocampus (right)	-16 mm	+28, -22, -16	3.61	3.1
Posterior 17/18/19 (left)	-12 to +8 mm	-20, -96, -4	6.54	8.7
Posterior 17/18/19 (right)	-12 to +12 mm	+26, -92, 0	7.79	11.0
Prefrontal (left)	-12 to +52 mm	-22, +42, +36	5.36	5.6
Rostral cingulate 24/32	-8 to 0 mm	-4, +36, -8	4.46	4.0

Table 3 Comparison of remembered saccades with reflexive saccades: foci of significant rCBF increase

Area activated	Extent of area activated (relative to AC-PC line)	Talairach coordinates of peak activation (x, y, z)	Z-score of peak activation	Percentage change in rCBF
<i>(a) Relative increases in rCBF</i>				
Cerebellum (left)	-16 mm	-34, -62, -16	3.19	2.9
Cerebellum (right)	-16 mm	+24, -62, -16	3.21	2.3
Midbrain/thalami	-8 to +4 mm	-2, -16, 0	3.92	2.7
Insula (left)	0 to +4 mm	-36, +6, 0	3.2	2.7
Insula/area 47 (right)	-12 to 0 mm	+38, +14, -8	4.86	3.1
Striatum (right)	+4 mm	+28, -6, +4	3.52	2.5
Caudal cingulate 32	+40 to +44 mm	-8, +4, +44	4.52	3.6
Supplementary motor area	+48 to +60 mm	-10, +4, +52	4.83	4.2
<i>(b) Relative decreases in rCBF</i>				
Hippocampus (left)	-16 to -4 mm	-38, -32, -12	4.48	3.4
Area 17 (occipital pole)	0 to +12 mm	+22, -94, 0	3.35	3.2

occurred. Left parietal area 40 was also activated (d), as was right area 22 (superior temporal gyrus/sulcus) in temporal lobe (f).

As in reflexive versus fixation, the FEF were activated bilaterally, but there was additional activation of SMA (b) and the adjacent cingulate gyrus (area 24/32). Although the cerebellum was only partially sampled due to the field of view of the camera, significant activation occurred bilaterally in the superior cerebellar hemispheres and vermis.

Remembered versus reflexive (Table 3)

There was relative activation of bilateral SMA and adjacent anterior cingulate in remembered compared with reflexive

(Fig. 3A). Relative activation was also detected in insular cortex bilaterally (i), the mediodorsal thalamus and central midbrain (h), and in both cerebellar hemispheres (g).

Reflexive versus remembered (Table 3)

In this comparison (Fig. 3B), there was relative bilateral activation of the occipital pole (j) and left mesial temporal structures (k).

Fixation task

Fixation versus reflexive (Table 1)

This comparison (Fig. 4A) showed significant activation of lateral, rather than medial occipital areas 18 and 19 (j). In

