

# The effect of spatial and temporal information on saccades and neural activity in oculomotor structures

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## Summary

It has been argued that saccade generation is supported by two systems, a 'where' system that decides the direction and extent of an impending saccade, and a 'when' system that is involved in the timing of the release of fixation. We evaluated the contributions of these systems to saccade latencies, and used functional MRI to identify the neural substrates of these systems. We found that advance knowledge of the direction and the timing of an impending target movement had both overlapping and discrete effects on saccade latencies and on neural activation. Knowledge of either factor decreased regular saccade latencies. However, knowledge of target direction increased the number of predictive and express saccades while knowledge of target timing did not. The brain activation data showed that advance knowledge of the direction or the timing of the target movement activated primarily overlapping struc-

tures. The precentral gyrus, in the region of the frontal eye fields, was more active in conditions in which some aspect of the target movement was predictable than in saccade control and fixation conditions. In the basal ganglia, activation discriminated between advance knowledge of target timing and target direction. The lenticular nuclei were more active when only target timing was known in advance, while the caudate was more active when only target direction was known in advance. These data suggest that the neural structures supporting the 'where' and 'when' systems are highly overlapping, although there is some dissociation subcortically. Knowledge of target timing and target direction converge in precentral gyrus, a region where there is strong evidence of context-dependent modulation of neural activity.

**Keywords:** saccades; predictability; frontal eye fields; supplementary eye fields; basal ganglia

**Abbreviations:** BOLD = blood-oxygen-level-dependent; CPT = completely predictable task; DPT = direction predictable task; FEF = frontal eye field; fMRI = functional MRI; MSEF = motor strip eye field; PEF = parietal eye field; SCT = saccade control task; SEF = supplementary eye field; TPT = timing predictable task; vPM = ventral premotor

## Introduction

It has been argued that saccade generation is supported by two systems, a 'where' system that decides the direction and extent of an impending saccade and a 'when' system that is involved in the timing of the release of fixation (e.g. Findlay and Walker, 1999). Psychophysical studies have suggested that the time to initiate a saccade can be reduced when advance knowledge is available to either of these two systems (Ross and Ross, 1981; Fischer *et al.*, 1984; Fischer and Ramsperger, 1986). When the direction of an impending target step can be predicted, saccade latency is reduced only when the target moves in the expected direction (Carpenter

and Williams, 1995). In contrast, when the timing of the target step can be predicted, latencies are reduced to targets anywhere in the visual field (Kingstone and Klein, 1993). Direction-selective facilitation probably reflects oculomotor preparation (Kowler, 1990; Paré and Munoz, 1996), the process whereby saccade programmes are partially or completely prepared before target presentation. Direction non-selective processes may reflect either fixation disengagement before target presentation—which allows the more rapid release of saccades (Reuter-Lorenz *et al.*, 1991; Munoz and Wurtz, 1992; Fischer and Weber, 1993; Kingstone and Klein,

1993; Tam and Ono, 1994)—or a generalized ‘readiness’ to respond that may reflect attentional rather than effector-specific processes (Ross and Ross, 1981; Reuter-Lorenz *et al.*, 1995).

When a subject has advance information about an impending movement, the faster reaction times are thought to reflect increased preparatory activity in structures that process that information. For example, tasks in which the subject knows the direction of an impending movement are associated with greater preparatory activation in motor structures than movements in which direction is not predictable. Specifically, neurones in frontal motor areas and striatum increase their activity during a delay when the direction of an impending limb movement is cued in advance relative to when it is not (Wise, 1985; Alexander and Crutcher, 1990). In humans, lateralized readiness potentials recorded from motor structures with electroencephalography are larger for movements in which the direction of an impending movement is known than when it is not (e.g. Wauschkuhn *et al.*, 1997). Likewise, tasks in which subjects can use predictable timing information to generate responses are thought to make larger demands on timing structures than those that do not (Ivry, 1993; Harrington and Haaland, 1999). For example, basal ganglia and cerebellar hemispheres are thought to be important to timing since damage to either of these structures results in an impairment in the generation of rhythmic movements and in the synchronization of movements with a rhythmic stimulus (Ivry *et al.*, 1988; Crawford *et al.*, 1989; Tian *et al.*, 1991; Ventre *et al.*, 1992).

When a target moves rhythmically between fixed locations, saccades that track the target become predictive, with near-zero latency (Findlay, 1981; Smit and Van Gisbergen, 1989). Both the ‘where’ and ‘when’ systems are likely to contribute to such saccades, since both the direction and the timing of the target movement are known in advance. However, it is not known to what extent each system contributes, nor whether these functions are subserved by the same or different neural structures. Studies of patients with brain lesions have implicated the frontal eye fields (FEFs), basal ganglia and cerebellum in the generation of predictive saccades because lesions to these areas affect predictive saccades more than reflexive saccades (Bronstein and Kennard, 1985; Tian *et al.*, 1991; Rivaud *et al.*, 1994; Isotalo *et al.*, 1995). It is not known, however, whether these lesions impair the ability to use advance knowledge of target direction, timing or both.

A recent model of saccade generation has postulated that the neural coding of the timing and direction of saccades is largely separate (Findlay and Walker, 1999). But can these two systems be neurally dissociated, given evidence that activity in at least two oculomotor structures, the FEFs and superior colliculus, seem to encode both where the saccade will go (Robinson, 1972; Bruce *et al.*, 1985; Schall *et al.*, 1995) and when it will be released (Hanes and Schall, 1996; Dorris *et al.*, 1997)? This evidence would seem to suggest that these two pathways may be overlapping rather than segregated. We manipulated the type of advance information

available about the target movement (direction versus timing) to evaluate the separate contributions of the ‘where’ and ‘when’ systems to saccade performance, and used functional MRI (fMRI) to identify the neural substrates of these systems. A preliminary report of these data has been published (Gagnon *et al.*, 2000).

## Methods

### Subjects

Seventeen right-handed subjects with an average age of 21.3 years (2.6 SD) participated in the psychophysical part of the experiment (12 females, five males). Of these, seven subjects (five females, two males) were scanned with fMRI. The average age of these seven subjects was 21.1 years (SD 3.1). The psychophysical results of these subjects, which are presented along with the fMRI data, did not differ from those of the entire group. Subjects reported no history of psychiatric or neurological disorders. Written informed consent was obtained prior to the scanning session and the subjects were compensated for their participation. The protocol was approved by the Research Ethics Committee of the Montreal Neurological Institute.

### Psychophysical testing

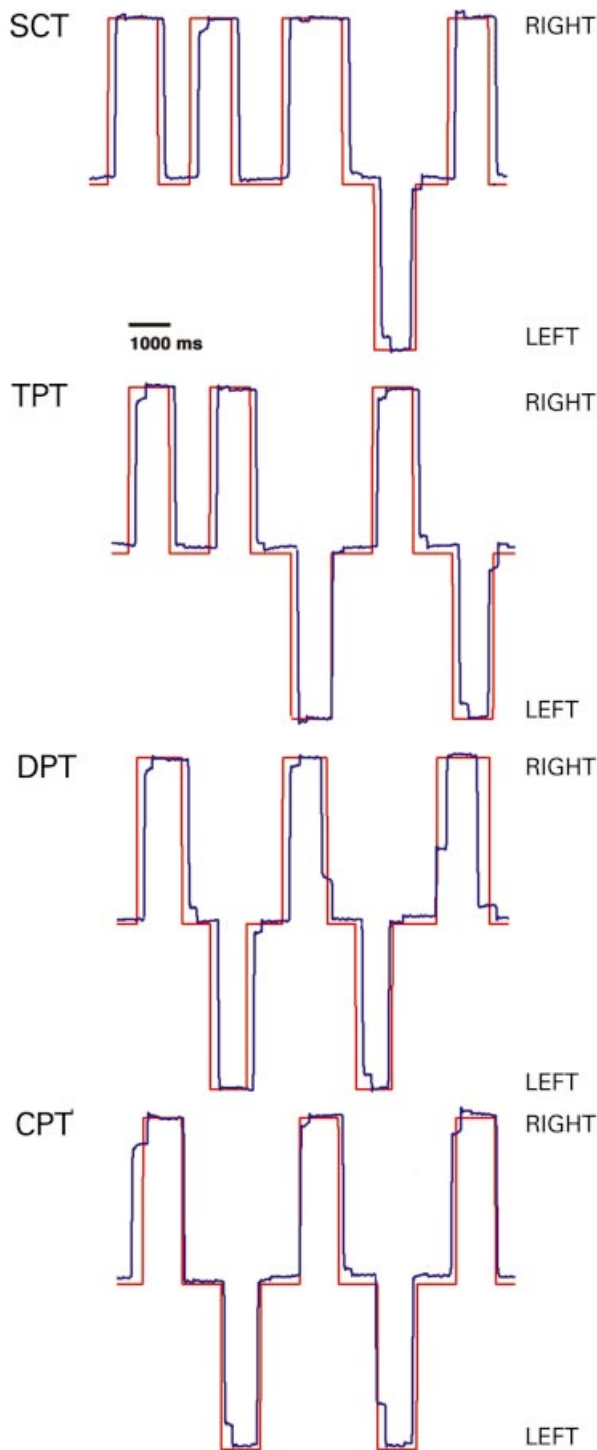
Subjects performed four different saccade tasks and a fixation task (see Fig. 1). Each task lasted 30 s. In all tasks, the target was a red square subtending  $0.5^\circ \times 0.5^\circ$  of visual angle. In all of the saccade tasks, the target moved in  $14^\circ$  steps at an average rate of once per second.

