Self-initiated versus externally triggered movements

II. The effect of movement predictability on regional cerebral blood flow

I. Harri Jenkins,1 Marjan Jahanshahi,2,3 Markus Jueptner,1 Richard E. Passingham1,4 and David J. Brooks1,2

1MRC Cyclotron Unit, Hammersmith Hospital, 2Institute of Neurology, 3MRC Human Movement and Balance Unit, London and 4Department of Experimental Psychology, University of Oxford, Oxford, UK

Summary
Event-related potential studies in man suggest a role for the supplementary motor area (SMA) in movement preparation, particularly when movements are internally generated. In a previous study combining PET with recording of movement-related cortical potentials, we found similar SMA activation and early pre-movement negativity during self-initiated and predictably paced index finger extensions. Early pre-movement negativity was absent when finger movements were paced by unpredictable cues. We postulated that preparation preceding self-initiated and predictably cued movements was responsible for equivalent levels of SMA activation in these two conditions. To test this, we have performed further studies on six normal volunteers with H215O-PET. Twelve measurements of regional cerebral blood flow were made in each subject under three conditions: rest; self-initiated right index finger extension at a variable rate of once every 2–7 s; and finger extension triggered by pacing tones at unpredictable intervals (at a rate yoked to the self-initiated movements). Activation associated with these conditions was compared using analysis of covariance and t-statistics. Compared with rest, unpredictably cued movements activated the contralateral primary sensorimotor cortex, caudal SMA and contralateral putamen. Self-initiated movements additionally activated rostral SMA, adjacent anterior cingulate cortex and bilateral dorsolateral prefrontal cortex (DLPFC). Direct comparison of the two motor tasks confirmed significantly greater activation of these areas and of caudal SMA in the self-initiated condition. These results, combined with our previous data, suggest that rostral SMA plays a primary role in movement preparation while caudal SMA is a motor executive area. In this experiment and in our earlier study, DLPFC was activated only during the self-initiated task, in which decisions were required about the timing of movements.

Keywords: PET; self-initiated movement; DLPFC; SMA; motor preparation

Abbreviations: AC = anterior commissure; BP = Bereitschaftspotential; DLPFC = dorsolateral prefrontal cortex; IRI = inter-response interval; MEG = magnetoencephalography; MRP = movement-related cortical potential; MT = movement time; PC = posterior commissure; PMC = (lateral) premotor cortex; rCBF = regional cerebral blood flow; REST = baseline resting condition; RT = reaction time; SI = self-initiated movement task; SMA = supplementary motor area; SMC = primary sensorimotor cortex; SPM = statistical parametric mapping; TRIG = triggered movement task; VAC = vertical line through; the anterior commissure; VPC = vertical line through the posterior commissure

Introduction
We previously have performed PET activation experiments designed to explore the functional anatomy of self-selected or self-initiated movements and, in particular, the role played by premotor and prefrontal cortical areas (Deiber et al., 1991; Playford et al., 1992; Jahanshahi et al., 1995). Our findings suggest that the rostral supplementary motor area (SMA) and the dorsolateral prefrontal cortex (DLPFC) are activated predominantly by tasks in which the timing and/or direction of movement are not specified by external cues. Evidence in support of a role for the SMA in mediating
volitional movements comes from a variety of other experimental techniques including single-cell microelectrode recordings and lesion studies in primates (Thaler and Passingham, 1989; Mushiake et al., 1990) and the measurement of movement-related cortical potentials (MRPs) in man. The early component of the Bereitschaftspotential (BP), a negative cortical potential that develops up to 1.5 s prior to self-initiated movements, has maximum amplitude at the vertex and has been considered to involve the SMA (Deecke et al., 1969).

Our understanding has been advanced by the study of patients with Parkinson’s disease, where akinesia (difficulty in initiating movements) is characteristic. Dick and colleagues found that Parkinson’s disease patients had a significantly smaller amplitude of the early phase of the BP than normal controls while performing self-initiated finger movements (Dick et al., 1989). Using PET, Playford and colleagues found that during performance of paced joystick movements in freely selected directions, Parkinson’s disease patients failed to activate mesial frontal cortex (SMA and adjacent anterior cingulate cortex) normally (Playford et al., 1992). In Playford’s study, in contrast to the electrophysiological studies of Dick and colleagues, it was the direction of movement rather than the timing that was self-generated. The findings of both studies, however, suggest that failure to activate mesial frontal cortex normally underlies the akinesia seen in Parkinson’s disease and add weight to the claim that the SMA is an important generator of the early phase of the BP.

In a more recent study (Jahanshahi et al., 1995), we combined the spatial resolution of PET with the temporal resolution of MRP recording, comparing self-initiated with externally cued finger extension in groups of control subjects and akinetic Parkinson’s disease patients. Subjects rested the index finger of the right hand on a zero force switch, and made simple right index finger extensions, at a mean frequency of once every 3 s; this was the self-initiated movement task. The frequency was chosen to ensure comparable performance (in terms of frequency of movement) between the control and patient groups under study. Each time the finger was extended, contact with the switch was broken and a tone was generated. This sequence of tones was then played back to the subjects to be used as stimuli for index finger extension movements in the externally triggered (paced) condition. The methodological details of this study are set out in the report by Jahanshahi and colleagues (Jahanshahi et al., 1995).