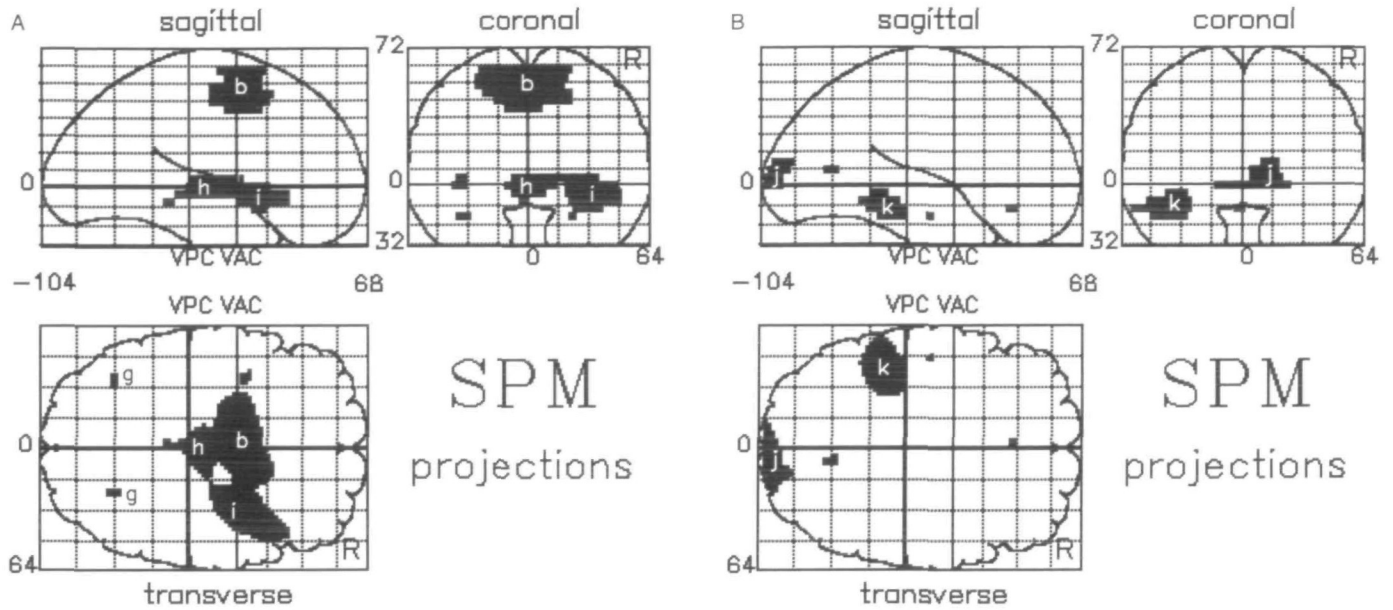


Fig. 3 Mean rCBF comparisons for saccades. (A) Remembered versus reflexive saccades: this comparison shows significant activity in cerebellum, thalamus, midbrain, bilateral insulae and SEF. (B) Reflexive versus remembered saccades: this comparison reveals foveal striate and extra-striate (for explanation *see* text), and left hippocampus activation.

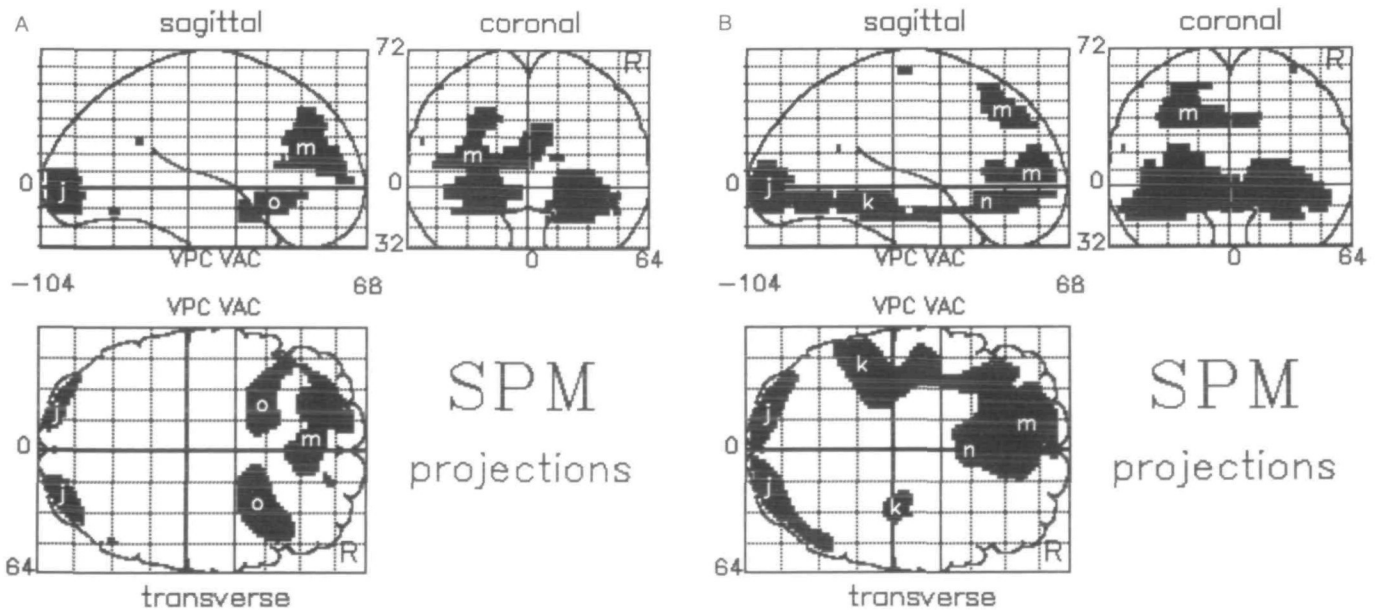


Fig. 4 Mean rCBF comparisons for fixation. (A) Fixation versus reflexive saccades: this comparison shows significant activity of foveal striate and extra-striate cortex, and frontal areas 47, 9, 10, 45 and 46. (B) Fixation versus remembered saccades: similar findings, with foveal striate and extra-striate, hippocampus, cingulate (areas 24/32) and anterior frontal regions 9, 10, 45 and 46.

this comparison the occipital pole was not differentially activated.

