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Mesial Motor Areas in Self-Initiated Versus Externally Triggered Movements Examined With fMRI: Effect of Movement Type and Rate

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Dieber, Marie-Pierre, Manabu Honda, Vicente Ibañez, Norihiro Sadato, and Mark Hallett.

Mesial motor areas in self-initiated versus externally triggered movements examined with fMRI: effect of movement type and rate. *J. Neurophysiol.* 81: 3065–3077, 1999. The human frontomesial cortex reportedly contains at least four cortical areas that are involved in motor control: the anterior supplementary motor area (pre-SMA), the posterior SMA (SMA proper, or SMA), and, in the anterior cingulate cortex, the rostral cingulate zone (RCZ) and the caudal cingulate zone (CCZ). We used functional magnetic resonance imaging (fMRI) to examine the role of each of these mesial motor areas in self-initiated and visually triggered movements. Healthy subjects performed self-initiated movements of the right fingers (self-initiated task, SI). Each movement elicited a visual signal that was recorded. The recorded sequence of visual signals was played back, and the subjects moved the right fingers in response to each signal (visually triggered task, VT). There were two types of movements: repetitive (FIXED) or sequential (SEQUENCE), performed at two different rates: SLOW or FAST. The four regions of interest (pre-SMA, SMA, RCZ, CCZ) were traced on a high-resolution MRI of each subject's brain. Descriptive analysis, consisting of individual assessment of significant activation, revealed a bilateral activation in the four mesial structures for all movement conditions, but SI movements were more efficient than VT movements. The more complex and more rapid the movements, the smaller the difference in activation efficiency between the SI and the VT tasks, which indicated an additional processing role of the mesial motor areas involving both the type and rate of movements. Quantitative analysis was performed on the spatial extent of the area activated and the percentage of change in signal amplitude. In the pre-SMA, activation was more extensive for SI than for VT movements, and for fast than for slow movements; the extent of activation was larger in the ipsilateral pre-SMA. In the SMA, the difference was not significant in the extent and magnitude of activation between SI and VT movements, but activation was more extensive for sequential than for fixed movements. In the RCZ and CCZ, both the extent and magnitude of activation were larger for SI than for VT movements. In the CCZ, both indices of activation were also larger for sequential than for fixed movements, and for fast than for slow movements. These data suggest functional specificities of the frontomesial motor areas with respect not only to the mode of movement initiation (self-initiated or externally triggered) but also to the movement type and rate.

INTRODUCTION

The identification and role of the mesial frontal cortical areas involved in human motor control are topics of continued debate. Initially, the supplementary motor area (SMA) was considered to be the only motor field within area 6 of the medial wall (Penfield and Welch 1951; Woolsey et al. 1952). Recently, however, several functionally distinct motor fields on the mesial surface of the hemisphere have been recognized (for a review, see Picard and Strick 1996). One of the central questions about the SMA concerns its role in self-initiated movements as opposed to movements triggered by external stimuli. Preferential involvement of the SMA in self-initiated movements has been suggested by the results of several electrophysiological and lesion experiments in monkeys (Chen et al. 1995; Mushiaki et al. 1991; Okano and Tanji 1987; Passingham 1987; Thaler et al. 1988, 1995; Wise 1984). Data from electroencephalographic (Jahanshahi et al. 1995; Papa et al. 1991) and functional neuroimaging studies in humans (Larsson et al. 1996; Rao et al. 1993; Tyszka et al. 1994; Wessel et al. 1997) are also consistent with this idea. However, the results of a study by Remy et al. (1994), who observed greater blood flow in the SMA with externally triggered movements, have been controversial. In addition to the mode of movement initiation, other variables in motor control may modulate the activity of the SMA. In particular, the SMA is said to have a role in motor sequences (Jenkins et al. 1994; Mushiaki et al. 1990, 1991; Shibasaki et al. 1993; Tanji and Shima 1994). Further, the sensitivity of the SMA to movement rate is a controversial issue, with some studies showing significant negative dependence at higher rates (MacKinnon et al. 1994; Sadato et al. 1996b), and others reporting nonsignificant negative (Blinkenberg et al. 1996) or positive (Schlaug et al. 1996) dependence.

Picard and Strick (1996) reviewed the anatomic and physiological data obtained from nonhuman primates and humans to formulate a functional anatomic classification of the mesial cortical areas. In their analysis of functional neuroimaging studies in humans, they distinguished between simple tasks, which require basic organization of movement, and complex tasks, which make additional motor or cognitive demands. They concluded that humans have at least four distinct mesial motor regions: anterior SMA (pre-SMA), posterior SMA

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(SMA proper, or SMA), and, in the anterior cingulate cortex, the rostral cingulate zone (RCZ) and the caudal cingulate zone (CCZ) (Picard and Strick 1996). In the superior frontal gyrus, the SMA proper, lying caudal to the level of the anterior commissure (VAC line), is activated mainly by simple tasks, and the pre-SMA, lying rostral to the VAC line, is activated during relatively more complex tasks. In the cortex of both banks of the cingulate sulcus, from the genu of the corpus callosum (Brodmann area 32) to the posterior border of Brodmann area 24, the large RCZ is activated by complex tasks, and the smaller CCZ is activated during simple tasks.

On the basis of Picard and Strick's (1996) classification of the mesial cortical areas according to the simple/complex dichotomy, we reexamined the role of each mesial area in self-initiated versus externally triggered movements. In addition, to assess the interaction between factors that modulate activity in the SMA, we introduced two other movement variables: type of movements (repetitive finger movements of a single digit versus sequential finger movements) and rate of movements (slow, ~ 0.25 Hz, vs. fast, ~ 1 Hz). We used functional magnetic resonance imaging (fMRI) to achieve better spatial resolution of the mesial cortical areas and to allow single-subject analysis.