We found that self-initiated movements (compared with rest) activated the rostral and caudal SMA and adjacent anterior cingulate cortex strongly and that there was significantly impaired activation of these areas in the Parkinson’s disease group. In conjunction with this, the amplitude of the early BP was reduced in the Parkinson’s disease group compared with the control subjects during self-initiated movements. We had expected to find significantly greater activation of SMA when comparing self-initiated movements with externally triggered movements by controls, but no difference was seen; the externally triggered movements produced extensive SMA activation compared with rest. Additionally, an early BP was detectable preceding both the self-initiated and externally triggered movements. In the control group, with PET, the only significant difference between the two conditions was found in the right DLPFC, where there was greater activation during self-initiated movements.

Our behavioural data from this experiment showed that all the subjects tended to generate fairly regular movements at a frequency of one every 3 s in the self-initiated task. We postulated that these pacing tones subsequently used for the externally triggered movement task would, therefore, have been predictable. Because of this predictability, we considered it possible that preparation to move at a specific time (not just general readiness for movement) was taking place during the triggered task, explaining the activation of the medial premotor areas and detectable early BP. This supposition was supported by an additional MRP condition from the same study (Jahanshahi et al., 1995) which showed that when triggered movements were made in response to pacing tones at unpredictable intervals ranging from 3 to 8 s, no identifiable BP was produced.

To test this hypothesis, we designed a further experiment, in which self-initiated finger extensions were contrasted with externally triggered finger extensions which were paced in an unpredictable fashion. The methods and procedures used were the same as those in our previously reported study (Jahanshahi et al., 1995); this was done to facilitate comparison of the two data sets.

**Methods**

**Subjects**

Six normal male volunteers took part in the study. Their mean age was 32 years (range 22–53 years). Handedness was assessed using a modified version of the Edinburgh handedness inventory (Oldfield, 1971); all were right handed. All subjects gave informed written consent. The PET studies were approved by the ethics committee of the Royal Postgraduate Medical School, Hammersmith Hospital, London, and permission to administer radioactive H$_{2}^{15}$O was given by the Administration of Radioactive Substances Advisory Committee of the Department of Health, UK.

**Experimental design**

**Experimental conditions**

Subjects placed the index finger of the right hand on a zero force touch switch. This was linked to a Goupil Golf computer, to which a loudspeaker was attached. This computer had been programmed in such a way as to allow the following three experimental conditions to be performed during PET scanning.

In the first condition (SI), the subjects were asked to make self-initiated right index finger extensions, during which they
briskly raised the finger, breaking contact with the switch, and then returned the finger to make contact with the response button. The computer generated a short audible tone 100 ms after the contact was broken. Subjects were trained briefly before scanning to generate the finger extension movement at random intervals between 2 and 7 s. The computer recorded the intervals between movements (inter-response interval; IRI) and also the duration (movement time; MT) of individual movements.

In the second condition (TRIG), the computer played back tones at the same intervals as were generated during the previous self-initiated task. Subjects were instructed to make the same extension movement of the index finger, but this time in response to the tone. The timing of the tones was not predictable because they had been generated in as variable a fashion as possible in the SI condition. Reaction times (RTs) and MTs were recorded for each movement in every frame of 30 s, followed by a second frame of 2 min and 45 s.

In the third condition (REST), subjects attended to the same sequence of tones played back by the computer (the tones generated during the previous self-initiated task and replayed during the triggered task), but made no movements. The sequence of tones during the SI and REST conditions served to control for activation resulting from their presence in the TRIG condition.

Changes in performance frequency during motor tasks involving discrete movements have been shown to exert a major effect on cerebral activation in functional imaging studies (Sabatini et al., 1993; Sadato et al., 1996; Jenkins et al., 1997). This could be a confounding variable in a study in which the motor task is self-initiated. Therefore, the conditions were performed in the order SI–TRIG–REST. By using this study design, the different tasks were yoked together, ensuring that the frequency of movements would not vary between the SI and TRIG conditions. This sequence of tasks was repeated four times during the PET session.

**Measurement of rCBF with PET**

Each subject underwent 12 consecutive scans during a single PET session lasting ~3 h (i.e. four blocks of the three yoked conditions). During each scan, the distribution of radioactivity following the intravenous injection of the positron-emitting tracer H\textsubscript{2}\textsuperscript{15}O was measured; this was used as an index of relative regional cerebral blood flow (rCBF). The changes in rCBF induced by specific behavioural tasks are coupled to changes in the pattern of local neuronal (synaptic) activity (Raichle, 1987; Jueptner and Weiller, 1995).

All subjects were scanned lying supine with their eyes closed in a darkened room. They were positioned such that the upper limit of the data set extended to the vertex of the skull. This was done to ensure that the SMA fell within the 10.65 cm axial field of view of the scanner. As a result of this, imaging of posterior fossa structures was only partial.

Scans were performed with a CTI 953B PET camera (CTI Inc., Knoxville, Tenn., USA). The physical characteristics of this camera are described elsewhere (Spinks et al., 1992). The camera was used in the ‘3D’ mode, whereby the inter-detector collimating septa were withdrawn (Bailey et al., 1991). Data were collected from 16 rings of detectors with an axial field of view of 10.65 cm. Attenuation of radiation by the head was corrected using a transmission scan collected over 20 min during exposure of \textsuperscript{68}Ge\textsuperscript{68}Ga rotating rod sources prior to the H\textsubscript{2}\textsuperscript{15}O activation scans. The emission data were then reconstructed by filtered back projection using a Hanning filter of cut-off frequency 0.5 cycles per pixel. The reconstructed images had a resolution of 8.5 × 8.5 × 4.3 mm at full width half maximum (Spinks et al., 1992). Every plane was displayed in a format of 128 × 128 pixels, each pixel having dimensions of 2.0 × 2.0 mm. The reconstructed data set comprised 31 planes.