In the frontal lobes there was bilateral inferolateral activation in areas 47 (o), 9, 10, 45 and 46 (m), and anterior cingulate (area 32).

Fixation versus remembered (Table 2)

Occipital lobe activation was similar to that described above for the fixation versus reflexive comparison apart from two additional features. First, bilateral foveal cortical activity (j) extended to the extreme occipital pole (Fig. 4B). Secondly,

extensive activation was found in the inferomedial left temporal lobe (k)—areas 20, 36 and 37, in the region of the hippocampus—and in area 21. A similar smaller focus was also found in right inferior temporal lobe (k).

Similar, but more extensive prefrontal activation (m) was seen in comparison with fixation versus reflexive, also involving anterior cingulate (n).

Discussion

Current views on the cerebral structures and pathways thought to be involved in the control of human saccades and fixation are based on recording, stimulation and lesion work in monkeys, and on observations following ablations in man. It has been proposed that reflexive (visually guided) saccades are triggered primarily by the PPC and secondarily by FEF, with inhibition of such saccades by the prefrontal cortex. Single remembered saccades are thought to be controlled by three successive regions, the PPC (visuospatial integration), dorsolateral prefrontal cortex (memorization and decision) and FEF (triggering) (Pierrot-Deseilligny, 1990).

The findings of the present study, using PET in intact normal human subjects, are broadly consistent with this schema, although no activation of the dorsolateral prefrontal cortex was found during remembered saccades. New observations include evidence for SMA, insula, superior temporal gyrus/sulcus, and thalamic activation specific to single remembered saccades. The present findings also provide evidence that active fixation is mediated by extensive areas of ventromedial and anterolateral frontal cortex. Additional observations on the location of foveal and extra-foveal striate cortex activation support the recent revision (based on patho-anatomical data) of the classic Holmes map (Horton and Hoyt, 1991).

Reflexive visually guided saccades

This study suggests a relatively simple cortical network controlling horizontal visually guided reflexive saccades, comprising striate, extra-striate, PPC and FEF.

There was bilateral activation in the posterior frontal lobes in the region of the precentral and middle frontal gyri. Similarly localized activation during voluntary saccades has been observed in other PET studies (Fox *et al.*, 1985; Mazoyer *et al.*, 1991; Petit *et al.*, 1993a,b). This area, therefore, appears to represent the FEF, and co-registration of PET and MRI data has confirmed localization in the precentral gyrus (Petit *et al.*, 1993a). The FEF has reciprocal projections to extra-striate, cingulate, superior temporal polysensory area, lateral intraparietal area, area 46, as well as to subcortical structures which include thalamus (medial dorsal and ventrolateral), striatum, superior colliculus and brainstem saccade generation areas (Barbas and Mesulam, 1981; Stanton *et al.*, 1988a,b). It is thought to be involved in the generation of many types of saccades, including both reflexive and remembered saccades (Bruce and Goldberg,

1985). In man, electrical stimulation of this area elicits contralateral saccades (Godoy *et al.*, 1990) and lesions impair remembered saccades (Pierrot-Deseilligny *et al.*, 1991a). Although lesions of the FEF do not result in any enduring impairment of reflexive saccades (Pierrot-Deseilligny *et al.*, 1991b), its prominent activation in this study suggests that in the intact state it does indeed have an important role. It seems likely that this role may be assumed by other areas (e.g. posterior parietal cortex) as an adaptive response within a short time after injury.

The present study demonstrated posterior parietal activation during saccades, which has only previously been identified in one other study using a remembered saccade paradigm (Petit *et al.*, 1993b). In our study the activation location (some 20 mm lateral to the midline) was medial to the intraparietal sulcus and so we cannot be certain that it represents the human equivalent of lateral intraparietal area, a region in monkeys in the inferior parietal lobe important in the processing of saccades (Andersen *et al.*, 1990; Barash *et al.*, 1991a,b).

Remembered saccades

The generation of single remembered saccades clearly involved more extensive recruitment of cortical and subcortical structures than was the case for reflexive saccades.

