The Neural Basis of Parallel Saccade Programming: A Functional Imaging (fMRI) Study

Yanbo Hu and Robin Walker

Abstract

■ The neural basis of parallel saccade programming was examined in an event-related functional imaging (MRI) study using a variation of the double-step saccade paradigm. Two double-step conditions were used: one enabled the second saccade to be partially programmed in parallel with the first saccade while in a second condition both saccades had to be prepared serially. The intersaccadic interval, observed in the parallel programming (PP) condition, was significantly reduced compared with latency in the serial programming (SP) condition and also to the latency of single saccades in control conditions. The fMRI analysis revealed greater activity (BOLD response) in the frontal and parietal eye fields for the PP condition compared with the SP double-step condition and when compared with the single-saccade control conditions. By contrast, activity in the supplementary eye fields was greater for the double-step condition than the single-step condition but did not distinguish between the PP and SP requirements. The role of the frontal eye fields in PP may be related to the advanced temporal preparation and increased salience of the second saccade goal that may mediate activity in other downstream structures, such as the superior colliculus. The parietal lobes may be involved in the preparation for spatial remapping, which is required in double-step conditions. The supplementary eye fields appear to have a more general role in planning saccade sequences that may be related to error monitoring and the control over the sequence of responses. ■

INTRODUCTION

Saccades are made to shift gaze and attention onto objects of interest enabling detailed analysis of the visual scene. As we can only shift our eyes to one object at any one time, there has been a natural tendency to regard saccade programming as a serial process, but some behavioral studies have provided evidence showing that the saccadic system can program more than one saccade in parallel. Becker and Jürgens (1979) showed that saccades made to targets that moved in two steps could be separated by very short intersaccadic intervals (ISIs) that were much shorter than the time required to generate a single saccade. Short ISIs have also been observed in other situations such as the antisaccade task (Hallett, 1978) and in visual search (Theeuwes & Godijn, 2002; Findlay, Brown, & Gilchrist, 2001; Theeuwes, Kramer, Hahn, & Irwin, 1998). In these paradigms, incorrect saccade can be followed, after a very short ISI, by a secondary corrective saccade directed to the saccade goal. Importantly, the ISI separating the first and second saccades is much less than the time to generate a single response (c.f. McPeek, Skavenski, & Nakayama, 2000; Mokler & Fischer, 1999; Amador, Schlag-Rey, & Schlag, 1998; Weber, Dürr, & Fischer, 1998; Hooge & Erkelens, 1996; Viviani & Swensson, 1982). The short ISI period has been interpreted as showing that the second corrective saccade was programmed in parallel (pipelined) with the first erroneous response.

Walker and McSorley (2006) used a variation of the double-step saccade paradigm to investigate parallel programming (PP) without having to rely on an examination of the smaller proportion of double responses made on error trials (cf. Sheliga, Brown, & Miles, 2002). Participants made a first stimulus-elicited saccade, was followed by a second ("voluntary") saccade made to a goal indicated by an arrow cue. A robust reduction in second saccade latency was observed compared with that of comparable single saccades. A similar reduction in second saccade latency (ISI) was also found when a first "voluntary" saccade, made to a location specified by an arrow cue, was followed by a second saccade made to a peripheral target. First, saccade latency was found to be modulated by the required direction of the second saccade, which is consistent with the view that both saccades may be programmed on a common "motor map" (Godijn & Theeuwes, 2002) such as that formed by neurons in the intermediate layers of the superior colliculus (SC; McPeek & Keller, 2002).

The Neural Basis of Parallel Saccade Programming

Single-neuron studies have demonstrated a role of the SC in the PP of saccades (McPeek, Han, & Keller, 2003; McPeek & Keller, 2002). McPeek and Keller (2002) revealed that neural activity associated with a second corrective

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saccade was maintained, in the topographical motor map formed by the SC, while the first erroneous saccade was initiated. The enhanced activity for the second saccade goal was observed only for saccades with short ISIs, which are assumed to be programmed in parallel. McPeek and Keller (2002) noted, however, that activity associated with the second saccade target would no longer correspond with the vector of the second movement once the first saccade has been made. Thus, the activity in the SC may have to be "remapped" into the new retinotopic location following the first saccade (Walker, Fitzgibbon, & Goldberg, 1995), which in turn may depend on a stored internal representation of the second saccade goal. The increased activity around the second saccade goal could enhance the salience of this location, enabling the advance preparation of the second saccade with a resulting reduction in latency (McPeek & Keller, 2002). The advanced preparation of the second saccade or prior target selection process observed in the SC could, however, be mediated by cortical regions such as the frontal eye fields (FEFs), which have topographically organized projections to the SC, that convey a range of cognitive saccade-related signals related to the control of fixation, saccade timing, and initiation (Sommer & Wurtz, 2000).

The FEFs have been implicated in parallel saccade programming and also in the control of generating saccade sequences. Murthy, Ray, Shorter, Priddy, & Schall (2007) implicated the involvement of Macaque FEF in the PP of rapidly corrected erroneous saccades in a visual search task. On some search trials, the target unpredictably changed position that resulted in high numbers of directional errors being made. The latency of the secondary corrective saccades could be predicted by the timing of activity of movement-related FEF neurons, and on some occasions, this activity began even before the first erroneous saccade was completed. Murthy et al. (2007) emphasize a distinction between activity of visually responsive neurons that may reflect "remapping" and that of movement-related neurons that may be attributed to processes associated with rapid and accurate error correction.

The observation of cortical activity, associated with a second saccade, could also reflect the readiness and intention to prepare a response—a process termed "*preparatory set*" (Hebb, 1972). Functional imaging studies, have demonstrated activity in the FEFs associated with preparation of a particular type of response (DeSouza, Menon, & Everling, 2003; Connolly, Goodale, Menon, & Munoz, 2002). In these studies, a precue is used, which reliably informs the participant of the nature of the upcoming response (prosaccade or antisaccade), whereas the direction and location of the target is unknown (DeSouza et al., 2003; Connolly et al., 2002). Enhanced activity is observed in the FEFs during this preparatory period, which is not associated with the differences in motor signals for the pro- and antiresponses (DeSouza et al., 2003). The increased activity in FEFs associated with second saccades following short ISIs may reflect the preparation of a subsequent response rather than the spatial encoding of the second saccade goal.