Each of the 12 emission scans comprised a background frame of 30 s, followed by a second frame of 2 min and 45 s. At the start of the background frame, an intravenous infusion of H\textsubscript{2}\textsuperscript{15}O (specific activity 13.2 mCi) was commenced, administered via a cannula sited in the left forearm. This infusion was continued at a rate of 10 ml/min for 2 min, and was followed by a normal saline flush of 30 s. In our experience, it takes on average 30–35 s for this activity to reach the brain (Silbersweig et al., 1993). Therefore, each experimental condition was started at the end of the background scan and was continued beyond the completion of the second frame (for a total of 3 min).

This process was repeated for all 12 scans, commencing the H\textsubscript{2}\textsuperscript{15}O infusion at 10 min intervals for each scan, to allow time for the radiation (\textsuperscript{15}O has a half-life of ~2 min) to decay to background levels. The integrated counts accumulated over the 165 s of the second frame, corrected for the background activity recorded during the first frame, were used as an index of rCBF during each condition.

All calculations and image manipulations were performed on SPARC computers (Sun Microsystems Inc., Mountain View, Calif., USA) using PROMATLAB (The MathWorks Inc., Natick, Mass., USA), and ANALYZE 5.0 software (Robb and Hanson, 1991) for image analysis (Biodynamic Research Unit, Mayo Foundation, Rochester, Minn., USA). Statistical analysis of rCBF images was performed using statistical parametric mapping (SPM, Wellcome Department of Cognitive Neurology, London).

In the first stage of analysis, the 31 original planes of data were interpolated linearly to 43 planes to render images with approximately cubic voxels. The 12 images from each subject were then realigned to the first scan (to remove any differences caused by head movement), using Automated Image Registration Software (Woods et al., 1992). After realignment, the 12 images were averaged to produce a mean image from each subject, on which the anterior commissure–posterior commissure (AC–PC) line was identified. All the images were then reoriented to this line and rescaled (Friston et al., 1991a) to fit a standard stereotactic space as defined in the brain atlas of Talairach and Tournoux (Talairach and Tournoux, 1988). This results in images with a maximum of...
26 planes parallel to the AC–PC line and an effective interplanar distance of 4 mm. Each pixel has in-plane dimensions of $2 \times 2$ mm. These slices were resampled in a non-linear way to account for differences in non-linear brain shape (Friston et al., 1991a). Each stereotactically normalized image was smoothed with a low pass Gaussian filter (full width half maximum of $10 \times 10 \times 6$ pixels; $20 \times 20 \times 12$ mm) (Friston et al., 1990) to compensate for inter-subject gyral variability and to attenuate high frequency noise, thus increasing the signal to noise ratio.

Focal changes in rCBF between conditions have two components, one due to the activating effect of the task in question, and the other due to any changes in global cerebral blood flow that may occur. These two effects can be considered as independent and additive (Friston et al., 1990). Therefore, variations in global blood flow between subjects and conditions were removed by analysis of covariance with global flow as the confounding variable. This resulted in the generation of a map of group mean blood flow for each of the 12 different scans (with the global CBF adjusted to 50 ml/dl/min). The mean rCBF values of each voxel in these maps, together with their associated error variances across the group of six subjects, were used for further analysis.

The conditions were then compared using the $t$ statistic, transformed to the standard normal distribution (Friston et al., 1991b). Four comparisons were undertaken using SPM software: SI versus REST; TRIG versus REST; SI versus TRIG; and TRIG versus SI. These comparisons allow the identification of areas activated by each of the two motor tasks compared with rest, and also the identification of any areas of significant difference in activation between the two motor conditions.

Results are reported at a threshold of $P < 0.05$ corrected for multiple comparisons. The effective number of independent comparisons is much less than the total number of voxels in the data set because of the smoothing employed during analysis (Friston et al., 1991b). In other words, neighbouring voxel rCBF values are correlated. The correction for multiple comparisons takes account of this, using an auto-correlation function estimated empirically from the smoothness of the SPM.

**Results**

**Behavioural data**

The mean IRI for self-initiated movements across the group of six subjects was 4.46 s, with a range of IRIs from 1.1 to 9.1 s. For the triggered condition, the mean RT for individual movements was 330 ms (SD = 110 ms). The mean MTs were 365 ms for the self-initiated condition (SD = 216 ms) and 493 ms for the triggered condition (SD = 238 ms). The MTs for the self-initiated condition were significantly shorter than for the triggered condition ($P = 0.002$, paired $t$-test).

**Measurement of rCBF with PET**

The axial extent of the data set was from 20 mm below the AC–PC line to 72 mm above it. Thus, imaging of posterior fossa structures (brainstem and cerebellum) was only partial.

**Comparison 1: self-initiated versus rest**

Areas showing significantly increased rCBF during self-initiated movements compared with rest were: striatum and insular cortex, DLPFC (areas 9, 10 and 46), parietal cortex area 40, and lateral premotor cortex (PMC), all bilaterally; the left (contralateral) primary sensorimotor cortex (SMC) and parietal areas 7 and 39 in the right hemisphere; and anterior cingulate cortex and rostral and caudal SMA medially. The anterior cingulate activation involved areas both anterior and posterior to the VAC line (a vertical plane through the anterior commissure) corresponding to the rostral cingulate premotor area and dorsal cingulate motor area identified using PET in the human brain by Fink and colleagues (Fink et al., 1997). The axial extent of the areas activated, the peak Z scores and the percentage increases in rCBF are given in Table 1. The SPM projections of this comparison are shown in Fig. 1A.