In addition to the same posterior parietal and FEF involvement, there was activation of the medial frontal lobe, in the region of the SMA. The location of this activity (−2 to +4 mm in relation to VAC) was immediately anterior to the location of upper limb SMA activation reported by Colebatch *et al.* (1991). This finding accords with studies in the monkey in which contraversive saccades have been evoked by microstimulation of an area in superior medial frontal lobe immediately rostral to the SMA and termed the 'supplementary eye field' (SEF) (Schlag and Schlag-Rey, 1987), and with human stimulation studies (Fried *et al.*, 1991) in which contraversive eye movements were elicited by electrical stimulation of the anterior SMA.

Previous PET studies of visually guided (Fox *et al.*, 1985) and non-visually guided self-paced saccades (Petit *et al.*, 1993a) have also reported SMA activation. We did not observe SMA activation during the performance of visually guided reflexive saccades in contrast to the study of Fox *et al.* (1985). It should be noted, however, that the saccadic paradigms in that study differed from those in the present study. In particular, in contrast to our reflexive paradigm, saccades were made back and forth between only two laterally placed targets which would therefore have been spatially predictable and/or remembered. Thus the stimuli cannot be regarded as truly reflexive. This feature may, therefore, have required a degree of internal generation of saccades and thereby favoured the recruitment of SMA.

The SEF (Schlag and Schlag-Rey, 1987) has connections with areas which include 7a, 7m, lateral intraparietal area, superior temporal polysensory area, FEF, cingulate, thalamus,

striatum and superior colliculus, as well as with saccade generating areas of the brainstem (Cavada and Goldman-Rakic, 1989a,b; Andersen *et al.*, 1990; Huerta and Kaas, 1990). Like the FEF, neurons in the SEF are active during reflexive and delayed saccades but not unrewarded spontaneous saccades (Schall, 1991a,b). In comparison with the FEF, however, preparatory set cells are more numerous in the SEF, implying that the SEF regulates initiation of a saccade which has been targeted by the FEF (Cavada and Goldman-Rakic, 1989a,b). Recruitment of SEF may be related not only to the timing but also to the degree of willed effort or self-generation required in saccade production, whereas FEF may be equally engaged in volitional and externally cued saccades (Schlag and Schlag-Rey, 1987). The findings of SEF activation during remembered but not reflexive saccades in this study are consistent with both these proposed roles. In two patients with lesions of the SMA there was no impairment of the performance of a single remembered (or reflexive) saccade, although the performance of sequences of remembered saccades was impaired (Gaymard *et al.*, 1990).

Caudal anterior cingulate activation adjacent to SMA was observed during the performance of remembered saccades, as has also been reported by Petit *et al.* (1993b). This region is sensitive to operations involving target detection (Skelly *et al.*, 1989) and the same cingulate area is activated by divided visual attention tasks in which memory demands are prominent (Corbetta *et al.*, 1991). In monkeys the area has been shown to be involved in various behavioural functions involving the eyes, face and hands (Showers, 1959), and to contain neurons with various oculomotor properties (Musil *et al.*, 1990). Since in monkeys, connections exist between this area and various cortical oculomotor areas including the FEF, SMA and PPC (Robinson *et al.*, 1978; Bruce and Goldberg, 1985; Schall, 1991a,b), all of which contain neurons which fire more intensely when a stimulus has behavioural significance, we believe that cingulate activation in this study may represent facilitation of spatial memory and motivation during the delay period.

As mentioned earlier we failed to observe activation of the dorsolateral prefrontal cortex in the remembered paradigm when compared with either the reflexive or fixation paradigms, despite clinical studies which have suggested that it plays a role in the inhibition of unwanted reflexive saccades (Guitton *et al.*, 1985; Pierrot-Deseilligny *et al.*, 1991b), or animal studies which have indicated involvement in short-term spatial memory (Funahashi *et al.*, 1989). This absence of activation in the comparisons of paradigms may have been due to the presence of common activation of dorsolateral prefrontal cortex during the different paradigms, or to specific details of the remembered paradigm. During the reflexive paradigm there would have been some degree of fixation by the subjects due to the foveation of the target before it was extinguished, which may have resulted in some dorsolateral prefrontal cortex activation as was clearly found during the fixation paradigm itself. If a dorsolateral prefrontal cortex

function is short-term spatial memory the relatively short delay period (500 ms) used in the remembered paradigm may not have produced very much activation. A combination of these various factors, therefore, may have led to 'cancelling out' of small amounts of dorsolateral prefrontal cortex activation common to both the reflexive and remembered paradigms.