The flexible control of voluntary actions also involves regions of the dorsomedial frontal cortex (DMFC), including the pre-SMA, which has a role in cognitive "set switching" (the ability to change from one response to another; Konishi et al., 1998) and the supplementary eye fields (SEF), located in the medial wall of DMFC, have a role in the control of saccade sequences (Isoda & Tanji, 2002; Heide et al., 2001) and in the learning of novel saccade sequences (Grosbras et al., 2001). Sommer and Tehovnic (1999) showed that reversible deactivation of monkey DMFC did not impair single saccades but did increase the latency and number of misdirected saccades made on double-step trials. Deactivation of DMFC selectively impaired either the first or second saccade of a sequence, and these impairments were not directionally selective. The precise anatomical location of SEF in humans has been ill defined, one functional imaging study using self-paced saccades, provided an anatomical location in the region of the upper paracentral sulcus, which varied across subjects (Grosbras, Lobel, Van de Moortele, Lebihan, & Berthoz, 1999). Imaging studies have revealed functional roles for the putative human SEF in working memory processes (Brown et al., 2004) consistent with the deficits in the generation of memory-guided saccade sequences observed in patients with DMFC lesions (Gaymard, Pierrot-Deseilligny, & Rivaud, 1990). The human SEF has also been implicated in high-level cognitive decision-making processes such as maintaining rules related to stimulus response mapping (Parton et al., 2007). Functional imaging studies have identified a further region associated with making novel saccade sequences in the rostral medial wall that has been referred to as the pre-SEF and pre-SMA (Grosbras et al., 2001).

The present study was designed to dissociate cortical activity, associated with the preparation to make a sequence of saccades in parallel, from those involved in programming two saccades serially. The control over the timing of saccade initiation, which is critical to PP, is most likely to involve the FEFs in dorsolateral frontal cortex (DLFC). The ability to perform a simple saccade sequence serially or in parallel will involve a range of high-level cognitive processes including the control of the sequence of responses, stimulus–response mapping, and error monitoring. The eye fields in the DMFC are known to have a role in these high-level cognitive processes in more complex saccade tasks (Husain, Parton, Hodgson, Mort, & Rees, 2003), but it is not known if they are involved in the PP of saccades. An event-related functional imaging study was performed to examine cortical activity (BOLD response) while participants prepared to make a sequence of two saccades in a double-step task. There were two types of double-step trial: in the PP trials, a peripheral target and symbolic cue appeared, simultaneously enabling both responses to be prepared during the delay period. In the serial programming (SP) double-step condition, participants knew they had to

prepare to make a sequence of two rapid saccades, but the location of the second saccade was not known until after the initiation of the first response. The SP double-step condition was included to dissociate activity arising from preparing a sequence of responses from that specifically associated with PP. It also acted as a control for the possibility that preparing two responses is more difficult than preparing a single response. Participants also made single stimulus-elicited and endogenous saccades in control trials. The use of an event-related design enabled activity associated with saccade planning to be dissociated from that associated with initiating the motor responses. The predictions are that programming saccade sequences will involve both the FEFs and SEFs, whereas activity associated with parallel saccade programming will involve additional FEF activity because of their role in the control of saccade timing and initiation. Although the SEFs are expected to be involved in the control of saccade sequences, no predictions are made for their role in PP.

METHODS

Participants

Fifteen participants were recruited from Royal Holloway, aged between 19 and 35 years, six of which were women. Participants gave their written informed consent in accordance with the Royal Holloway, University of London Psychology Department Ethics Committee regulations. The study conformed to the regulations set out in the Royal Holloway, University of London MRI rules of operation.

Behavioral Eye Tracking Sessions

Apparatus

Eye movements were recorded outside the scanner using a video-based eye-tracker (EyeLink II, SR Research, Mississauga, Ontario, Canada) with a sample rate of 250 Hz and a spatial accuracy of $<0.5°$. Stimuli were presented using Experiment Builder Software (SR Research, Mississauga, Ontario, Canada) and were presented on a 21-in. color monitor (1024 × 768 resolution, 100 Hz) from a viewing distance of 57 cm. A chinrest was used to maintain the viewing distance and to restrict head movements. Saccades were detected by the Eyelink "parser" software, which identified saccade start and endpoints using a 22°/sec velocity and 8000°/sec^2 acceleration criterion.

Behavioral Paradigm

The behavioral paradigm was first performed in behavioral training sessions outside the scanner to ensure participants were practiced on the task before they performed the same task in the scanner. The training session was performed 1 or 2 days before the fMRI session and enabled detailed measures of saccade latency and error rates. Participants completed four blocks of trials in the oculomotor laboratory and 10 blocks of trials in the MRI scanner. There were four trial types: two double-step saccade conditions and two single-saccade control conditions, and these were interleaved in a random order in a block of trials. All trials started with the onset of a central fixation stimulus that appeared along with two colored peripheral circles (red on the left and blue on the right) located at 5.6° in the upper left and right visual field (direction, 45° from horizontal). The peripheral circles acted as markers of the endogenous saccade goal. The timing of the stimulus sequence included random delay periods similar to those used for an event-related fMRI design. The initial fixation frame was presented for a random fixation period (of 2000–6000 msec) and a similar variable delay (of 2000–6000 msec) was used for the preparation period. For the response period, a fixed interval of 1500 msec was used. The sequence of events for the four trial types is shown in Figure 1, and the stimulus sequence is described in more detail below.

Single reflexive (stimulus-elicited) saccades. Following the random fixation period, a peripheral target (a black circle) appeared at 5.6° on a horizontal axis level with fixation. Simultaneously with target presentation, a partial offset of the fixation stimulus occurred so that it formed a vertical "diamond" shape (this change occurred as a control for the changes of fixation in the arrow cue condition). Participants delayed making a saccade to the target until the offset of fixation, which occurred after a further random delay of 2000–6000 msec. The peripheral target changed from black to gray 200 msec after fixation offset (as a control for the visual change that occurs in the double-step conditions) and remained visible for another 1300 msec.

Single voluntary saccades. Following the random fixation period, the partial offset of fixation occurred so it formed an arrow cue pointing toward one of the peripheral markers located at 5.6° in the upper left and right visual fields (45° from horizontal). Participants were instructed to remain fixated until the offset of the arrow, which occurred after a random delay of 2000–6000 msec. The remaining stimulus frame stayed for 1500 msec after the offset of the arrow.