### Saccade control task (SCT)

The target moved from the centre to  $14^\circ$  left or  $14^\circ$  right at random. The timing of the target’s movements were randomized between 700, 900 or 1100 ms for movements from the central position and 900, 1100 or 1300 ms for movements from the left and right positions. Thus, neither the timing nor the direction of the target movement was predictable. This task was similar to the reflexive saccade tasks used in previous neuroimaging studies (Anderson *et al.*, 1994; O’Driscoll *et al.*, 1995; Doricchi *et al.*, 1997; Petit *et al.*, 1997).

### Timing predictable task (TPT)

The target was presented in the centre for 1000 ms, after which it stepped either to  $14^\circ$  left or to  $14^\circ$  right at random. It remained at the eccentric position for 1000 ms before stepping back to the centre. Thus, in this task the timing of the target movement was predictable, but the direction of the step from the centre was not.



**Fig. 1** Samples of a single subject's eye trace for each saccade task. The  $x$ -axis is time and the  $y$ -axis is position. The target position is represented in red and the eye position in blue. The direction of the target step from centre was random in the SCT and TPT, but was known in advance in the DPT and CPT. The timing of the target movement was unpredictable in the SCT and DPT, but was known in advance in the TPT and CPT. Note that in the SCT and TPT, the eye movement generally occurred after the target movement. In the DPT, the saccade often preceded the target movement. In the CPT, saccades were made in approximate synchrony with the target movement.

### *Direction predictable task (DPT)*

The target stepped in a repeating sequence from the centre to  $14^\circ$  right, to the centre, to  $14^\circ$  left, and back again. The direction of the target movement was always predictable. The timing of the target movement was randomized in the same way as in the SCT. Thus, in this task the direction and amplitude of each target step was known in advance while the moment the target would move was not.

### *Completely predictable task (CPT)*

The target stepped in a repeating sequence from the centre to  $14^\circ$  right, to the centre, to  $14^\circ$  left, and back again. The target remained at each location for 1000 ms. Thus, both the direction and the timing of the target movement were predictable.

### *Fixation*

The target remained stationary in the centre of the screen. Subjects were instructed to maintain their gaze on the target for the duration of the task.

An instruction screen preceded each task and identified which component of the task would be predictable (timing, direction, both or neither). Subjects were told to track the target as best they could, and not to precede or fall behind the target.

Each saccade task and fixation were presented twice in a single 'run' that each subject performed four times in the laboratory session and four times in the MRI scanner. Thus each task was performed eight times for 30 s in the laboratory (and in the scanner) for a total of 240 target steps in each task. Each individual run lasted 6 min (5 min of testing, plus the time between tasks and the instruction screens). Tasks were presented in palindromic order (ABCDEEDCBA) within each run, and the order was counterbalanced across subjects using a digram-balanced Latin square to ensure that each task appeared at least once in each position, and to ensure that each task preceded and followed each of the other four tasks at least once.

The stimuli were presented on a 17 inch NEC monitor running at 135 Hz. Eye movements were monitored in the laboratory using a 250 Hz high-speed video-based infrared pupil tracker (SR Research, Mississauga, Ontario, Canada). A three-target calibration and validation was performed across  $28^\circ$  of visual angle prior to testing. The average fixation error on validation was  $<0.5^\circ$ , which is consistent with the expected variability in fixation. A drift correction was calculated by the system at the start of each run.

### *MRI*

Subjects were scanned on a 1.5 tesla Siemens Vision scanner (Siemens Medical Systems, Erlangen, Germany). A spoiled

gradient-recalled echo pulse sequence [TR (repetition time) = 22 ms, TE (echo time) = 10 ms, flip angle = 30°] was used to acquire 3D high-resolution T<sub>1</sub>-weighted anatomical scans through the whole head. This yielded 170 slices with 1 mm thickness and a nominal in-plane resolution of 1 mm × 1 mm (field of view = 256 mm, matrix = 256 × 256). T<sub>2</sub>\*-weighted functional images sensitive to blood-oxygen-level-dependent (BOLD) contrast were acquired using a single-shot gradient-recalled echo-planar imaging sequence (TR = 3000 ms, TE = 50 ms, flip angle = 90°). Twenty-three 6 mm thick axial-oblique slices were selected from sagittal localizer images acquired about the midline. Slice coverage was chosen so that the whole brain was scanned including the cerebellum. In-plane resolution for these images was 5 mm × 5 mm (field of view = 320 mm, matrix = 64 × 64). To minimize head movement and motion artefact, each subject's head was immobilized using ear-stabilizing cushions and a saddle-shaped plastic guide positioned on the bridge of the subject's nose.

Subjects viewed the stimuli in the scanner via a NEC MultiSync MT1030+ (NEC Technologies, Inc., Itasca, Ill., USA) active-matrix projector running in 1024 × 768 mode at 60 Hz (light output 1100 ANSI lumens; contrast ratio 300 : 1). The projector was connected to PC supporting EyeLink software via a DB15 VGA cable. A mirror system positioned above the head coil allowed the subjects to view a screen positioned behind them in the bore of the magnet. Subjects performed the same run in the scanner as in the psychophysical session. For each run (performed four times), 120 scans of 3 s duration were acquired, yielding a total of 480 scans for each subject.

### **Evaluation of head movement and blinks**

As some of our activations were located posteriorly in the central sulcus (see Results), we assessed whether either head movement or blinks could account for activity differences between tasks. Head movement was recorded outside the scanner in a separate session in two subjects while they performed, head unrestrained, the same four runs as in the psychophysical and scanning experiments. Head movement was monitored with an OPTOTRAK system (Northern Digital, Inc., Bakersfield, Calif., USA), an optoelectronic position-sensing system that measures the position of infrared-emitting diodes in 3D space (200 Hz sampling rate and spatial resolution of 0.5 mm). Three infrared-emitting diodes were mounted on the headband of the eye tracker to measure head movement in the three orthogonal planes (*x*-, *y*- and *z*-axes). We used the standard deviation of head position as the measure of head movement amplitude in each task, and compared the amplitude across all tasks using a repeated measures one-way ANOVA (analysis of variance).

To evaluate the contribution of blinks to activity in the central sulcus (Tehovnik *et al.*, 2000), we measured the number of blinks made in each 30 s trial of each of the five

tasks. A within-subjects one-way ANOVA was used to compare the number of blinks across tasks.