**Comparison 2: triggered versus rest**

Areas showing significantly increased rCBF during triggered movements compared with rest were: the left (contralateral) SMC, left parietal area 40, left insula, left striatum and caudal SMA medially, extending to cingulate sulcal cortex corresponding to the dorsal cingulate motor area (Fink et al., 1997). The axial extent of the areas activated, the peak Z scores and the percentage increases in rCBF are given in Table 2. The SPM projections of this comparison are shown in Fig. 2A.

**Comparison 3: self-initiated versus triggered**

Areas showing significantly increased rCBF during self-initiated compared with triggered movements were: the DLPFC (areas 9, 10 and 46), parietal area 40, insular cortex and PMC, all bilaterally; frontal area 44 on the right only, parietal areas 7 and 39 on the right only, and right striatum; and anterior cingulate cortex (again anterior and posterior to the VAC line) and both rostral and caudal SMA medially. The axial extent of the areas activated, the peak Z scores and the percentage increases in rCBF are given in Table 3, and the SPM projections of this comparison are shown in Fig. 3A.

**Comparison 4: triggered versus self-initiated**

Areas showing significant relative increases in rCBF during triggered compared with self-initiated movements were: the left posterior parts of the middle and inferior temporal cortex, the occipito-parietal cortex in the left hemisphere (areas 39
Table 1 Significant rCBF increases during self-initiated movement compared with rest

<table>
<thead>
<tr>
<th>Area activated</th>
<th>Extent of area activated (relative to AC–PC line)</th>
<th>Talairach co-ordinates of peak activation</th>
<th>Z score of peak activation</th>
<th>Mean flow increase (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
<td>z</td>
</tr>
<tr>
<td>Putamen (L)</td>
<td>+4 to + 8 mm</td>
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<td>-2</td>
<td>+4</td>
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<tr>
<td>Putamen (R)</td>
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<td>+24</td>
<td>+6</td>
<td>+8</td>
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<tr>
<td>DLPFC (L)</td>
<td>+20 to +40 mm</td>
<td>-28</td>
<td>+34</td>
<td>+36</td>
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<tr>
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<td>+38</td>
<td>+32</td>
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<td>Insula (L)</td>
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<td>-32</td>
<td>+14</td>
<td>+12</td>
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<tr>
<td>Insula (R)</td>
<td>+8 to +16 mm</td>
<td>+38</td>
<td>+4</td>
<td>+12</td>
</tr>
<tr>
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<td>-38</td>
<td>+32</td>
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<td>-46</td>
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<td>-66</td>
<td>+40</td>
</tr>
<tr>
<td>Area 39 (R)</td>
<td>+32 to +40 mm</td>
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<td>-52</td>
<td>+32</td>
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<td>SMA/CMAr</td>
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<td>+10</td>
<td>+40</td>
</tr>
<tr>
<td>SMC (L)</td>
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<td>-18</td>
<td>+56</td>
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<tr>
<td>PMC (L)</td>
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<td>-12</td>
<td>-14</td>
<td>+60</td>
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<td>PMC (R)</td>
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<td>-6</td>
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<tr>
<td>SMA/CMA (L)</td>
<td>+44 to +68 mm</td>
<td>-2</td>
<td>-4</td>
<td>+56</td>
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</table>

Foci of significant change in rCBF for comparison indicated in the table title. The coordinates in a standard stereotactic space (Talairach and Tournoux, 1988) are given in mm in $x$, $y$ and $z$ for the maximally significant pixel in each area, where $x$ is the lateral displacement from the midline ($H11002$ for left hemisphere); $y$ is the anteroposterior displacement relative to the anterior commissure ($H11002$ posterior to this); and $z$ is the vertical position relative to the AC–PC line ($H11002$ if below this). The vertical extent of each area activated (in mm relative to the AC–PC line) is tabulated, and the level of significance is given by the $Z$ score (where $Z$ is the standard deviation of the standard normal distribution). The mean percentage rCBF increase compared with rest is given for each area, measured at the pixel of maximal significance. $L$ = left hemisphere; $R$ = right hemisphere; CMAr = rostral cingulate premotor area; CMA = dorsal cingulate motor area.

Fig. 1 SPM projections of the sites of significantly increased rCBF for comparison of self-initiated movements with rest (threshold at $P < 0.05$ corrected for multiple comparisons). The activated areas are shown projected onto single sagittal, coronal and transverse planes conforming to the stereotactic atlas of Talairach and Tournoux (Talairach and Tournoux, 1988). For the purposes of illustration, the equivalent SPMs from the related study of Jahanshahi and colleagues (Jahanshahi et al., 1995) (B) are shown alongside the data from the current study (A), demonstrating a very similar pattern of activation in both. VPC = vertical line through the posterior commissure.

and 19), the posterior cingulate gyrus (areas 23/30 in occipito-temporal cortex) and medial ventral prefrontal cortex (areas 9 and 10). The axial extent of the areas activated, the peak $Z$ scores and the percentage increases in rCBF are given in Table 4, and the SPM projections of this comparison are shown in Fig. 4. These results may reflect a lesser depression
of activity in these areas during the triggered task compared with the self-initiated task, leading to a relative ‘activation’.
This issue is dealt with in more detail in the Discussion.