Double-step SP condition. Following the fixation foreperiod, the partial offset of the fixation stimulus produced a horizontal "diamond" shape. Simultaneously with the change at fixation, a peripheral target (a black circle) appeared on the horizontal axis left or right of fixation (as in the single reflexive [SR] condition above). Participants were instructed to make a saccade toward the peripheral target as quickly as possible after fixation offset. The peripheral target changed from black to either red or blue 200 msec after fixation offset, during which time a saccade to that target should be initiated. The color change indicated the goal location of the upper field

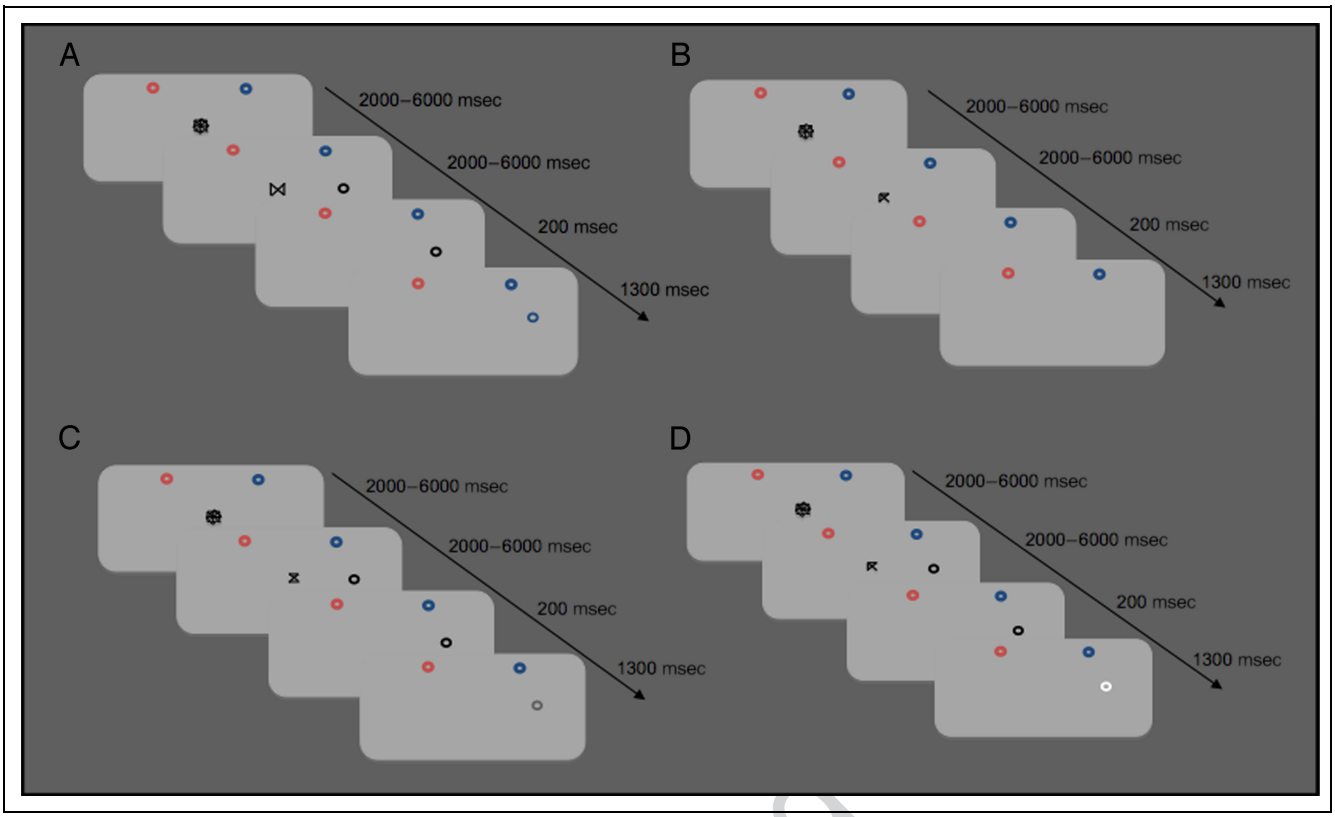


Figure 1. The sequence of events for the four trial types: (A) SR saccade, (B) SV saccade, (C) double-step SP, and (D) double-step PP.

target, and participants were required to make a second saccade toward the appropriate colored marker as quickly as possible. The last frame remained on for 1300 msec.

Double-step PP sequence. Following the fixation foreperiod, the partial offset of the fixation stimulus occurred, so it formed an arrow cue pointing to one of the marker stimuli located in the upper visual field. Simultaneously with this change, a peripheral target (black) appeared on the horizontal axis (as in the SR condition above). The peripheral target remained black for 200 msec and then changed to white for 1300 msec to match the peripheral changes in the SP double-step condition. Participants were instructed to make two continuous saccades, the first to the peripheral target and the second to the endogenous saccade goal in the upper visual field, as quickly as possible.

An important aspect of the stimulus design was that the stimulus display in the preparatory period, before fixation offset ("go signal"), was unique to that trial type. Thus, participants were aware of the saccades they would be required to make on that trial and could start to prepare the appropriate response. This enabled participants to start planning to make one or two saccades during this period. The experiment was carried out in four separate blocks of 32 trials with eight trials per condition and each block took approximately 6–7 min to complete.

Behavioral Results

Discarded Data

Saccades were excluded from further analysis if the latency was less than 100 msec or greater than 500 msec (3.58%). Trials where small multistepping responses were observed (9.18%) and those made in the wrong direction (5.83%) were also discarded.

Saccade Latency

The mean latency of saccades observed in the two double-step and two single-step (control) trials are shown in Table 1. The latency of single stimulus-elicited and single voluntary (SV) saccades were 287.9 and 291.8 msec, respectively

Table 1. Mean Saccade Latency (*SE* in Parentheses) for the First and Second Saccades Made in Double-step Trials (PP and SP Conditions) and in the Single-step Control Trials (SV and SR Conditions)

Condition	*First Saccade (msec)*	*Second Saccade (msec)*
SR	287.9 (6.1)	N/A
SV	291.8 (10.2)	N/A
SP	318.6 (12.6)	291.8 (12.1)
PP	275.5 (8.9)	239.7 (14.4)

($t(14) = 0.53, p > .05$). The main focus of interest here is the mean latency (ISI) of second (voluntary) saccades made in the double-step conditions compared with the latency of comparable single saccades. The mean latency of the second voluntary saccades in the PP condition (239.7 msec) is ~52 msec less than that of SV saccades ($t(14) = -2.27, p < .05$). By contrast, the latency of second saccades in the SP condition (291.8 msec) is similar to that of SV saccades ($t(14) = -1.15, p > .05$).