The region of increased activation in the right caudal superior temporal sulcus or gyrus (area 22) may be equivalent to the superior temporal polysensory area of the monkey. A similar location of activation has been observed during selective attention to stimulus motion (Corbetta *et al.*, 1991). Nearly all neurons in the superior temporal polysensory area are visually responsive and the caudal (posterior) segment of superior temporal sulcus in the monkey has connections with important oculomotor regions including frontal areas 6, 8 and 46 (Seltzer and Pandya, 1989), the superior colliculus (Lobeck *et al.*, 1983) and parietal areas 7a, 7m and lateral intraparietal area (Cavada and Goldman-Rakic, 1989a). Lesions of this area (in monkeys) impair the ability to orient the eye and head to visual stimuli (Luh *et al.*, 1986) and to make saccades to peripheral visual targets (Skelly *et al.*, 1989).

Bilateral insula cortical activation occurred during remembered saccades in comparison with reflexive saccades. Right insula activation with PET has been reported during the performance of large amplitude self-paced saccades in the dark (Petit *et al.*, 1993a) and during selective visual attention (Corbetta *et al.*, 1991). Contralateral insula activation has also been reported during voluntary limb movements (Chollet *et al.*, 1991; Colebatch *et al.*, 1991) whilst electrical stimulation in monkeys produces motor activity, particularly of facial muscles (Showers and Lauer, 1961) and eye movements (Sugar *et al.*, 1948). All these features suggest that the insula is a secondary motor area which is activated in paced stereotyped tasks.

The insula has reciprocal projections to limbic structures including cingulate and hippocampus, as well as to superior temporal sulcus, orbitofrontal cortex, area 46 and many thalamic areas, including the mediodorsal nuclei (Mesulam and Mufson, 1985). Taking into consideration these connections, the present findings suggest a role for the insula in spatial attention, memory or motivational aspects of oculomotor control.

There was a relative decrease in hippocampal activity during the performance of remembered saccades compared with fixation, a prominent focus of activation being observed in the left inferomedial temporal lobe, encompassing the hippocampus/parahippocampal gyrus, with a similar but less marked focus on the right. The same area was relatively activated during reflexive compared with remembered saccades. In the monkey, the hippocampus has a role in spatial memory (O'Keefe and Dostrovsky, 1971; Watanabe and Niki, 1985; Riches *et al.*, 1991) as well as in the motivational and meaningfulness attributes of visual stimuli (Riches *et al.*, 1991; Vidyasagar *et al.*, 1991). The

hippocampus has connections with insula, cingulate and orbitofrontal cortex, as well as to ventral lateral intraparietal area (Blatt *et al.*, 1990), 7a, 7m (Cavada and Goldman-Rakic, 1989a) and area 46 (Selemon and Goldman-Rakic, 1988). Thus, along with insula and cingulate, change in hippocampal regional blood flow in the context of remembered saccades may reflect a role in spatial memory and motivation.

Bilateral superior cerebellar hemisphere and vermis activation during remembered compared with reflex saccades was observed, and because the full extent of activation in this structure was limited by the field of view of the camera we are unable to comment further on this observation.

Increased relative mediodorsal thalamic activation occurred during remembered when compared with reflexive saccades. Thalamic activity has also been reported during self-paced and remembered saccades (Petit *et al.*, 1993a,b). In monkeys, saccade-related neurons have been recorded in this thalamic area (Schlag-Rey and Schlag, 1984) which is a site of convergence/relay of the various limbic (Vogt *et al.*, 1979; Ilinsky *et al.*, 1985; Mesulam and Mufson, 1985), sensory association and oculomotor areas (Harting *et al.*, 1980; Ilinsky *et al.*, 1985; Selemon and Goldman-Rakic, 1988; Huerta and Kaas, 1990).

Activation of the FEF, thalamus and SMA may represent part of the cortico-basal ganglia-thalamo-cortical 'oculomotor' loop proposed by Alexander *et al.* (1986). Our failure to identify activation of the basal ganglia part of the loop, including the caudate nucleus and substantia nigra pars reticulata (Hikosaka and Wurtz, 1985; Hikosaka *et al.*, 1989a) may be due to limited sensitivity of the PET technique, or due to some aspect of the paradigm used to elicit saccades. In a PET study of self-paced saccades in which the subjects were instructed to make large amplitude, high-frequency saccades activation of the lentiform nucleus (putamen, globus pallidus) has been obtained (Petit *et al.*, 1993a).