**Discussion**

If we compare the results for the normal volunteers in this study with those of the control subjects in our previous study using a similar design (Jahanshahi et al., 1995), the concordance of the results for the comparison of the self-initiated task with rest for the PET is striking (Fig. 1). This demonstrates the robustness of the technique and suggests that these results can be regarded with confidence.

The mean IRI for self-initiated movements in the control group from our first study was 3.14 s (Jahanshahi et al., 1995), whereas it was 4.46 s for our second study. The subjects succeeded in producing a wide range of IRIs during the self-initiated task in the present study, thus achieving our objective of generating an unpredictable sequence of tones as cues for the triggered task. A measure of the unpredictability of the cueing stimuli during the triggered task is the mean IRI for self-initiated movements in the control group from our previous study using a similar design (Jahanshahi et al., 1995) in which the triggering tones were assumed to be predictable [230 ms (SD = 61 ms)], despite the previous controls being older (mean age of 64.8 years compared with 32.2 years in the present study; the earlier controls were age-matched to a group of Parkinson’s disease patients). The difference in mean RTs is significant (P = 0.0002, unpaired t-test). These data support the notion that unpredictability of the cueing stimuli during the triggered

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**Table 2** Significant rCBF increases during externally triggered movement compared with rest

<table>
<thead>
<tr>
<th>Area activated</th>
<th>Extent of area activated (relative to AC–PC line)</th>
<th>Talairach co-ordinates of peak activation</th>
<th>Z score of peak activation</th>
<th>Mean flow increase (%)</th>
</tr>
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<tr>
<td>Putamen (L)</td>
<td>+4 to +12 mm</td>
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<td>4.14</td>
<td>1.4</td>
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<td>Insula (L)</td>
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<td>1.7</td>
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<td>Area 40 (L)</td>
<td>+20 to +28 mm</td>
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<td>SMA/CMAd</td>
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<td>4.41</td>
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See footnote to Table 1 for explanation of data and unlisted abbreviations.
Table 3 Significant rCBF increases during self-initiated movement compared with externally triggered movement

<table>
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<tr>
<th>Area activated</th>
<th>Extent of area activated (relative to AC–PC line)</th>
<th>Talairach co-ordinates of peak activation</th>
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<td>Area 44 (R)</td>
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<td>CMAr</td>
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<td>+48 to +68 mm</td>
<td>-10, -16, +60</td>
<td>4.66</td>
<td>2.4</td>
</tr>
<tr>
<td>PMC (R)</td>
<td>+44 to +64 mm</td>
<td>+16, -2, +56</td>
<td>5.49</td>
<td>2.6</td>
</tr>
<tr>
<td>SMA/CMArd</td>
<td>+44 to +68 mm</td>
<td>+2, -4, +56</td>
<td>5.86</td>
<td>2.6</td>
</tr>
</tbody>
</table>

See footnote to Table 1 for explanation of data and unlisted abbreviations.

(A) Self-initiated vs. triggered (variable)

(B) Self-initiated vs. triggered (regular)

Fig. 3 SPM projections of the sites of significantly increased rCBF for the comparison of self-initiated movements with triggered movements (threshold at $P < 0.05$ corrected for multiple comparisons). The activated areas are shown projected onto single sagittal, coronal and transverse planes conforming to the stereotactic atlas of Talairach and Tournoux (Talairach and Tournoux, 1988). For the purposes of illustration, the equivalent SPMs from the related study of Jahanshahi and colleagues (Jahanshahi et al., 1995) (B) are shown alongside the data from the current study (A), showing that when triggered movements are predictable, significant differences are limited to the DLPFC (in this case only in the right hemisphere), but when they are unpredictable, differences are also found in mesial frontal and parietal cortex.

The task in the current study prevented preparation for movement at a specific time, resulting in a significantly longer mean RT than found previously.

We should also comment on the difference in mean MT found between the two conditions. The shorter MTs found during self-initiated movements could be the result of one or other of several factors: greater speed of movement; reduced amplitude of movement; or a change in ‘dwell time’ at the greatest excursion of index finger extension. There have been a number of functional imaging studies of the effect of changing various movement parameters on rCBF, namely frequency of movement (Sabatini et al., 1993; Schlaug et al., 1995; Blinkenberg et al., 1996; Rao et al., 1996; Sadato et al., 1996; Jenkins et al., 1997), force (Dettmers et al., 1995) and velocity (Turner et al., 1998). A finding common to all these studies is that changes in movement...
A PET study of movement preparation

Table 4 Significant rCBF increases during externally triggered movement compared with self-initiated movement

<table>
<thead>
<tr>
<th>Area activated</th>
<th>Extent of area activated (relative to AC–PC line)</th>
<th>Talairach co-ordinates of peak activation</th>
<th>Z score of peak activation</th>
<th>Mean flow increase (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal 21/37 (L)</td>
<td>−12 to +4 mm</td>
<td>x: +46, y: −54, z: +4</td>
<td>4.24</td>
<td>2.1</td>
</tr>
<tr>
<td>Area 39/19 (L)</td>
<td>+8 to +20 mm</td>
<td>x: −44, y: −58, z: +12</td>
<td>4.87</td>
<td>2.6</td>
</tr>
<tr>
<td>Med.occ.temp 23/30</td>
<td>+8 to +24 mm</td>
<td>x: −4, y: −60, z: +20</td>
<td>5.45</td>
<td>2.1</td>
</tr>
<tr>
<td>Medial 10/9</td>
<td>+20 to +24 mm</td>
<td>x: −4, y: +50, z: +20</td>
<td>3.89</td>
<td>2.2</td>
</tr>
</tbody>
</table>

See footnote to Table 1 for explanation of data and unlisted abbreviations. Med.occ.temp. = medial occipitotemporal region.