Functional Imaging: Data Acquisition and Analysis

EPI images were acquired with a 3-T Siemens Trio scanner. There were 10 sessions (each consisting of 32 trials) for each participant, and 102 volumes were acquired. Functional data were collected using EPIs, which covered the whole brain, with a voxel size of 3 × 3 × 3 mm (TR = 3000 msec, TE = 32 msec, resolution = 64 × 64, field of view = 192 × 192, flip angle = 90°, number of slices = 42 interleaved sequence). Stimuli were presented using Experiment Builder (SR Research, Mississauga, Ontario, Canada) software via a projector located outside the scanner room. A mirror on the head coil enabled participants to view the stimuli projected onto a rear projection screen located at the back of the scanner bore. Before the functional imaging session, a T1-weighted structural image was acquired using an MP-RAGE sequence (TR = 1830 msec, TE = 5.5 msec, resolution = 256 × 256, flip angle = 11°, number of slices = 160, field of view = 256 × 256).

Data were analyzed using SPM5 (Functional Imaging Laboratory, UCL, London, United Kingdom, 2005, www.fil.ion.ucl.ac.uk/spm) and Matlab 6.5 (The MathWorks, Natick, MA, 2002). The MarsBaR-0.41 toolbox for SPM (Brett, Anton, Valabregue, & Poline, 2002) was used for the ROI analysis.

Image Preprocessing

Spatial realignment was performed using SPM5 to realign all images within each session to the mean image to correct for head movements using data sampled every 4 mm and second degree B-spline interpolation. All the images were normalized to the MNI space (defined by Montreal Neurological Institute), the default EPI template in SPM5 using both linear affine and nonlinear transformations (Friston et al., 1995). Spatial smoothing was performed using an 8-mm Gaussian smoothing kernel to improve the signal-to-noise ratio.

First-level Regression Analysis

A general lineal model (GLM) was applied to identify BOLD activation in relation to the separate event types. There were four different trial types, and each trial type has three events: (i) fixation, (ii) response preparation, (iii) go signal–response. Each event in a trial type was modeled as one regressor (3 × 4) and the GLM design matrix included these 12 task-related regressors. In addition, six head movement regressors derived from the realignment stage (head movement parameters) were included as covariates of no interest. The GLM was applied to each voxel independently to identify voxels that were significantly activated for the different events of each condition. Regressors were checked to ensure that they were not significantly correlated with each other. A high-pass filter (cutoff = 128 sec) was used to improve the detection efficiency by filtering out the low-frequency noise caused by physiological effects, for example, breathing and scanner-related drifts. The analysis was carried out independently for each participant and focused exclusively on activity in the preparatory preresponse period.

Random Effects Group Analysis

After parameter estimation, six t contrasts were generated, which produced SPM{t} contrast maps, which were entered into a second level ("random effects") group analysis. The resulting SPM{t} maps for the significant contrasts were surface rendered onto the T1 MNI canonical template using MRIcron to show the probable anatomical location of activity (see Figure 2A–D). The random effects analysis was performed, using one-sample t tests, to examine significant activity (at $p < .05$, FDR corrected) at the group level for each of the six contrasts of interest. The contrast between the PP and SV condition (Figure 2A) revealed significant bilateral activation including regions of the middle frontal gyrus, precentral gyrus, superior and inferior parietal lobe, precuneus, superior temporal gyrus, and left medial frontal gyrus. The contrast between the PP and SR condition (Figure 2B) revealed a similar pattern of activity although not in the superior temporal gyrus. The contrast between the SP and SV condition (Figure 2C) revealed active voxels in the left middle frontal gyrus, bilateral superior parietal lobe, left precuneus, left medial frontal gyrus and left inferior frontal gyrus, left precentral gyrus, bilateral middle frontal gyrus, and inferior temporal gyrus. The contrast between the SP and SR condition (Figure 2D) revealed activity in the left middle frontal gyrus and bilateral in the superior parietal lobe. The contrast between the PP and SP conditions, however, did not reveal any significant regions of activity. An ROI analysis was performed to examine the change in signal across conditions as a method of reducing the severity of the corrections for multiple comparisons required for the whole-brain analysis (see Poldrack, 2007).

ROI Analysis

An ROI analysis was performed on the functional group data focussing on activity in the preparatory (preresponse) period. The ROIs were defined functionally using an orthogonal t contrast to compare the level of BOLD response observed in the preparatory period for all four of the saccade conditions (at the group level) with that observed during baseline. Thus, each saccade condition made an