## **Analysis**

### **Psychophysical data**

For each target step, the automated software (SR Research, Mississauga, Ontario, Canada) selected a 600 ms block of time centred on the time at which the target changed position. Within this selection, the first saccade with amplitude >3° was selected. The criteria for a saccade were set to 4000°/s<sup>2</sup> for acceleration and 22°/s for velocity. (Saccades had to meet both criteria.) Empirical tests with this system established that these criteria detected saccades as small as 0.25° while excluding artefacts. The experimenter verified all saccade selections. The dependent variables for each saccade were latency, amplitude and peak velocity. For the TPT and SCT, the direction of the target's movement was unpredictable from the centre to the periphery, but predictable from the periphery back to the centre. Thus, only saccades from the centre were analysed in these tasks. For each saccade variable, a one-way within-subjects ANOVA was used to test for differences among the saccade conditions, with the *P*-value Bonferroni corrected for multiple comparisons ( $\alpha = 0.016$ ). Two-tailed paired *t*-tests were used to test for differences *post hoc* if the overall *F* of the ANOVA was significant. Left and rightward saccades were also compared within each saccade task using paired *t*-tests, with a Bonferroni correction for multiple comparisons. For each saccade task, the percentage of predictive saccades (latency <70 ms) (Smit and Van Gisbergen, 1989), express saccades (latencies between 70 ms and 120 ms) (Fischer and Weber, 1993) and regular saccades (latencies >120 ms) were calculated. Directional errors were also tabulated.

### **MRI data**

Individual anatomical MRI images were transformed into 3D proportional stereotaxic space (Talairach and Tournoux, 1988) using a three-dimensional image cross-correlation algorithm (Collins *et al.*, 1994) where the MRI is resampled by a linear transform to match the target volume (a database of 305 MRI volumes transformed to Talairach space through identification of neuroanatomical landmarks) (Evans *et al.*, 1993, 1994). Transforming each individual MRI into stereotaxic space in this manner is effective in normalizing the images for individual differences in brain size.

Data were motion-corrected by co-registering all time points using a local routine developed at the Montreal Neurological Institute, with the third scan of each run as the reference. Functional data from each run were then subjected to low-pass filtration with a 6 mm full-width half-maximum Gaussian kernel.

Observed fMRI activation (positive BOLD signals) reflects decreases in the concentration of deoxyhaemoglobin within

**Table 1** Psychophysical results

Performance measure	CPT	DPT	TPT	SCT
Latency (ms)	15 (51)	78 (24)	148 (20)	169 (13)
Amplitude (°)	14.7 (1.8)	14.8 (1.6)	15.9 (1.7)	16.0 (1.8)
Peak velocity (°/s)	398 (46)	420 (42)	442 (40)	444 (26)

Mean (standard error) of each saccade variable in each saccade task. CPT = completely predictable task; DPT = direction predictable task; TPT = timing predictable task; SCT = saccade control task.

the microvasculature of metabolically active brain areas (Ogawa *et al.*, 1992). This paradoxical decrease in deoxyhaemoglobin concentration occurs despite an increase in oxidative metabolism due to a disproportionately large increase in blood flow (Hoge *et al.*, 1999).

Loci of significant increases in the BOLD signal from one task to another were calculated using in-house software (Worsley *et al.*, 2000). These programs employ a random effects analysis that uses a general linear model with correlated errors. To take into account lag in the haemodynamic response present in fMRI data, a gamma-density response function with a mean lag of 6 s and a standard deviation of 3 s was used to convolve the design matrix of the model. The analyses also accounted for autocorrelations between scans, as well as any drift artefact. The 3 s instruction screen preceding each task, as well as the 3 s 'blank' time after each task, were excluded from the analysis. The first two scans of each run were also excluded from the analysis to ensure the MRI signal was in steady state.

Pairwise differences between tasks were calculated for each individual subject. Each task was performed eight times, twice within each run. For each subject, the differences in BOLD signal between two tasks were calculated within each run and then averaged across the four runs. Images reflecting activity differences for each individual were then transformed into the standard Talairach stereotaxic space (in the same manner as for the anatomical images) and resampled at a higher resolution ( $2 \times 2 \times 2$  mm). Group maps representing activity differences between tasks averaged across subjects were then calculated and overlaid on high resolution 3D group average anatomical scans.

Brain areas of interest in our analyses were established *a priori* based on neuroimaging and electrophysiological studies of saccade generation and studies of predictive saccades in neurological populations. Regions of interest included the FEFs (Bruce *et al.*, 1985; Bruce and Borden, 1986; Rivaud *et al.*, 1994) and adjacent premotor cortex (Fujii *et al.*, 1998), the supplementary eye fields (SEFs) (Schlag and Schlag-Rey, 1987; Schall, 1991), the parietal eye fields (PEF) (Gnadt and Andersen, 1988; Barash *et al.*, 1991a, b), basal ganglia (Hikosaka and Sakamoto, 1986; Crawford *et al.*, 1989; Harrington *et al.*, 1998) and the cerebellum (Inhoff *et al.*, 1989; Isotalo *et al.*, 1995). [The superior colliculus is also involved, but activation of this structure has been observed with fMRI only with a special correction for brain

pulsation (DuBois and Cohen, 2000).] The PEFs were defined as located in the intraparietal sulcus, 32–58 mm above the anterior–posterior commissure line, based on previous neuroimaging studies of saccades (Muri *et al.*, 1996; Petit *et al.*, 1996, 1999; Berman *et al.*, 1999). Lesion studies suggest that the lateral cerebellar hemispheres are selectively involved in the functioning of an internal timing system, whereas the medial division is preferentially involved in executing the response (Ivry *et al.*, 1988; Malapani *et al.*, 1998). Timing-related activation in the cerebellar hemispheres has been identified at coordinates that correspond to lobule VI (Schmahmann *et al.*, 1999; Kawashima *et al.*, 2000; Schubotz *et al.*, 2000). Thus, *a priori* regions in the cerebellum were the vermis and underlying nuclei (within 15 mm of the midline) and lobule VI of the hemispheres. Only the above *a priori* regions were considered in the analyses.

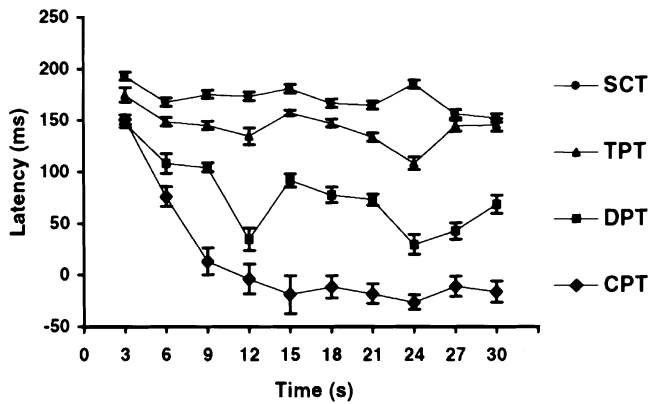
Three sets of activity differences were examined. First, each saccade task was compared to fixation. Secondly, each saccade task with a predictable component (CPT, DPT and TPT) was compared with the SCT. Thirdly, we identified the brain regions that showed a significant linear increase in the BOLD signal over time within a given task to determine which brain areas increase their activity with increasing familiarity with the target movement.

The significance criterion for the comparisons of the saccade tasks to fixation and the linear increases over time was set to a *t*-value of 4.37. This was based on the minimum given by a random field theory and a Bonferroni correction using a search volume of 1000 mm<sup>3</sup> (Worsley *et al.*, 1996). Because saccade tasks in which the target had a predictable component (CPT, DPT and TPT) were expected to activate many of the same areas as the SCT, the *t*-value threshold for these comparisons was set to 3.0 to increase power. This threshold was combined with a minimum cluster size criterion of 383 mm<sup>3</sup> (Cao, 1999), so that reducing the *t*-threshold did not increase the rate of false positives. Activation peaks that meet both magnitude and cluster size criteria are significant at  $P < 0.05$ , Bonferroni corrected.

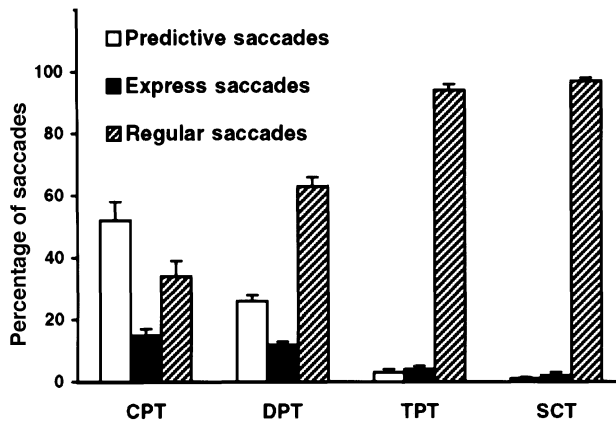
## Results

### Psychophysical results

Directional errors were excluded from saccade analyses as these were rare and constituted only 1.9% of all saccades.