Fig. 4 SPM projections of the sites of significantly increased rCBF for triggered movements compared with self-initiated movements (threshold at P < 0.05 corrected for multiple comparisons). The activated areas are shown projected onto single sagittal, coronal and transverse planes conforming to the stereotactic atlas of Talairach and Tournoux (Talairach and Tournoux, 1988).

parameters resulted in changes in activation of the contralateral primary SMC. We found no such change in this study when comparing self-initiated with triggered movements. This suggests that the difference in movement times has not had a significant impact on the activation found in the comparison of self-initiated with triggered movement.

The central finding of our study is that the unpredictably triggered movements produced significantly less activation of mesial frontal cortex than the corresponding self-initiated movements. The triggered movements were generated in a similar manner to those in our earlier companion study (Jahanshahi et al., 1995) except for the greater variability in interstimulus intervals, preventing stimulus anticipation and movement preparation. The results, we believe, provide further evidence of a role for the SMA and adjacent anterior cingulate cortex in the preparation of internally generated movements in man. Parallel evidence in support of this view comes from recordings of long-lead activity changes of cells in the SMA in monkeys, with abundant cells firing well in advance of movement when the animals make movements of their own volition, and fewer cells responding when they act in response to external cues (Okano and Tanji, 1987).

The SMA activation found during self-initiated movements in our study involves areas caudal to and rostral to the vac line which roughly demarcates the pre-SMA and the SMA proper (Tanji, 1994; Passingham, 1996). The peak activation during this task compared with rest was found close to this line. In contrast, the small area of activation found in caudal SMA during unpredictably triggered movements fell well behind the vac line in SMA proper. In monkeys, the SMA proper projects to the SMC and pyramidal tracts (Muakkassa and Strick, 1979; Dum and Strick, 1991). The pre-SMA receives projections from prefrontal cortex (Bates and Goldman-Rakic, 1993), and projects to the SMA proper (Lupino et al., 1990). The pre-SMA contains a higher proportion of neurons with activity changes during preparation for movement than does the SMA proper (Matsuzaka et al., 1992).

PET evidence suggests that, in man, selective rostral SMA activation is found when comparing performance of paced joystick movements in freely chosen directions with those specified by external cues (Deiber et al., 1991). In contrast, caudal SMA is activated by all movement, including when subjects perform simple repetitive movements of the hand or arm (Colebatch et al., 1991) or overlearned sequences of finger movements automatically (Jenkins et al., 1994). Furthermore, the caudal but not the rostral SMA shows a frequency-dependent change in rCBF during paced movements akin to those found in the contralateral SMC and cerebellum (Jenkins et al., 1997). We propose that the activation of the caudal SMA during unpredictably triggered movements reflects primary involvement of this area in movement execution rather than preparation, whereas the significantly greater activation of rostral SMA found during the self-initiated task demonstrates the importance of this area in movement preparation.

Wessel and colleagues have compared self-paced finger opposition movements with externally triggered movements using H215O-PET (Wessel et al., 1997). Their study design differs in that frequency of movement was not comparable in the two tasks. For the self-paced task, subjects made finger opposition movements every 4–6 s, whereas the
triggered movements were paced by a metronome at a frequency of 2 Hz and were essentially continuous. Therefore, changes in the frequency of movement contribute to the pattern of activation found when the two tasks were compared. However, the self-paced movements resulted in significantly greater activation of the rostral SMA and the rostral cingulate premotor area. They argued that these increases were the result of increased time devoted to planning the movements in this condition.

In recent months, Deiber and colleagues reported the results of a functional MRI experiment contrasting activation of mesial frontal areas during self-initiated and triggered finger movements (Deiber et al., 1999). Their experimental approach was similar to that used in the current study and in our previous work (Jahanshahi et al., 1995) in that the SI condition was used to generate a series of signals (visual rather than auditory in their study) that were played back during the triggered task, yoking the conditions together. They also asked subjects to generate variable intervals in the SI condition, though these did not cover as extensive a range as in our study. These authors found, as we did, that self-initiated movements were associated with greater intensity and extent of activation in pre-SMA, SMA proper and cingulate motor areas. Comparing the two motor tasks directly, a significant difference in extent of activation was found in the pre-SMA and cingulate motor areas, but not in the SMA (Deiber et al., 1999).

In our experiment, and in our earlier companion study (Jahanshahi et al., 1995), we found that there was activation of the adjacent cingulate sulcal cortex in association with activation of the SMA during the self-initiated movement task compared with rest. Non-human primate studies have shown a somatotopic organization in several cingulate motor areas (Luppino et al., 1991; Dum and Strick, 1993), and Dum and Strick have demonstrated that there are direct pyramidal projections from several distinct cingulate motor areas (Dum and Strick, 1993). The exact correspondence between these areas in the non-human primate and in the human brain remains to be fully established (Picard and Strick, 1996; Fink et al., 1997). However, it is of importance to note that in the present study cingulate sulcal cortex was activated both behind and in front of the VAC line during self-initiated movements, and Shima and colleagues report that in non-human primates, on a self-paced movement task, more cells fire early in the rostral than in the caudal cingulate motor cortex (Shima et al., 1991). In contrast, triggered movements activated only the dorsal cingulate motor area. Wessel and colleagues found greater activation of the caudal cingulate motor area during triggered movements in their study (Wessel et al., 1997), but the increase in frequency of movement compared with their self-paced task makes interpretation difficult.