During the performance of both the reflexive and remembered paradigms subjects sometimes made errors. In the reflexive paradigm these were mainly missed saccades with occasional anticipatory saccades (mean rate 8%), and in the remembered paradigm errors were either reflexive or missed saccades (mean rate 20%). Such errors in the remembered paradigm would have led to an overall reduction of activation in cortical areas associated with this task, and thereby made it less likely for true differences to reach significance in the comparison of remembered and reflexive paradigms. We do not consider, therefore, that such errors have led to erroneous attribution of specific areas of activation in these paradigms.

Fixation

A zone of predominantly left ventromedial frontal lobe extending from area 11 ventrally to areas 10 and 32 dorsally, including the anterior pole of the cingulate, was activated during fixation in comparison with saccades. Significantly, lesions in the same distribution in man result in impairment

of central fixation (Paus *et al.*, 1991). A further zone of left ventrolateral frontal lobe, encompassing lateral 9 and 10, anterolateral 8 and inclusive of areas 45 and 46 were also activated by fixation. In monkeys, area 46 contains 'attentive fixation' neurons (Suzuki and Azuma, 1977), and inhibitory neurons suppressing inappropriate saccades during remembered saccadic tasks (Funahashi *et al.*, 1989). In man, lesions damaging these areas may result in impaired fixation ability (Paus *et al.*, 1991).

Lateral orbitofrontal area (area 47) was only activated in a comparison of fixation with remembered saccades. Orbitofrontal cortex receives substantial input from limbic structures (Mesulam and Mufson, 1985) and has connections with frontal and parietal oculomotor areas (Selemon and Goldman-Rakic, 1988). It is of interest that (left) lateral orbitofrontal activation has also been recorded by others in a task requiring selective (in comparison with divided) attention to specific visual stimulus characteristics (Corbetta *et al.*, 1991). Bilateral lesions to orbitofrontal cortex in primates results in perseveration and interferes with the ability to make switches in behavioural set (Mishkin and Manning, 1978; Colby and Miller, 1986). Thus orbitofrontal cortex appears to participate in ongoing fixation probably by facilitating limbic (e.g. motivational and/or memory) input into oculomotor centres.

Striate and extra-striate cortex

The two saccadic paradigms activated medial striate cortex some 30–35 mm anterior to the occipital pole, and 10 mm above the AC–PC line. It is pertinent to note that the portions of retinae stimulated in the performance of these tasks were bilateral peripheral segments at 5–25° eccentricity along the horizontal meridian. The cortical sites activated accord with the known anatomy of human striate cortex in which the central 5° of visual field occupies approximately the posterior third and the peripheral 5–20° the middle third (Horton and Hoyt, 1991), and with the PET study of Fox *et al.* (1987).

Patho-anatomical data suggest that foveal representation in human striate cortex extends posteriorly and wraps around laterally out onto the occipital pole surface (Horton and Hoyt, 1991). Our finding of activation of this area—centred ~2.5 cm lateral to the midline—with a tiny foveal stimulus provides functional support of those findings. Some foveal stimulation clearly occurred during the reflexive task (i.e. some saccades were targeted within the 200 ms illumination period) as there was striate cortex activation at the occipital pole in the reflexive versus remembered comparison.

Extensive bilateral, predominantly dorsal, extra-striate occipital cortex regional blood flow increases were observed in medial areas 18 and 19 during performance of saccades. This zone probably includes the putative areas V2, dV3 and V3A in man (Clarke and Miklossy, 1990) and the human equivalent of monkey area PO (parieto-occipital) (Baizer *et al.*, 1991). The true locations and extent of these regions in man have not been confidently elucidated and we were

not able to discern discrete foci of cortical activation which might be ascribed to separate visual association areas.

Fixation (foveal) associated extra-striate responses were predominantly confined to lateral area 18 adjacent to the occipital pole. On the right there was extension of this activity ventrolaterally into occipito-temporal cortex (areas 19 and 37). These findings agree with earlier reports of fixation-related lateral visual association activation with PET (Fox and Raichle, 1984) and occipito-temporal area activation with intracarotid isotope cerebral blood flow studies (Melamed and Larsen, 1979).

Acknowledgement

This work was supported by the Wellcome Trust.

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Received September 15, 1993. Revised March 14, 1994.

Accepted April 24, 1994