**Fig. 2** Changes in saccade latency across time. The 30 s of each task were divided into 10 consecutive 3 s bins. Each point represents the average saccade latency in that bin for the seven subjects, averaged over the eight times they performed the task. Error bars at each point are the standard error of the mean for the group. Both advance knowledge of the timing and the direction of the target movement independently reduced saccade latencies relative to the latencies in the SCT.



**Fig. 3** Percentage of saccades in each category. Predictive saccades were defined as latencies <70 ms, express saccades as latencies between 71 and 120 ms, and regular saccades as latencies >120 ms. Error bars represent the standard error of the mean. Predictive saccades and express saccades occurred almost exclusively when the direction of the impending target movement was known. Knowledge of target timing, without knowledge of target direction, did not significantly increase predictive or express saccades.

There were no significant differences between leftward and rightward saccades. Thus, psychophysical data were pooled across directions. The four saccade tasks and typical performance for one subject are shown in Fig. 1.

Since the saccade could be partially or completely prepared in advance, we hypothesized that knowledge of target direction would facilitate saccade latency to a greater extent than knowledge of target timing. Saccade latencies were significantly different between each saccade task (Table 1). The average saccade latency for each task over time is plotted in Fig. 2. There were main

effects of knowledge of target timing [ $F(1,6) = 20.30$ ,  $P < 0.004$ ] and target direction [ $F(1,6) = 145.55$ ,  $P < 0.001$ ] on saccade latencies, and a trend for an interaction [ $F(1,6) = 5.63$ ,  $P < 0.055$ ]. The CPT was associated with the shortest saccade latencies, followed by the DPT, the TPT and the SCT; the latencies of each task were significantly different from each other (all  $P$ -values were <0.012). The average latencies of saccades in the CPT were <70 ms, while the latencies of saccades in the DPT task were in the express saccade range (between 70 and 120 ms) and the latencies of saccades in both the TPT and SCT were in the regular saccade range (>120 ms).

There was a significant difference in the percentage of predictive saccades [ $F(3,18) = 48.84$ ,  $P < 0.001$ ], express saccades [ $F(3,18) = 21.85$ ,  $P < 0.001$ ] and regular saccades [ $F(3,18) = 103.95$ ,  $P < 0.001$ ] in the four saccade tasks. In the two conditions in which direction information was available in advance (CPT and DPT), predictive saccades and express saccades occurred significantly more often than they did when direction information was not available (TPT and SCT; see Fig. 3) (all  $P$ -values were <0.005). In the TPT, there was no significant increase in predictive saccades relative to the SCT ( $P > 0.13$ ). There was a trend toward an increase in the percentage of express saccades relative to the SCT ( $P > 0.06$ ) when timing was predictable; however, the difference (mean  $\pm$  standard error) (TPT 3%  $\pm$  0.75; SCT 2%  $\pm$  0.75) corresponded to 0.3 of one saccade between the two conditions in a single run. Thus, in conditions in which a target is fixated foveally, subjects who are untrained will generally not make predictive saccades or express saccades unless they have prior knowledge of the direction of the impending target step.

When predictive and express saccades were excluded from the latency analyses, knowledge of target direction and timing still reduced saccade latencies. In the DPT, latencies (mean  $\pm$  standard error) of regular saccades were reduced by 12 ms  $\pm$  2 compared with the regular saccades in the SCT [ $t(6) = 5.2$ ,  $P < 0.002$ ]. In the TPT, regular saccade latencies were reduced by 11 ms  $\pm$  1.5 relative to the SCT [ $t(6) = 7.05$ ,  $P < 0.001$ ]. In the CPT, when both direction and timing were known, regular saccade latency was reduced by 20  $\pm$  5 ms, an effect that was significantly larger than the effect of either factor alone ( $P < 0.03$ ).

Saccades under internal control have been reported to have reduced amplitudes and peak velocities compared with saccades that are visually guided (Bronstein and Kennard, 1987; Kalesnykas and Hallet, 1987; Smit *et al.*, 1987). Thus, conditions in which the proportion of predictive saccades increased were expected to have lower amplitudes and peak velocities than conditions in which the saccades were predominantly visually guided. Across the four saccade tasks, there were significant differences in both amplitude [ $F(3,18) = 29.96$ ,  $P < 0.001$ ] and peak velocity [ $F(3,18) = 9.55$ ,  $P < 0.001$ ] of saccades (Table 1). Saccades in the two conditions that had a high

**Table 2** Saccade tasks minus fixation

Region of activation	BA CPT > fixation				DPT > fixation				TPT > fixation				SCT > fixation				
	x	y	z	t-score	x	y	z	t-score	x	y	z	t-score	x	y	z	t-score	
FEF (L)	6	-30	-8	52	6.62	-30	-8	50	5.15	-30	-10	48	5.85	-30	-8	48	4.41
Lateral FEF (L)	6	-53	-10	55	9.55	-54	-10	53	6.19	-54	-10	54	7.09	-54	-10	53	5.54
FEF (R)	6	46	-4	53	7.42	46	-6	54	5.69	46	-6	52	4.17 <sup>n.s.</sup>	41	-2	52	3.86 <sup>n.s.</sup>
Dorsal FEF (R)	6	42	-3	58	7.05	34	-6	60	5.75	34	-5	60	3.73 <sup>n.s.</sup>				
SEF	6	2	-2	60	7.91	0	8	52	5.75	-4	-6	67	5.66	3	-2	65	4.63
Dorsal premotor (L)	6	-30	-2	65	7.79	-30	-2	65	5.20	-30	-2	65	6.39	-30	-2	65	4.80
Ventral premotor (L)	4/6													-46	-10	39	4.45
Ventral premotor (R)	6	52	-2	43	8.88	48	-2	42	6.62	52	-2	42	4.82	50	-4	36	4.17 <sup>n.s.</sup>
Superior parietal lobe (L)	7	-40	-44	58	7.48	-38	-46	58	5.91	-36	-50	64	4.86	-40	-44	58	4.40
Superior parietal lobe (R)	7	36	-41	63	5.83	36	-44	58	4.76					16	-68	57	4.18 <sup>n.s.</sup>
Medial superior parietal (L)	7	-24	-67	58	4.98	-23	-64	58	4.27 <sup>P &lt; 0.07</sup>	-24	-71	54	4.47	-24	-66	56	4.18 <sup>n.s.</sup>
Medial superior parietal (R)	7	16	-64	59	5.05	22	-64	57	4.44								
Putamen (L)		-28	-2	1	4.92	-24	-4	2	5.09	-22	-4	1	4.66				
Putamen (R)		24	0	9	5.47	24	-6	2	5.37	24	-6	4	4.32 <sup>n.s.</sup>				
Medial cerebellum (L)		-6	-76	-18	7.18	-6	-77	-19	6.73	-8	-78	-17	4.42				
Medial cerebellum (R)		7	-70	-10	6.81												

FEF = frontal eye field; SEF = supplementary eye field; L/R = left/right; BA = Brodmann area; n.s. = not significant; CPT = completely predictable task; DPT = direction predictable task; TPT = timing predictable task; SCT = saccade control task.

proportion of predictive saccades (CPT and DPT) had shorter amplitudes than the conditions in which predictive saccades were few (TPT and SCT) (all  $P$ -values were  $<0.001$ ). The average peak velocity of saccades was lowest in the CPT, which was significantly lower than the peak velocity in the DPT ( $P < 0.014$ ), which in turn was significantly lower than the peak velocity in the SCT (all  $P$ -values were  $<0.019$ ). There was a trend for the peak velocity of saccades in the DPT to be significantly lower than in the TPT ( $P < 0.068$ ). Peak velocity did not differ between the TPT and the SCT ( $P > 0.82$ ). These results reflect the expected effect on saccade metrics of the higher proportion of voluntary saccades in conditions in which the target direction was predictable.