We found significant activation of the lateral PMC during self-initiated movements compared with rest, and greater activation of this region during self-initiated movements than during unpredictably triggered movements. Primate studies show that cells in both lateral and medial premotor areas are active during movement preparation (Kurata and Wise, 1988; Mushiake et al., 1991) but, crucially, lesion studies in monkeys suggest that the lateral premotor areas are more important when the movements chosen are dependent on external cues (Passingham, 1993). At first sight, our results would appear to be at variance with this experimental finding. However, it would be a mistake to equate pacing tones with external cues which specify the nature of the movement made (the first is telling the subjects when to move, the second is telling them what type of movement to make). The hypothesis based on monkey data concerns external cues which tell the animal what to do. In a PET experiment, we scanned normal volunteers while they learned sequences of finger movements, and compared this with performance of a sequence learned before scanning (Jenkins et al., 1994). The sequences were learnt by trial and error, using auditory feedback in the form of tones of differing pitch. Thus the choices made were dependent on the auditory feedback. In that study, we found significantly greater activation of lateral PMC bilaterally during novel sequence learning compared with performance of a pre-learned sequence when the tones were purely pacing but not cueing direction.

In our previous study of self-initiated movements (Jahanshahi et al., 1995), the only area that was significantly more activated by the self-initiated task compared with the predictable (regular) triggered task was the right DLPFC (Fig. 1B). In the current study, comparing self-initiated with unpredictable triggered movements, this area was again relatively activated, though bilaterally this time (Fig. 1A). In the first study, we postulated that the only difference between the self-initiated and predictably triggered conditions was that subjects had to decide when to move during the self-initiated condition (Jahanshahi et al., 1995). We suggested that the DLPFC may be involved specifically in this decision. There are other possible roles of the DLPFC to consider. The DLPFC is thought to play a role in working memory (Goldman-Rakic, 1987; D’Esposito et al., 1995; Ungerleider, 1995) and the subjects’ decision when to make the next finger extension will be influenced by information about the preceding IRIs held in working memory. In a number of other PET studies, activation of the DLPFC has been related to the selection of appropriate movements (Deiber et al., 1991, 1996; Frith et al., 1991; Playford et al., 1992). In the current study, only movement timing had to be selected (i.e. when to move, not which movement to make).

Activation of the superior (area 7) and inferolateral (area 40) parietal cortex was found during self-initiated movements in this study and was significantly greater during this condition than during the variable triggered task. Activation of the parietal association areas has been found previously in PET activation studies involving the selection of responses (Deiber et al., 1991; Playford et al., 1992), motor learning (Seitz et al., 1990; Jenkins et al., 1994), visuospatial attention (Corbetta et al., 1993) or attention to tactile stimuli (Pardo et al., 1991). Explanations for activation of parietal areas 7
Correspondence of PET findings with previous MRP data

The view that the SMA is a principal generator of the early phase of the BP has been disputed by Botzel and colleagues, using a multiple dipole source localization method to analyse BP data produced by repetitive self-paced finger extensions (Botzel et al., 1993). They found that the early BP was best modelled by bilateral sources in the motor cortex, rather than by a dipole in the region of the SMA. Neshige and colleagues recorded MRPs from subdural and epidural electrodes in the human cortex during epilepsy surgery (Neshige et al., 1988). Their results, too, suggested that scalp-recorded BPs may be the result of the summation of BPs arising from the primary motor cortices with little contribution from the SMA.

On the other hand, Ikeda and colleagues, also recording from subdural electrodes placed over the SMA and foot area of primary motor cortex in patients awaiting epilepsy surgery, found that the SMA and primary motor areas generated MRPs of similar magnitude, form and temporal evolution during self-paced voluntary movements of the foot (Ikeda et al., 1992). These authors pointed out that the recordings from the SMA in the study of Neshige and colleagues were obtained with epidural electrodes, which tend to give lower amplitude responses than subdural electrodes. Ikeda and colleagues also identified somatotopy within the SMA, by measuring MRPs for finger, foot and tongue movements along with vocalizations (Ikeda et al., 1992). It may well be that these measurements were made in the area which we have termed posterior or caudal SMA earlier in this discussion.

The H$_2^{15}$O-PET activation data from this study, combined with the PET and MRP findings presented in our earlier report (Jahanshahi et al., 1995), strongly suggest that the medial premotor areas play an important role in the preparation of voluntary self-initiated movements and that SMA is a principal generator of the early phase of the BP. We have shown concordance between the presence and amplitude of the early BP and activation of the SMA and adjacent anterior cingulate cortex with PET. During self-initiated and predictably paced movements (Jahanshahi et al., 1995), there is mesial frontal activation (with no significant difference between the two conditions); these two tasks both result in a clear early BP with no significant difference in amplitude. In contrast, unpredictable pacing designed to prevent movement preparation (this report) produces significantly less mesial frontal activation than self-initiated movement, and similar unpredictably paced movements produce no significant pre-movement negativity (Jahanshahi et al., 1995). If, as Botzel and colleagues suggest, the early BP is generated primarily by bilateral primary motor cortex activation (Botzel et al., 1993), then one would expect to find bilateral SMC activation during the motor tasks which are associated with a prominent early BP. We did not find this; unpredictably triggered movements in this second study activated contralateral primary SMC to the same extent as and 40 in these studies have focused on a possible role in spatial attention, or in the process of movement selection. In the present study, neither of these explanations is adequate since there was only selection of movement timing rather than type, and spatial attention was not a factor. It is of note that the parietal area 40 (area 7b in the macaque monkey) is connected reciprocally to premotor cortex (Petrides and Pandya, 1984) and dorsal prefrontal cortex (Cavada and Goldman-Rakic, 1989); activation in these areas was also significantly greater during the self-initiated movement condition than during the variable triggered task.