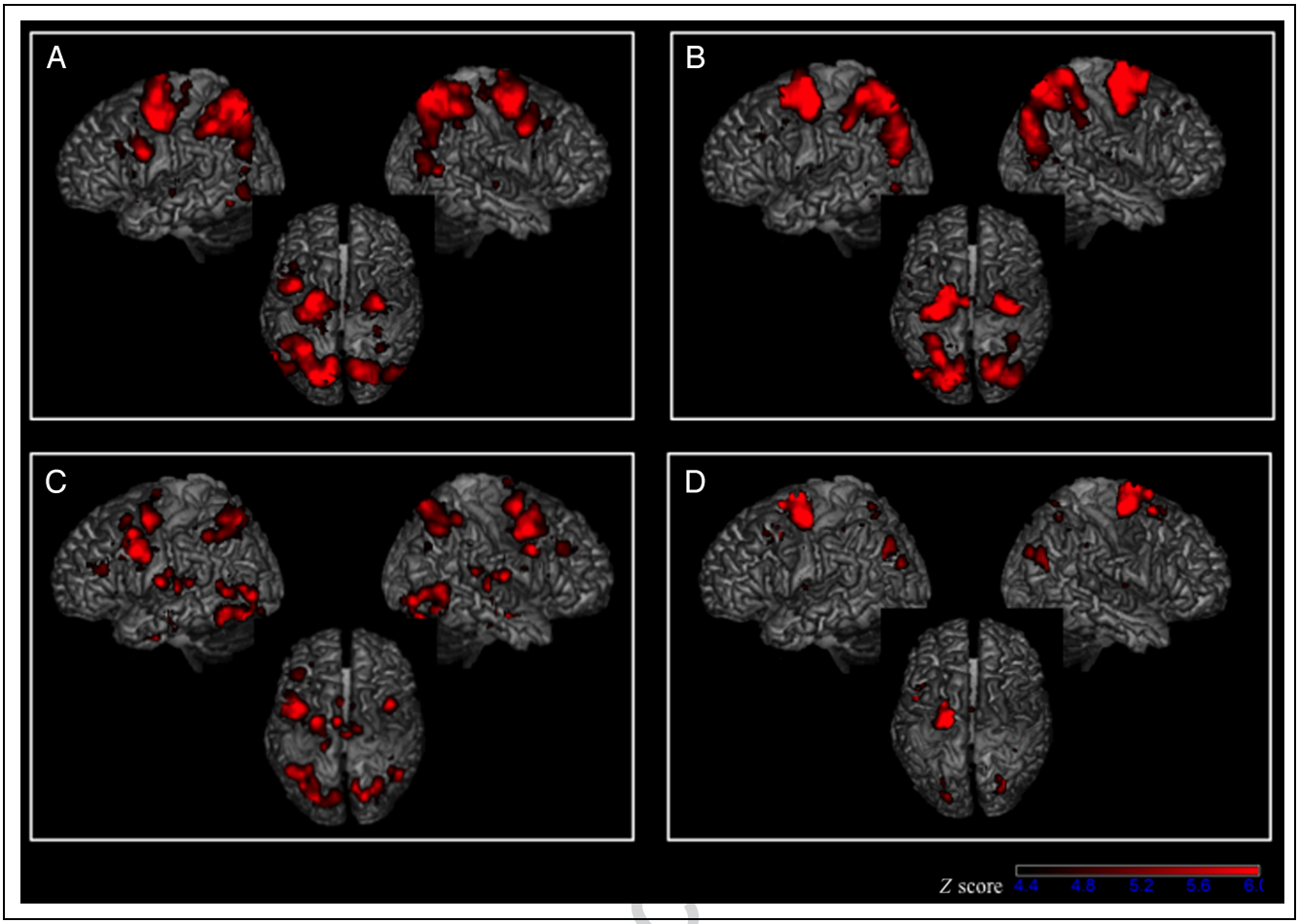


Figure 2. Cortical activation observed during the preparatory period, as revealed by *t* contrasts (*t* values are represented by color scale as shown; $p < .05$, corrected). Active voxels have been surface rendered (some active voxels located below surface have been shown projected onto the surface) onto a normalized 3-D template image using MRIcro. In each case, the left hemisphere is shown on the left and the right hemisphere is on the right. Significant activity was observed for the following contrasts: (A) PP versus SV saccade conditions: bilateral activation observed in the middle frontal gyrus, precentral gyrus, superior and inferior parietal lobe, precuneus, superior temporal gyrus, and left medial frontal gyrus; (B) PP versus SR condition, similar activations observed except not in the superior temporal gyrus; (C) SP versus SV condition, activations were found in the left middle frontal gyrus, bilateral superior parietal lobe, left precuneus, left medial frontal gyrus and left inferior frontal gyrus, left precentral gyrus, bilateral middle frontal gyrus and inferior temporal gyrus; (D) SP versus SR condition: activation in the left middle frontal gyrus and bilaterally in superior parietal lobe.

equal contribution to the definition of the observed ROIs. Bilateral activation was observed in the DLFC, including the middle frontal gyrus and the precentral sulcus (threshold $p < .001$, uncorrected); also in a second smaller region located more medially in DMFC (threshold $p < .01$, uncorrected) and another region in the posterior parietal cortex (PPC) that included the anterior part of the intraparietal sulcus (IPS; threshold $p < .001$, uncorrected). The coordinates (in MNI space; see Table 2) for each of the ROIs, which are consistent with the locations of the putative human FEF, SEF, and parietal eye field regions (Mort et al., 2003; Grosbras et al., 2001; Tehovnik, Sommer, Chou, Slocum, & Schiller, 2000).

The effect size (percent signal change) observed for each ROI (based on the SPM5{*t*} maps) was calculated using the default procedures of SPM and MarsBaR-0.41. MarsBaR estimates the signal change by multiplying the beta values for the single event by a new scaling regressor calculated specifically for that event. An estimated baseline is obtained from the "session regressors"—constant terms included the SPM design matrix with model variance in the design that might arise because of global differences in image intensity between scanning sessions. In the ROI analysis, they provide an estimate of the mean response in that ROI, which is used as the denominator in the calculation of percent signal change. The percent signal change is calculated as the maximum value of the estimated event response for a particular condition divided by the mean estimated session baseline for that ROI. Figure 3 shows the percent signal change, observed for each saccade condition, in the ROIs identified in the DLFC, PPC, and DMFC.

DLFC (Middle Frontal Gyrus and Precentral Sulcus)

The percent signal change observed in the ROIs identified bilaterally in the DLFC is shown in Figure 3A. An ANOVA

Table 2. Summary of the Results of Paired Contrasts Performed to Examine the Signal Change Observed across Saccade Conditions for the ROI Analysis