Overall, the psychophysical results suggest that advance knowledge of target direction reduces regular saccade latencies and makes an important contribution to the generation of both predictive and express saccades. Advance knowledge of target timing reduces saccade latencies independently from advance knowledge of direction, possibly by facilitating fixation disengagement, or by establishing a non-specific state of 'readiness'.

## fMRI results

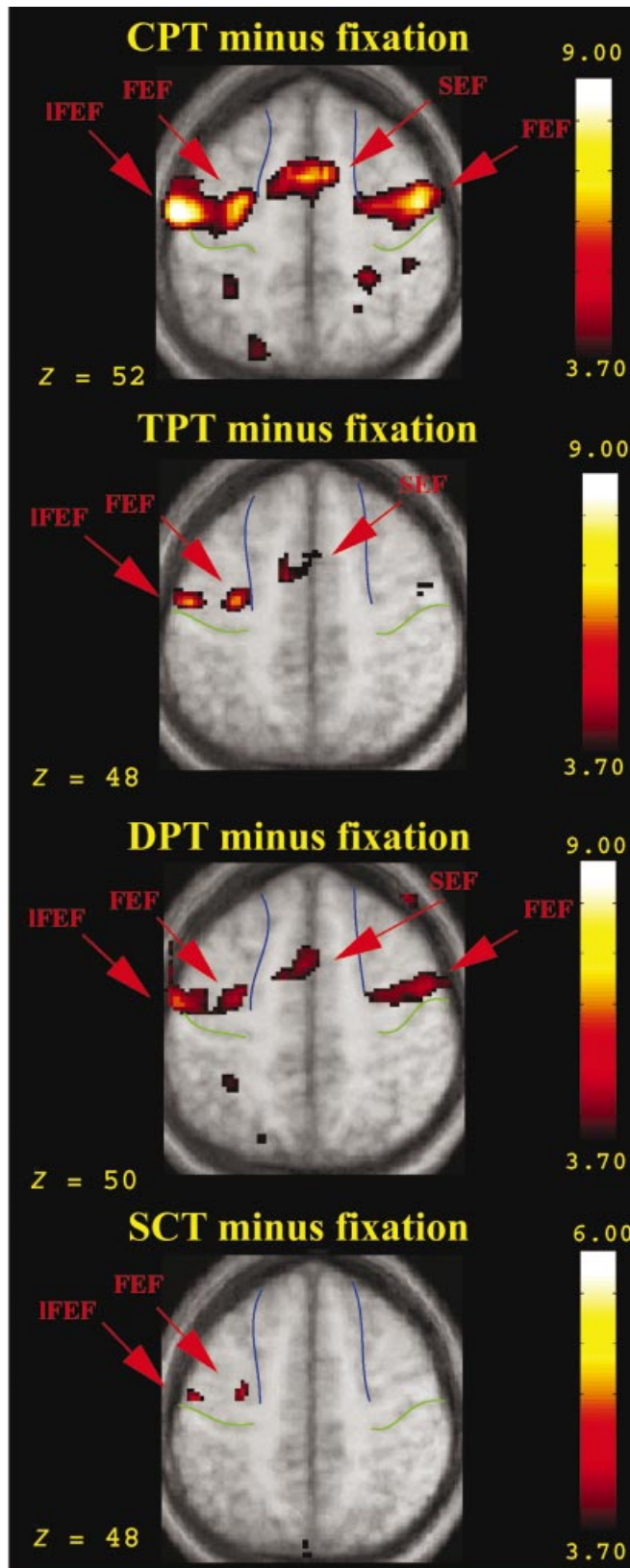
### Saccade tasks minus fixation

In humans, the FEFs are thought to be located in area 6 along the precentral gyrus (Darby *et al.*, 1996), near the junction of the precentral sulcus and superior frontal sulcus (for a review, see Paus, 1996). Activity in this region was significantly greater in all saccade tasks than fixation. In conditions in which the direction was known in advance (CPT and DPT),

the FEFs were significantly more active bilaterally than in fixation (Table 2). When the saccade metrics could not be prepared in advance (TPT and SCT), activity increases relative to fixation reached significance in the left FEF and were sub-threshold on the right. Within the left FEF region, there were two distinct activity foci, one laterally and one medially (Fig. 4). Distinct medial and lateral peaks in FEF have been observed in some previous studies (e.g. Petit *et al.*, 1997; Shulman *et al.*, 1999; Gitelman *et al.*, 2000). In the behavioural data, subjects tended to generate large initial saccades followed by small secondary saccades (Fig. 1). It is possible that the medial and lateral foci correspond to the large and small saccade regions of FEFs (Petit *et al.*, 1997; Berman *et al.*, 1999), with small differences in gyral anatomy accounting for the presence of distinct peaks on the left and the elongated peak on the right.

In addition to the FEFs proper, two other peaks in the precentral gyrus were found, one ~1 cm dorsal to the FEF in the superior frontal gyrus in the dorsal premotor area, and another ~1 cm ventral to the FEFs, in the precentral gyrus in the ventral premotor area (Table 2). Discrete activations of both of these regions have been observed in previous studies of saccades, smooth pursuit and attentive tracking (Petit *et al.*, 1996; Doricchi *et al.*, 1997; Culham *et al.*, 1998; Berman *et al.*, 1999; O'Driscoll *et al.*, 1999, 2000; Connolly *et al.*, 2000).

Increased activity was found in medial area 6 in all subtractions comparing saccade tasks with fixation (Table 2 and Fig. 4). Inspection of the individual activation foci revealed that the peaks were centred on a medial notch in the paracentral sulcus, corresponding to the SEFs in humans (Grosbras *et al.*, 1999).



Relative to fixation, bilateral increases in activity were observed in the putamen in all tasks with a predictable target component, but not in the SCT (Table 2). The medial cerebellum was also significantly activated in all tasks in which the target movement had a predictable component, but again not in the SCT.

### *Saccades to predictable target movement versus SCT*

To identify oculomotor brain regions that selectively increase activity when the timing or direction of an impending saccade is known, we subtracted out the motor component of saccades by comparing activation in each of the tasks with a predictable component (CPT, DPT and TPT) with activation in the SCT in which the target movement was random. These comparisons address more directly the areas involved in the putative ‘where’ and ‘when’ systems, since the control task is matched in motor demands to the experimental tasks. The brain areas that were significantly more active in each task with a predictable component than in the SCT are reported in Table 3. Below we report the areas more active in all three saccade tasks with a predictable component than in the SCT (‘common activations’), the activity increases that were observed only when both timing and direction were known (‘combined’) and the activity differences specific to advance knowledge of target timing or direction.

*Common activations.* In all tasks in which the target had a predictable component, the left dorsal FEF was more active than it was in the SCT. Although the coordinates of FEF were somewhat posterior to those observed when the tasks were compared with fixation, similarly posterior locations of the FEFs in the precentral gyrus have been reported (Petit *et al.*,

**Fig. 4** Horizontal sections illustrating increased activity in FEFs and SEF in each saccade task compared with fixation. The central sulcus is traced in green and the superior frontal sulcus in blue. The left hemisphere is shown on the left side of each image. Activity increases are superimposed on the averaged anatomical MRI from the seven subjects.  $t$ -values  $>4.37$  are significant ( $P < 0.05$ , Bonferroni corrected). In humans, the FEFs have been localized to the precentral gyrus near the junction of the superior frontal sulcus. The horizontal section shown is at the level where the maximum FEF activity increase was observed. Activation along the precentral gyrus was significantly higher in all saccade conditions with a predictable component than in the SCT. Two distinct peaks were observed on the left, one near the superior frontal sulcus and one more laterally. Previous neuroimaging studies have also observed joint activation of a medial and lateral peak along the precentral gyrus during saccades, although the distinct functions of these peaks are not known. The midline peak represents the SEFs, which were significantly activated in all saccade tasks relative to fixation. (Note that in the SCT, the SEF activation was located dorsally to the maximal FEF activation (see Table 2) and thus does not appear in the illustrated slice.) SEF activity was greatest in the CPT in which both the timing and direction of the target movement were known.