Activation was found in the striatum during both the self-initiated and variably triggered conditions compared with rest. No significant difference in activation was identified in the left striatum between the two movement conditions, but there was a difference in the right striatum, with relatively greater activation during the self-initiated movement task (Table 3). This provides some support for a role in the preparation of stereotyped voluntary movements, given that activation was diminished when preparation to move at a cued time was made impossible. Single-cell recording studies in monkeys have shown that there are cells in putamen which exhibit set activity in advance of arm movements in visually cued delayed response tasks (Alexander and Crutcher, 1990; Jaeger et al., 1993) and in advance of self-initiated goal-directed arm movements (Schultz and Romo, 1992). However, there are also many cells in the putamen which discharge after the onset of muscle activity (measured with EMG) in visually guided step-tracking tasks in monkeys (Aldridge et al., 1980). This might explain the lack of a difference in activation of the contralateral striatum in our study. The sensitivity of H$_2^{15}$O-PET may not be sufficient to detect changes reliably in putamen rCBF resulting from preparatory activity over and above activity related to movement execution.

Although the externally triggered movement task did not produce greater activation of any motor or premotor areas than the self-initiated task, there was significant relative activation of posterior occipito-temporal areas (Table 4 and Fig. 4). None of these areas was significantly activated in the comparison of triggered movements relative to rest, suggesting that their relative activation in this comparison may reflect a decrease of rCBF in these areas during self-initiated movements compared with rest. To confirm this, we explored the SPM contrast of rest with each of the motor tasks at the same threshold of P < 0.05 corrected for multiple comparisons. As expected, compared with the resting state, decreases in activation of posterior cortical areas were found during the self-initiated task which were not apparent during the triggered task. Regional activation during behavioural tasks may be accompanied by decreases in rCBF elsewhere (Seitz and Roland, 1992) and, in the case of motor tasks performed with eyes closed, these decreases are found in posterior cortical areas subserving redundant processing of visual signals (Jenkins et al., 1994).
self-initiated movements in the absence of early pre-movement negativity (Jahanshahi et al., 1995).

One criticism of this interpretation of our data could be that it depends on the assumption that mesial frontal activation and the early BP are temporally related. As PET takes a minimum of 30 s to measure activation-induced rCBF changes and the BP duration is 3 s, this assumption cannot be tested directly. The results of a recent study by MacKinnon and colleagues do, however, lend weight to our conclusions (MacKinnon et al., 1996). This group combined H215O-PET activation with simultaneous recording of pre-movement potentials. Subjects performed simple repetitive finger to thumb oppositions under two active conditions: at rapid rate (2 Hz) and intermittently (without cueing). While the rapid rate movements activated caudal SMA, the discrete intermittent movements activated a more rostral portion of the SMA. Like us, they found contralateral but not ipsilateral primary SMC activation during the motor tasks. The results of their MRP recordings were in keeping with previous studies, the early BP having maximal amplitude at Cz (over the vertex). They generated several different dipole source solutions, but constrained dipole placement by the foci of activation found in their PET analysis. The data (PET and MRP) were best fitted by dipoles within the mesial frontal cortex, which they localized to the rostral SMA (pre-SMA) and dorsal tier of the cingulate gyrus. The model of Botzel and colleagues (Botzel et al., 1993) did not provide an adequate solution for their data.

The temporal relationship between different cortical areas contributing to pre-movement activity has been investigated more directly using magnetoencephalography (MEG) in combination with activation PET (Pedersen et al., 1998). The Readiness Field, a magnetic field recorded by MEG which is the equivalent of the BP, was studied. MEG alone does not provide sufficient resolution to identify the anatomical locations of individual sources reliably. This group therefore combined MEG with PET (co-registered with MR). Studying self-paced index finger movements, they found a pre-movement readiness field arising from four separate cortical sources. These were active sequentially. The first MEG signal was found frontally in the left DLPFC. This was followed in succession by a signal from the SMA, the left lateral premotor cortex, and then left primary motor cortex. Their data would seem to indicate a temporal hierarchy of processing, with pre-movement activity arising in the premotor areas before primary motor cortex. They failed to find any bilaterality of activation with PET, but their data are drawn from just two subjects, so this result at least must be treated with caution.

In conclusion, the current study was designed to resolve questions raised by the results of previous work (Jahanshahi et al., 1995) concerning the role of the premotor areas in movement preparation. We suggested that a condition in which movements were cued at unpredictable intervals would result in significantly less activation of mesial premotor areas than would self-initiated movements. Our results bear this out. Furthermore, this corresponds to a lack of significant pre-movement negativity found with recording of MRP’s in the same condition (Jahanshahi et al., 1995). We believe that this provides further evidence in support of the notion that the SMA is a principal generator of the early BP.

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