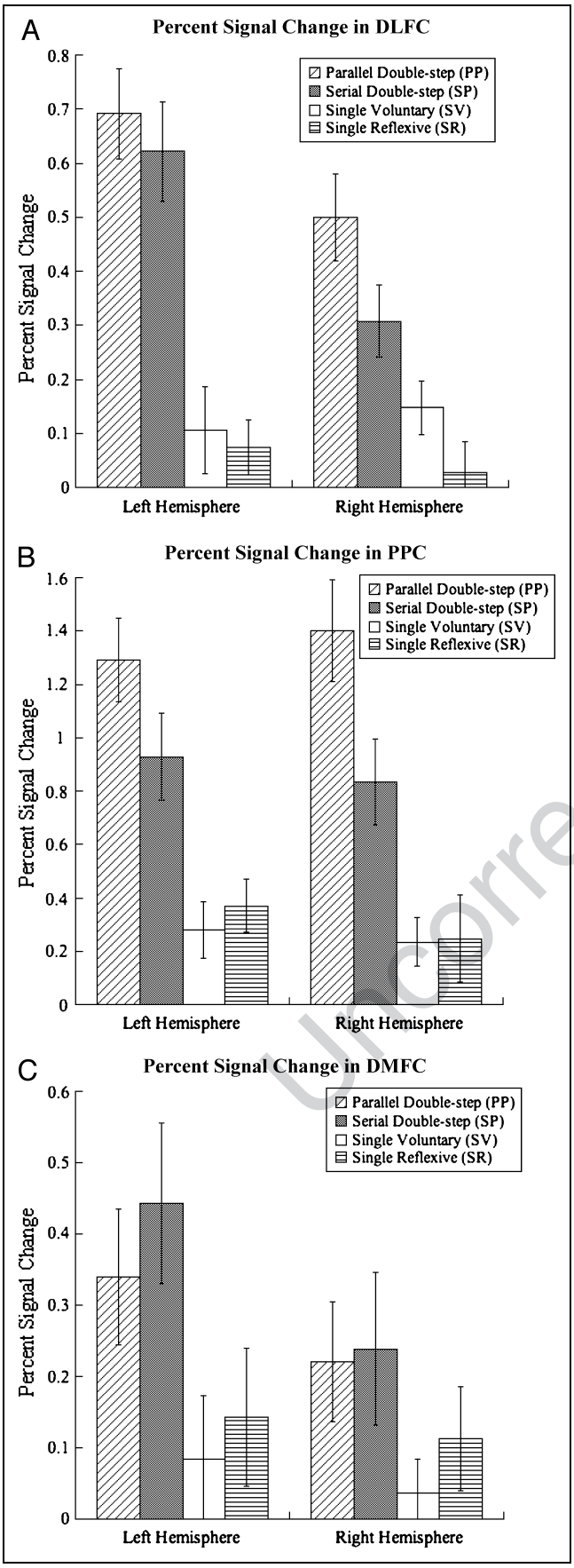
ROIs	*DLFC (FEF)*	*PPC (Parietal Eye Field)*	*DMFC (SEF)*
MNI Coordinates			
Left hemisphere	−26, −10, 52	−17, −65, 56	−7, 2, 53
Right hemisphere	27, −10, 47	20, −69, 59	N/A
Contrast			
Parallel versus serial			
L	$t < 1$	$t(14) = 2.1\ p < .05$	$t(14) < 1$
R	$t(14) = 2.2\ p < .05$	$t(14) = 2.6\ p < .05$	N/A
Parallel versus sing. vol.			
L	$t(14) = 6.8\ p < .001$	$t(14) = 6.0\ p < .001$	$t(14) = 2.5\ p < .05$
R	$t(14) = 3.5\ p < .05$	$t(14) = 5.2\ p < .05$	N/A
Parallel versus sing. reflex.			
L	$t(14) = 8.8\ p < .001$	$t(14) = 6.2\ p < .001$	$t(14) = 3.3\ p < .005$
R	$t(14) = 6.4\ p < .001$	$t(14) = 4.6\ p < .001$	N/A
Serial versus sing. vol.			
L	$t(14) = 4.9\ p < .001$	$t(14) = 3.6\ p < .01$	$t(14) = 2.2\ p < .05$
R	$t(14) = 1.6\ p > .05$	$t(14) = 3.1\ p < .01$	N/A
Serial versus sing. reflex.			
L	$t(14) = 6.2\ p < .001$	$t(14) = 3.2\ p < .01$	$t(14) = 2.6\ p < .05$
R	$t(14) = 3.64\ p < .01$	$t(14) = 2.8\ p < .05$	N/A
Sing. vol. versus sing reflex.			
L	$t(14) < 1$	$t(14) = 1.4\ p > .05$	$t(14) < 1$
R	$t(14) = 1.8\ p > .05$	$t(14) < 1$	N/A

ROIs were identified (functionally; threshold $p < .001$, uncorrected) in the DLFC, the PPC, and the DMFC. For the DLFC and the PPC, active voxels could reliably be observed in both hemispheres, whereas in the DMFC, activity was reliably observed in the left hemisphere only. The coordinates (in MNI space) of peak activity for each ROI are also shown. The percentage signal change for each ROI observed during the preparatory period was extracted using MarsBaR-0.41. Paired contrasts (*t* tests) were then performed on the percentage signal change observed in each ROI for each saccade condition during the preparatory period. The resulting *t* statistics and significance level are shown for each ROI.

revealed that the percent signal change was greater overall for the left hemisphere than the right hemisphere ($F(1, 14) = 6.09, p < .05$). Signal change was significantly influenced by the saccade condition ($F(3, 42) = 2.06, p < .001$), and there was a significant two-way interaction between saccade condition and hemisphere ($F(3, 42) = 9.53, p < .001$). Paired contrasts (*t* tests) were used to explore these effects and are summarized in Table 2. Signal change was significantly increased bilaterally for the PP condition compared with that observed in both of the single-saccade control conditions. Activity was significantly greater for the PP condition than the SP condition only in the right hemisphere ($t(14) = 2.21\ p < .05$)—although it can be seen in Figure 3A that this is due to increased left hemisphere activity in the SP rather than a decrease in activity associated with PP. Activity in the SP condition was greater bilaterally compared with the SR saccade condition and in the left hemisphere only when contrasted with the SV condition. There was no difference in activity when contrasting the SV and SR control conditions and no effect of hemisphere.

PPC and IPS

Figure 3B shows the percent signal change observed in the left and right hemisphere PPC ROIs for each saccade condition. An ANOVA showed there was no difference between hemispheres ($F < 1$), but activity was significantly modulated by saccade condition ($F(3, 42) = 15.46, p < .001$). There was no interaction between hemisphere and saccade condition ($F(3, 42) = 1.64, p > .05$). Paired comparisons (Table 2) show that activity was significantly greater



bilaterally for the PP condition compared with the SP condition and also when compared with both of the single-saccade conditions. Signal change observed for the SP double-step condition was also significantly greater bilaterally than for both single-saccade conditions. There was no difference in the level of PPC activity when contrasting the SV and SR saccade conditions.

DMFC and Superior Frontal Gyrus

Figure 3C shows the pattern of signal change in the DMFC. Activity was significantly greater overall in the left hemisphere than in the right hemisphere ($F(1, 14) = 5.69, p < .05$), and there was a significant effect of saccade condition ($F(3.42) = 3.67, p < .05$) but no interaction effect ($F(3, 42) = 2.97, p > .05$). Paired contrasts (Table 2) showed that signal change for the PP and SP conditions were comparable. Activity in the PP and SP double-step conditions was significantly greater for the single-saccade conditions. There was no difference in activity in DMFC when contrasting the two single-saccade conditions.