**Table 3** Saccade tasks with a predictable component minus the saccade control task

Region of activation	BA	Talairach coordinates			t-score
		x	y	z	
<b>CPT &gt; SCT</b>					
Dorsal FEF (L)	4/6	-44	-24	61	4.01
Dorsal FEF (R)	4/6	41	-16	56	3.41
SEF (L)	6	-8	-14	60	3.11
<b>TPT &gt; SCT</b>					
Dorsal FEF (L)	4/6	-32	-11	60	3.82
PEF (R)	40	54	-52	46	3.31
Globus pallidus (L)		-20	-5	-7	3.00
Globus pallidus (R)		16	-3	-7	3.13
Putamen (R)		24	10	-9	3.13
<b>DPT &gt; SCT</b>					
Dorsal FEF (L)	6	-32	-14	60	3.18
Caudate (L)		-12	10	6	3.48

FEF = frontal eye field; SEF = supplementary eye field; PEF = parietal eye field; L/R = left/right; BA = Brodmann area; CPT = completely predictable task; DPT = direction predictable task; TPT = timing predictable task; SCT = saccade control task.

1996; Sweeney *et al.*, 1996; Luna *et al.*, 1998; Petit and Haxby, 1999).

**Combined.** When both the direction and the timing of the target movement were predictable, activity in the right dorsal FEF and the SEF were significantly higher than in the SCT.

**Timing only.** When only target timing was predictable, the lenticular nuclei (Fig. 5) were significantly more active than in the SCT. Significant activity increases in the lenticular nuclei consisted of activity increases in the globus pallidus bilaterally and in the putamen on the right. The right intraparietal sulcus was also more active when the target timing was predictable than in the SCT. This activation may correspond to the PEFs localized within the intraparietal sulcus (Andersen *et al.*, 1992; Muri *et al.*, 1996).

**Direction only.** When the direction but not the timing of an impending saccade was known in advance, the left head of caudate was significantly more active than in the SCT (Fig. 5).

### *Increases in activity over time*

Saccade latencies showed a significant linear decrease over time in the CPT ( $r = -0.75$ ,  $P = 0.01$ ) and DPT ( $r = -0.72$ ,  $P = 0.02$ ) and showed a trend in the TPT ( $r = -0.52$ ,  $P = 0.13$ ) (Fig. 2). Everling and Munoz (2000) found that pre-saccadic activity in FEFs was correlated with saccade reaction time, such that higher FEF activity was related to shorter latencies. Electrophysiological studies have shown that neurones in SEF increase their activity over time as a monkey learns novel oculomotor associations (Chen and Wise, 1995). Thus, we hypothesized that oculomotor areas subserving perform-

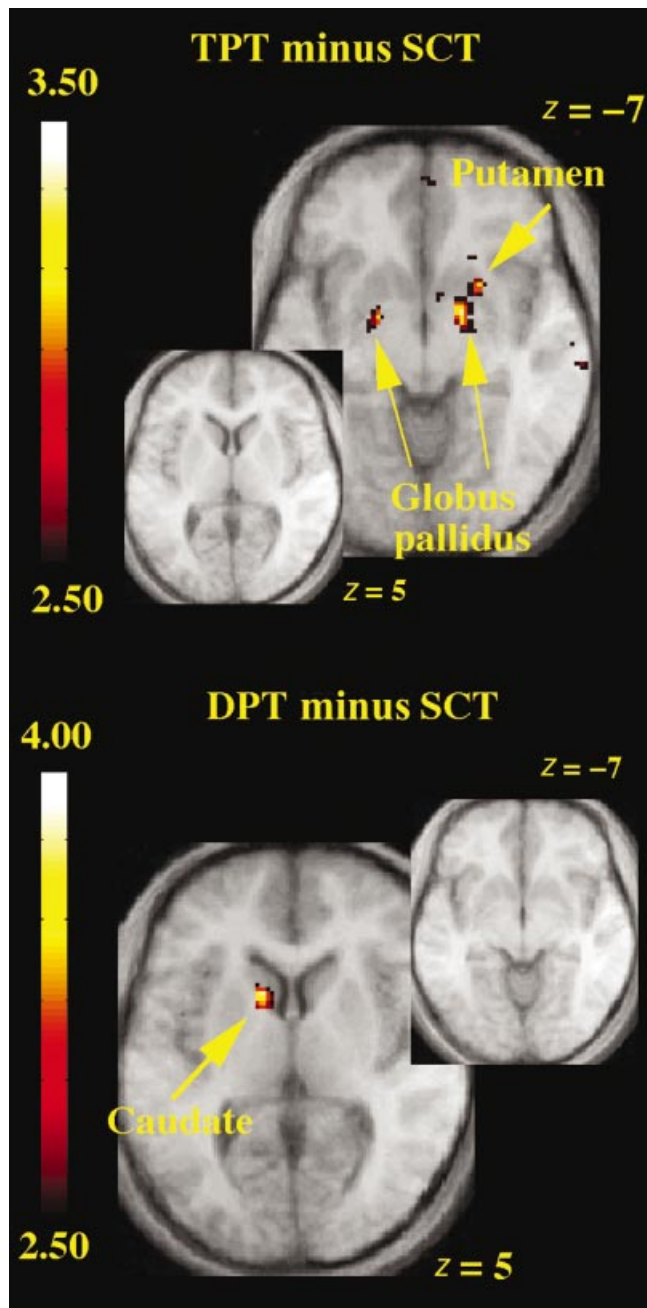
ance changes over time would increase their activity with increased exposure to the target in the predictable conditions, but not in the SCT or fixation.

Activity in the precentral gyrus and in the dorsomedial frontal cortex showed significant linear increases within each repetition of each of the predictable saccade conditions (Table 4 and Fig. 6), but not in the SCT or fixation. The precentral gyrus increases were located along the central rather than precentral sulcus, and thus were posterior to the FEF proper. In the CPT, the linear increases in precentral gyrus were bilateral while in the TPT and DPT they were found in the left hemisphere only. Since saccades to the left and right did not differ, these differences could reflect a greater contribution of the left precentral gyrus to oculomotor learning in humans.

### ***Evaluation of the contribution of head movement and blinks to activation***

Both the eyeblink region and head movement region of motor cortex are located along the central sulcus posterior to the FEF proper (Rasmussen and Penfield, 1948). Either of these two factors could account for the location of our posterior activations in the central sulcus (Figs 3 and 4). Furthermore, blinks are known to produce modest increases in FEF activity (Bodis-Wollner *et al.*, 1999).

We were able to exclude both head movement and blink rate as contributors to activity differences between tasks and to the increase in activity along the central sulcus. The amplitude of head movement was small in all tasks (standard deviations of position measured in degrees,  $\pm$  standard error: CPT  $0.05 \pm 0.01$ ; DPT  $0.05 \pm 0.01$ ; TPT  $0.04 \pm 0.01$ ; SCT  $0.06 \pm 0.01$ ; fixation  $0.07 \pm 0.02$ ). Head movement did not differ between tasks [ $F(4,4) = 1.94$ ,  $P > 0.27$ ]. Amplitude of



**Fig. 5** Dissociation of basal ganglia activation when target timing versus direction is known. The left hemisphere is shown on the left side of each image. The top panel illustrates areas in basal ganglia where activation was higher in the TPT, when target timing was known, than in the SCT. The bottom panel illustrates areas where activation was higher in the DPT, when target direction was known, than in the SCT. In both the top and bottom panels, two slices through basal ganglia are shown, with the ventral slice ( $z = -7$ ) on the right and the dorsal slice ( $z = 5$ ) on the left. Increased activity is observed in the lenticular nucleus when only timing information is known (*top panel, right*), but not when only direction is known (*bottom panel, right*). Increased activity of the caudate nucleus is observed when only target direction is known (*bottom panel, left*) but not when only target timing is known (*top panel, left*). This pattern is distinct from that observed in the dorsal precentral gyrus where knowledge of either target timing or direction is associated with increased activity.

head movement did not increase with time in any task (all  $P$ -values were  $>0.4$ ). Although two subjects is not an adequate sample size to truly assess head movement effects, the small amplitude of the head movements ( $\sim 1^\circ$  in all conditions) suggests that head movements are not an important contributor to the activations. Further, our findings are consistent with data from a previous study (Darby *et al.*, 1996) in which EMG activity was recorded from the sternocleidomastoid muscle and was found not to increase during the performance of saccades of similar amplitudes to those generated in the current study.

In general, subjects made few blinks in the saccade tasks (mean  $\pm$  standard error) [CPT  $2.4 \pm 1$ ; DPT  $2.2 \pm 0.8$ ; TPT  $1.7 \pm 0.6$ ; SCT  $1.5 \pm 1.1$ ; fixation  $14.5 \pm 5.5$ ;  $F(4,24) = 7.90$ ,  $P < 0.001$ ]. There were significantly more blinks during fixation than during each of the saccade tasks (all  $P$ -values were  $<0.04$ ). There were no significant differences in blink rate between saccade tasks with a predictable component and the SCT, and there were no significant changes in blink rate over time (all  $P$ -values were  $>0.3$ ). Since there were more blinks in fixation than in the saccade tasks, activity increases during the saccade tasks relative to fixation cannot be related to blinks. Likewise, as blinks did not differ between tasks with a predictable component and the SCT, they cannot account for the activity differences between these tasks. Finally, since blink rate did not change over time in any of the tasks, they cannot account for the changes over time observed along the central sulcus.

Overall, the behaviour that did change with time was saccade-related (i.e. latency), suggesting that the increase in activity with time was not related to artefact, but may have subserved relevant performance changes.

## Discussion

Advance knowledge of the direction and the timing of an impending target movement had mainly overlapping effects on saccade latencies and on neural activity, although discrete effects were also found. Knowledge of either direction or timing decreased the latency of regular saccades, but only knowledge of target direction increased the number of predictive and express saccades (Fig. 3). Advance knowledge of target direction and target timing activated common neural structures. Greater activity in the precentral gyrus (in the region of the FEFs) was observed when knowledge of direction or timing or both were available compared with the saccade condition when neither was available. The basal ganglia were the areas where activity distinguished between knowledge of target direction and timing. There was greater activity in the caudate nucleus when the target direction was known in advance, but greater activity in the lenticular nucleus when timing information was known in advance. These findings will be discussed in relation to previous electrophysiological, lesion and neuroimaging studies.

**Table 4** Significant increases in the BOLD signal over time for each task

Task/region of activation	BA	Talairach coordinates			<i>r</i>	<i>t</i> -score
		<i>x</i>	<i>y</i>	<i>z</i>		
Completely predictable task						
MSEF (L)	6	-36	-24	54	0.38	5.42
MSEF (R)	4/6	46	-14	51	0.45	6.73
SMA (L)	6	-8	-18	54	0.45	6.69
Timing predictable task						
MSEF (L)	6	-42	-15	48	0.34	4.71
SMA (L)	6	6	-15	48	0.32	4.47
Direction predictable task						
MSEF (L)	6	-38	-22	47	0.34	4.75
MSEF (L)	4	-38	-24	62	0.36	5.12
SMA (L)	6	-4	-14	60	0.36	5.08

MSEF = motor strip eye field; SMA = supplementary motor area; L/R = left/right; BA = Brodmann area; *r* = correlation.

### Convergence in the precentral gyrus

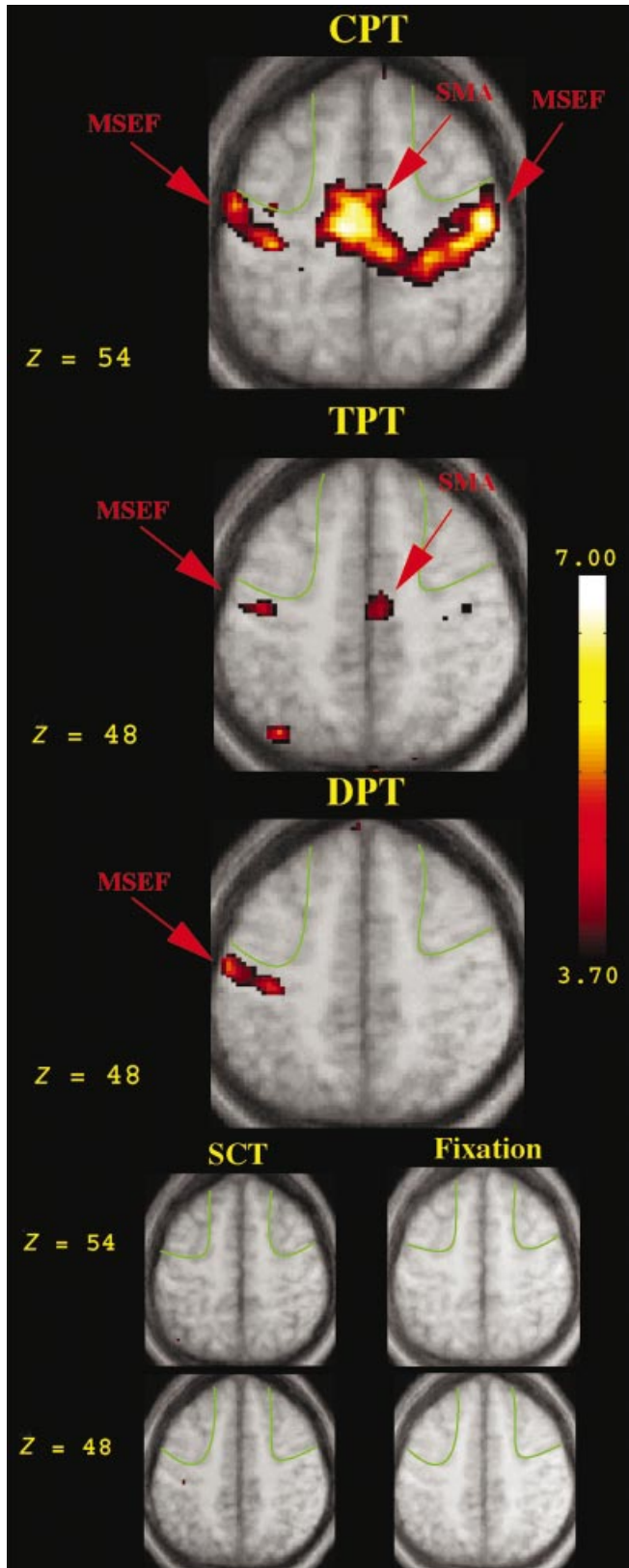
It has previously been postulated that the 'where' and 'when' components of saccade generation are integrated in the FEFs (Frens *et al.*, 1999; Quail and Optican, 1999). This idea is supported by findings that: (i) neurones in the FEFs have fixed-vector movement fields specifying where to direct a saccade (Bruce *et al.*, 1985); and (ii) activity in FEFs prior to a saccade is negatively correlated with saccade latency (Hanes and Schall, 1996; Everling and Munoz, 2000). Our results are consistent with this hypothesis, as FEF activity was modulated by advance knowledge of both target direction and target timing, and was greatest with knowledge of both (Fig. 4 and Tables 2 and 3).

Our results are in accord with single-unit studies that have shown that the precentral gyrus, which in humans includes the FEFs, has context-dependent or 'set-related' activity that reflects the interface of cognition and motor control (Georgopoulos, 2000). For example, the level of activity in FEFs is different for movements made toward compared with away from a target (e.g. O'Driscoll *et al.*, 1995; Connolly *et al.*, 2000; Everling and Munoz, 2000). Within a task, activity in FEFs is primed by experience with the target in preceding trials (Hanes *et al.*, 1998; Bichot and Schall, 1999). Thus, our results and those in non-human primates suggest that the FEFs do not code only saccade metrics but also the context in which the saccade is made.