In the analysis described above, the ROIs were defined functionally, with the data from all four conditions making an equal contribution. There is, however, a potential issue (termed "double dipping") when ROIs are defined functionally as the same set of data is used to define the region and also to estimate the effect size in that region (see Kriegeskorte, Simmons, Bellgowan, & Baker, 2009). A further analysis was performed to examine this potential bias with the ROIs again being defined functionally (as before), but in this case, the data from each individual condition was contrasted with baseline to produce a number of functionally defined ROIs. The rationale for this approach is that if activity is greatest for one condition (e.g., PP). then it will make a greater contribution to the functional definition of the ROI; this bias will be reduced, however, if the ROI is defined using data from a different condition. ROIs were identified in the DLFC and PPC, but not in the DMFC and percent signal change calculated using MarsBaR. Paired contrasts showed that activity in the DLFC ROI was significantly greater in the PP condition than in the SP condition (right hemisphere only) when the ROI was defined functionally with the data from all four conditions, making an equal contribution, and also when data from the SP condition only was used to identify the ROI, but not when the ROI was defined using data from the PP condition or either of the single-saccade conditions. This shows that the activity

Figure 3. The percentage signal change observed in the ROIs identified bilaterally in the DLFC, the PPC, and the left DMFC. The MNI coordinates for each of these ROIs are shown in Table 2 and are consistent with the FEFs, the "parietal eye field" (in the IPS), and the SEF. The average percentage signal change (with *SE*) observed in each ROI during the preparatory preresponse period is shown for the four saccade conditions.

in the DLFC may be influenced by the data used to define the ROI, and this could reflect a shift between the dorsomedial and lateral subdivisions of the FEF (cf. Mort et al., 2003). For the PPC, the pattern of results across saccade conditions was not biased by the data set used to functionally define the ROI.

DISCUSSION

The neural basis of programming sequences of saccades, serially and in parallel, was investigated by implementing a double-step saccade paradigm in an event-related functional imaging study. A reduction in the ISI for second saccades in the PP condition is consistent with the view that both saccades could be programmed, at least partially, in parallel. The event-related design enabled the analysis of functional imaging data focused on examining neural activity (BOLD response) during the preresponse, preparation period. A random effects group analysis revealed saccade-related activity, during the preparatory period, bilaterally in regions of the parietal and frontal cortex of both hemispheres. Contrasts between the double-step saccade conditions and the single-step control conditions revealed large regions of activity bilaterally in the middle frontal gyrus, precentral gyrus, precuneus, superior temporal gyrus, the superior and inferior parietal lobe, and the left medial frontal gyrus. An ROI analysis examined the signal change (BOLD response) reliably observed in areas of the posterior parietal, DLFC, and DMFC. The ROIs were identified functionally and correspond to the putative human FEFs in the DLFC, the PPC including the IPS ("parietal eye fields" in IPS), and the SEFs located in the DMFC. An analysis of the percent signal change revealed greater left hemisphere activity for the FEF and SEF regions in double-step conditions compared with single-saccade conditions. A dominant role for the left FEF and SEF has been demonstrated for the control of novel saccade sequences (Grosbras et al., 2001) and for the left SEF in the control of self-paced saccades (Grosbras et al., 1999). Grosbras et al. proposed that a left hemisphere network has a greater role in the cognitive control of saccades (see also Mort et al., 2003). The coordinates of the foci of FEF activity in the present study (Table 2) are more consistent with the dorsomedial or superior subdivision of the FEF (Mort et al., 2003; Grosbras et al., 2001; Luna et al., 1998) The main focus of the present study was dissociating cortical activity associated with PP of saccades, and the ROI analysis revealed that this was associated with greater activity in the FEF region (right hemisphere) and in the PPC (bilaterally), but not in the SEF. The functional significance of these findings will be discussed.

Saccade Timing

The elevated activity observed in FEF (right hemisphere) and PPC (bilaterally) for the PP saccade condition in the present study could plausibly reflect processes associated with the endogenous control over the timing of both saccades. The FEFs have projections with the intermediate (saccade-related) layers of the SC, which enables higher-level cortical structures to exert an influence over oculomotor behavior (Sommer & Wurtz, 2000). The signals conveyed by the FEF to the SC projections are complex and include visual and visuomotor activity as well as cognitive processes such as delay period activity (Sommer & Wurtz, 2000) as well as in aspects of saccade timing (Sommer & Tehovnic, 1997). The timing of saccade initiation has been related to the activity of FEF neurons (Hanes, Thompson, & Schall, 1995), and reversible inactivation of this region specifically delays the timing of saccades made in the double-step paradigm (Sommer & Tehovnic, 1997). Murthy et al. (2007) revealed a role for FEF neurons in parallel saccade programming and showed that the timing of secondary corrective saccades, made after a short ISI, could be specifically related to activity of movement-related neurons. A similar relationship has also been observed in neurons in the SC (Port & Wurtz, 2003; McPeek & Keller, 2002), and it is possible that this activity is itself mediated by higher-level cortical inputs. The FEFs (especially the right FEF) appear to have a role in the decision processes of when the second saccade will be initiated under conditions where both saccade goals are known before the initiation of the first saccade.

Goal Representation

The elevated cortical activity observed for the PP double-step condition could also reflect processes associated with representing both saccade goals concurrently. Neurons in the IPS are thought to have a role in the topographical representation that encodes the location of salient objects, enabling behaviorally relevant responses to be made. This representation integrates visual information, with motor responses and higher-level cognitive information of the relevance of the object to on-going behavior and reward (Gottlieb, 2007). The "salience" (stimulus properties) and "relevance" (to behavior) of an object (termed "priority"; Fecteau & Munoz, 2006) is represented across various structures such as the FEF and the SC. This representation of priority is critical to the processes involved in the control of selective attention and overt behavior. Increased cortical activity, observed for the PP condition compared with the SP condition in the present study, could reflect the priority representation associated with two saccade goals. These representations could facilitate the orienting of covert attention and overt saccadic responses to the second goal location (Rolfs, Jonikaitis, Deubel, & Cavanagh, 2010), which is reflected in the reduction in ISI.