The condition with the highest FEF activity, the CPT, elicited the highest proportion of predictive and express saccades (Table 1 and Fig. 3). In humans, lesions to the FEFs abolish predictive saccades, but have minimal effects on regular saccades (Rivaud *et al.*, 1994). Consistent with this, frontal cortical potentials are significantly larger for anticipatory saccades (i.e. predictive saccades) and express saccades than for regular saccades (Everling *et al.*, 1996). In non-human primates, the level of pre-stimulus activity in FEFs is negatively related to saccadic reaction times, and is

higher for express saccades than regular saccades (Everling and Munoz, 2000). A similar pattern is observed in the superior colliculus; activity in build-up neurones is higher for express saccades than regular saccades, and is highest for anticipations or predictive saccades (Dorris and Munoz, 1998). The FEFs have been postulated to be the source of the activity increases in the superior colliculus (Everling and Munoz, 2000; Sommer and Wurtz, 2000), as the FEFs project to the superior colliculus (Fries, 1984; Stanton *et al.*, 1988*b*), and neurones in the FEFs are involved in both 'fixation disengagement' (Dias and Bruce, 1994; Everling and Munoz, 2000) and oculomotor preparation (Thompson *et al.*, 1996). Both of these functions are likely to be important to the normal generation of predictive and express saccades.

In our study, neural activity in the precentral gyrus increased over time in each of the saccade tasks with predictable target movement, but not during the SCT or fixation (Fig. 6 and Table 4). Thus, these increases seem to be specific to the conditions where experience expedited saccade generation. The increases were localized along the central sulcus, rather than the precentral sulcus, and thus were posterior to the FEF proper (Paus, 1996). The location of this activation could correspond to a second eye field reported in humans, located in the motor strip [motor strip eye field (MSEF)] (Rasmussen and Penfield, 1948; Tehovnik *et al.*, 2000). In terms of its location, the MSEF could be the human homologue of the ventral premotor (vPM) eye field, which was described by Fujii *et al.* (1998) as being directly posterior to the spur of the arcuate sulcus (i.e. FEFs, Bruce *et al.*, 1985) and adjacent to motor area 4. Since area 4 in humans is buried in the central sulcus (Brodmann, 1909; Economo and Koskinas, 1925), the homologue of the vPM eye field would be expected to border the central sulcus. Microstimulation of the vPM eye field in monkey elicits saccades that are craniotopically, rather than retinotopically, organized (Fujii *et al.*, 1998). Voluntary, internally guided



saccades are thought to be coded in craniotopic, rather than retinotopic, coordinates (Allin *et al.*, 1996). If the MSEF corresponds to the vPM eye field, the increasing activation over time along the central sulcus may be related to a behavioural transition from retinally guided to internally guided saccades (Fig. 2).

### SEFs

In neuroimaging studies, SEF activation is generally observed during all saccade tasks (Anderson *et al.*, 1994; Sweeney *et al.*, 1996), and is enhanced when subjects are required to generate saccade sequences (Petit *et al.*, 1996; Kawashima *et al.*, 1998). Lesions to the SEF in humans do not affect single saccades, but do impair the execution of saccade sequences (Gaymard *et al.*, 1990, 1993). In our study, the SEF was significantly more active in all saccade conditions than it was in fixation (Fig. 4 and Table 2), and was significantly more active in the CPT than in the SCT (Table 3). In the CPT, saccades were generated in a sequence under mainly internal control. In contrast, in the DPT, in which SEF activation did not differ from the SCT, the movements were triggered by an unpredictable start signal that probably made it disadvantageous to prepare more than one saccade at a time. In the TPT, the saccade could not be prepared in advance since the direction of the movement was unknown. Thus, the pattern of SEF activation observed here is consistent with the notion that the SEF is involved in the generation of all saccades (Schlag and Schlag-Rey, 1987), and plays a larger role in tasks that involve the generation of saccade sequences (Sommer and Tehovnik, 1999).

Another important role ascribed to SEFs is motor learning. Several studies have reported that activity in SEFs increases

**Fig. 6** Significant linear increases in activity over time in the precentral gyrus and supplementary motor area in each of the saccade tasks with a predictable component. The precentral sulcus and superior frontal sulcus are traced in green. The left hemisphere is shown on the left side of each image. The activity increases are superimposed on the averaged anatomical MRI from the seven subjects.  $t$ -values  $>4.37$  are significant ( $P < 0.05$ , Bonferroni corrected). The regions in the precentral gyrus where activity significantly increased over time are localized in the central sulcus, posterior to the FEF proper, and possibly in the MSEF (Tehovnik *et al.*, 2000) identified in humans by Rasmussen and Penfield (1948). The TPT and DPT conditions are shown at the slices with the maximal MSEF increases. For the CPT, the slice illustrated is the slice where bilateral activation was strongest. [The slice with peak MSEF activity (see Table 4) was 2 mm dorsal at +54.] No significant increases in activity over time were observed in these regions in the SCT or in fixation. The supplementary motor area also showed significant increases over time in each of the predictable tasks, but not in the SCT or fixation. The increase in supplementary motor area activity in the DPT is dorsal to the slice illustrated (see Table 4). The activity increases over time in the MSEF and supplementary motor area may play a role in the changes in saccade latency over time seen in each of the predictable saccade tasks (Fig. 2).

during the learning of novel motor associations (Mann *et al.*, 1988; Chen and Wise, 1995). Lesions to the dorsomedial frontal cortex impair the acquisitions of motor routines (Ackermann *et al.*, 1996; Nakamura *et al.*, 1999). Our data are consistent with the role of the SEFs in motor learning. Activity in this region increased significantly over time in all tasks with a predictable component, that is, in all tasks in which performance could be improved with experience, but did not significantly increase in fixation or the saccade control condition.

The increases over time in the dorsomedial frontal cortex were located posterior to the increases in activity observed in the subtractions. It is possible that the more posterior region corresponds to the supplementary motor area rather than the SEF, and could be the source of the 'readiness potential' observed at the vertex of the brain with electroencephalography. The 'readiness potential' is not effector-specific (it is observed during hand and eye movements), is stronger during voluntary than reflexive responses (Porter and Lemon, 1995), and is negatively correlated with reaction time (Rohrbaugh *et al.*, 1976). Thus, increases in activity in this region in all the predictive saccade conditions may be related to a 'readiness' or 'motor-set' that increases with experience on those tasks and facilitates saccade generation.

### ***Differentiation of the pathways in basal ganglia***

Although we found that the 'where' and 'when' systems activated overlapping neural structures, activity within the basal ganglia distinguished between conditions in which the timing versus the direction of the target movement was predictable (Fig. 5 and Table 3). The lenticular nuclei, including the right putamen and the globus pallidus bilaterally, were significantly more active in the TPT than the SCT. The left caudate was significantly more active in the DPT than the SCT.

The putamen, like the caudate, receives projections from FEF (Stanton *et al.*, 1988a; Cui *et al.*, 2000) and is thus well positioned to play a role in the guidance of saccades. Several studies have suggested that the putamen is critically involved in tasks requiring movement timing (Kimura, 1986; Kimura *et al.*, 1990; Jaeger *et al.*, 1995) and that, in humans, the right putamen may play a larger role (Rao *et al.*, 2001). In non-human primates, a population of putamen neurones have a response that is time-locked to the target; these neural responses are observed only when the stimulus will elicit a movement, suggesting that they are not strictly sensory, but are involved in the rapid initiation of a behavioural response (Romo *et al.*, 1992). The increase in activity in putamen in the repetitive timing condition is consistent with such an interpretation, since responses in the TPT were visually guided, but with significantly shorter latencies than those in the SCT. Surprisingly, the CPT was not associated with greater activation of putamen than the SCT. However, in single-unit studies, preparatory activity in the putamen has been shown to increase for each sensorially triggered

movement. When a sequence of movements is triggered, the activity increases only until the initiation of the first movement of the sequence (Kimura, 1990), and does not persist during the execution of movements under internal control. Thus, the CPT may not have been associated with greater activation of the putamen because in this condition, in which the eye movements tended to precede the stimulus, the movements were no longer tied to the visual stimulus but rather were executed as a sequence under internal control.

In the DPT, there was robust activation of caudate that was not observed during the TPT. Previous studies have provided support for the notion that caudate selectively codes 'where' information, particularly when the 'where' information can facilitate movement preparation (Postle and D'Esposito, 1999a, b). However, several neuroimaging studies of memory-guided saccades (in which impending direction is known) have failed to activate caudate (Anderson *et al.*, 1994; O'Sullivan *et al.*, 1995; Sweeney *et al.*, 1996). Further research is needed to clarify the specific conditions in which caudate activity will increase with direction information.

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