It has been shown that neurons in monkey FEF are able to represent more than one saccade goal simultaneously (McPeek, 2006), although this has not been related to the reduction in the ISI characteristic of PP. McPeek

(2006) showed that saccades that curve toward a distractor are accompanied by residual activity of neurons coding the distractor location (McPeek, 2006). Thus, saccade target selection does not appear to operate in a strict "winner-take-all" fashion, as activity associated with the second saccade goal can be maintained during the preparation and execution of the first saccade (McPeek & Keller, 2002). An fMRI study performed by Heide et al. (2001) revealed increased FEF activity for memory-guided triple-step saccade sequences, which was attributed to the endogenous control processes required for saccade generation and also to spatial memory processes involved in encoding the briefly presented saccade targets used in their paradigm. The increased FEF activity for the PP condition observed in the present study could reflect the simultaneous encoding of more than once of the potential saccade goal, and it also shows that the FEFs have a role in the preparation of saccade sequences that does not depend on the high demands on spatial memory processes in situations where briefly presented targets are used.

Preparatory Set

A noteworthy finding of the present study is that the percent signal change observed in the FEF during the preparatory period was greater for the SP double-step condition than for the SR saccade condition. For these two conditions, the initial stimulus configurations are similar, but the shape of the fixation stimulus informed the participant of the upcoming requirement to make either one or two saccades. The processes involved in encoding the first saccade were comparable for both conditions, but the knowledge that two saccades would be required in the SP double-step condition resulted in elevated activity in both the FEF and parietal eye fields. The elevated activity for the SP condition is not consistent with a generalized increase in load associated with encoding two saccade goals but reflects the anticipation of a second response. Similarly, an increase in BOLD response in the human FEF occurs when participants prepare to make an antisaccade compared with that observed when a prosaccade is required before knowledge of goal location (DeSouza et al., 2003; Connolly et al., 2002), which has been interpreted as a role for the FEFs in the preparatory set. In these fMRI studies, activity in the IPS and SEF regions did not show preparatory set activity (although IPS activity approached significance in DeSouza et al., 2003). The elevated FEF and IPS activity observed for the SP condition in the present study may reflect preparatory processes involved in the decision to make one or two saccades similar to that observed in tasks where the decision is to prepare either a prosaccade or antisaccade.

Spatial Remapping

The signal change observed in the FEF and PPC regions was greater for both of the double-step conditions compared with the single-saccade conditions with the greatest increase being observed for the PP condition. This increase in activity may reflect the process of coordinate transformation (or "spatial remapping"), which is required to compensate for the retinal displacement produced by the first saccade in double-step paradigms (Mays & Sparks, 1980; Becker & Jürgens, 1979; Hallett & Lightstone, 1976). Spatial remapping is required in the double-step task to make an accurate saccade after a change of fixation and is a function of neurons in the parietal eye field (Li & Andersen, 2001; Duhamel, Colby, & Goldberg, 1992; Zipser & Andersen, 1988) and FEF (Umeno & Goldberg, 2001; Goldberg & Bruce, 1990) in nonhuman primates. Parietal neurons are modulated by extraretinal (eye position) signals (Andersen, 1989), which are required for computing the vector of second saccades in double-step saccade tasks (Li & Andersen, 2001; Xing & Andersen, 2000). Goldberg and Bruce (1990) showed that the activity of FEF neurons were tuned to the dimension of the saccade and not to the retinal coordinates of the two visual targets. They proposed that the function of these neurons was to transform the visual and spatial location of the saccade target into the desired motor coordinates of the desired saccade (Goldberg & Bruce, 1990).

A role for human PPC in spatial remapping processes has been shown in imaging studies using a memory-guided double-step task with briefly presented targets thought to involve working memory processes (Medendorp, Goltz, & Tutis Vilis, 2006; Medendorp, Goltz, Tutis Vilis, & Crawford, 2003; Tobler et al., 2001). The location of significant voxels in parietal cortex, as reported by Medendorp et al. (2006), are similar to those of the parietal ROI in the present study. This region has also been implicated in the control of saccades made in the double-step paradigm in study in which TMS study was used to interfere with the remapping process. Morris, Chambers, and Mattingley (2007) showed that a train of TMS pulses applied to the right posterior parietal region (at coordinates similar to those for PPC in Table 2) produced a selective deficit in the accuracy of second saccades without having an influence on the timing of second saccades. The increase in activity in the intraparietal region for the SP and PP conditions in our study could, therefore, be related to the spatial remapping processes required for the second saccade. As noted above, spatial updating and the representation of the second saccade goal are possible for the PP condition but not in the SP condition during the preparatory period. It is possible, however, that the elevated parietal activity in the SP condition reflects the activity associated with the preparation for the spatial updating process that will be required once the first saccade has been made.

Control of Saccade Sequences

A significant increase in activity was found bilaterally in the DMFC consistent with the location of the human SEF (Grosbras et al., 1999). The SEF activity was greater

for both of the double-step conditions than for the single-saccade conditions—but in contrast to the PPC and FEF, there was no difference between the PP and SP double-step conditions. The increased SEF activity for double-step conditions is consistent with the role for this region in the control of saccades made in a sequence (Isoda & Tanji, 2002; Heide et al., 2001) and in higher-level aspects of saccade programming (Parton et al., 2007). The SEFs have also been implemented in the control of saccades produced in tasks with a high level of cognitive control, such as no-go and change of plan tasks (Stuphorn & Schall, 2006; Husain et al., 2003). The double-step paradigm used in the present study did not require a change of plan but did require cognitive control for the initiation of the correct sequence order and for the monitoring of errors. Thus, the SEF seems to have a role in the control of saccade sequences, but not in the PP of saccades.

In conclusion, this study revealed a role for the FEF, parietal eye field, and SEF in the preparation to initiate saccades in a double-step paradigm. In the PP condition greater activity was observed in the right FEF and bilaterally in the parietal cortex, but not in the SEF. As has been noted, it is difficult to disambiguate the cognitive processes involved in different conditions in situations where a number of different cognitive "states" (spatial attention, spatial and temporal expectation, motor preparation, etc.) are involved (Sparks, 1999), but the involvement of the FEF in PP may plausibly reflect the increased salience for the representation of concurrent saccade goals along with the preparatory set, whereas the parietal activity could reflect advance preparation for spatial remapping of the second saccade goal.

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Reprint requests should be sent to Yanbo Hu, Department of Psychology, Royal Holloway, University of London, Egham Hill, United Kingdom, TN13 2QE, or via e-mail: Yanbo.Hu@rhul.ac.uk.

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