METHODS

Subjects

We studied nine normal volunteers (8 men and 1 woman), aged 26–52 (mean, 35) years. The subjects were all right-handed as measured by the Edinburgh Inventory (Oldfield 1971). The protocol was approved by the Institutional Review Board, and all subjects gave their written informed consent for the study.

Tasks

The subjects performed two motor tasks, each of which had a distinct mode of initiation: self-initiated (SI; rate decided by the subject) and visually triggered (VT; rate imposed by a signal). According to Jahanshahi et al. (1995), the term self-initiated is more suitable than “self-paced” because in the self-initiated mode the desired rate of movement was specified, and on each trial the subjects had to decide when to initiate the movement to maintain the desired rate. A visual signal was used to keep the rhythm and number of movements constant in the SI and VT tasks. The subjects wore goggles, and in the SI task, each movement elicited a red flash of light. The sequence of flashes generated in the SI task was recorded and played back in the VT task. Thus the rate of movement in the VT task was yoked to that generated in the SI task.

Two types of movements, both involving digits of the right hand (digit 2, index finger; digit 3, middle finger; digit 4, ring finger; digit 5, little finger), were performed: a repetitive movement in which the thumb was opposed to the index finger (2–2–2–2... , FIXED) and a sequence movement in which the thumb was opposed to each of the other four fingers (2–3–4–5–5–4–3–2–2–3–4–5... , SEQUENCE). Each type of movement was performed at two different rates: a slow rate—one movement approximately every 4 s (~ 0.25 Hz, SLOW)—and a fast rate—one movement approximately every second (~ 1 Hz, FAST). In the SI task, the subjects were instructed to generate movements at an average rate centered ~ 0.25 or 1 Hz. They were asked specifically not to pursue a very regular rate but rather to introduce some irregularity in the rhythm of their movements to minimize automaticity in the SI task and anticipatory behavior in the VI task.

Eight movement conditions were tested: self-initiated, repetitive movement, slow rate (SI, FIXED, SLOW); visually triggered, repetitive

movement, slow rate (VT, FIXED, SLOW); self-initiated, repetitive movement, fast rate (SI, FIXED, FAST); visually triggered, repetitive movement, fast rate (VT, FIXED, FAST); self-initiated, sequence movement, slow rate (SI, SEQUENCE, SLOW); visually triggered, sequence movement, slow rate (VT, SEQUENCE, SLOW); self-initiated, sequence movement, fast rate (SI, SEQUENCE, FAST); and visually triggered, sequence movement, fast rate (VT, SEQUENCE, FAST). A visual control condition (VISUAL) also was included: when the sequence of flashes recorded during the SI, FIXED, FAST condition was played back, the subjects were asked not to make any movement. The order of conditions was pseudorandomized across subjects, with the constraint that the SI tasks had to be performed before the VT tasks within a movement type and rate, in accordance with the yoked experimental design described earlier.

Subjects were taught to perform a brisk and precise tap of the thumb to the fingers. The sequence and repetition rate of the finger movements were monitored by an electrically equipped glove. A session consisted of an OFF-ON cycle of three rest periods and three movement periods (3 repetitions of the same movement condition), and began with a rest period. Each period was 30 s long so that the performance of one session lasted 3 min. One session was performed for each movement condition without replication. Subjects practiced each movement condition once before the experiment started.

Magnetic resonance imaging

Images were obtained by a whole-body 1.5 T magnetic resonance imaging (MRI) scanner (Signa, General Electric, Milwaukee, WI), equipped with a full-head Medical Advance coil permitting complete isotropic coverage. Head motion was minimized by placing tight but comfortable foam padding around the subject's head. High-resolution MR images were obtained for anatomic reference. A three-dimensional, T1-weighted sequence (TR/TE/flip: 100 ms/5 ms/70°) was used to obtain 15 contiguous high-resolution sagittal images of 6-mm thickness, with a 24-cm field of view and a 256×256 matrix. The images covered the mesial structures, the left hemisphere (contralateral to the movements), and part of the right hemisphere. The inter-hemispheric fissure served as the reference for positioning the sagittal slices, with slices on the left and right sides of the brain separated by the fissure. High-resolution echo planar imaging scans then were obtained in the same planes with a T2*-weighted acquisition (TR/TE/flip: 3000 ms/40 ms/90°), which produced a 64×64 matrix with a 24-cm field of view and 3.75-mm in-plane resolution. In each hemisphere, analysis was restricted to the two slices covering the mesial cortical areas. A time-course series of 60 images/slice was acquired for each trial, in an OFF-ON cycle paradigm of 30 s of rest and 30 s of movement.

Data analysis

To remove motion artifacts, the fMRI time series from each subject were realigned according to the method of Friston et al. (1995a), with the first image of each slice used as a reference. Within-plane spatial smoothing was applied with a two-dimensional Gaussian kernel of 5.6×5.6 mm of full width at half-maximum (FWHM). No smoothing was applied in the interplane direction. No spatial normalization of the data was performed because the brain was only partly sampled. Therefore the data were analyzed on an individual basis. The fMRI time series were analyzed by statistical parametric mapping (SPM; SPM software, Wellcome Department of Cognitive Neurology, London, UK). The effect of global differences in scan intensity was removed by scaling each scan in proportion to its global intensity. Statistical analysis was performed for each condition in a general linear model, in which regionally specific activation is explored as to how well the reference waveform fits to the observed time series of the fMRI signal (i.e., hemodynamic response) at each and every voxel (Friston et al. 1995b). The reference waveform was obtained by

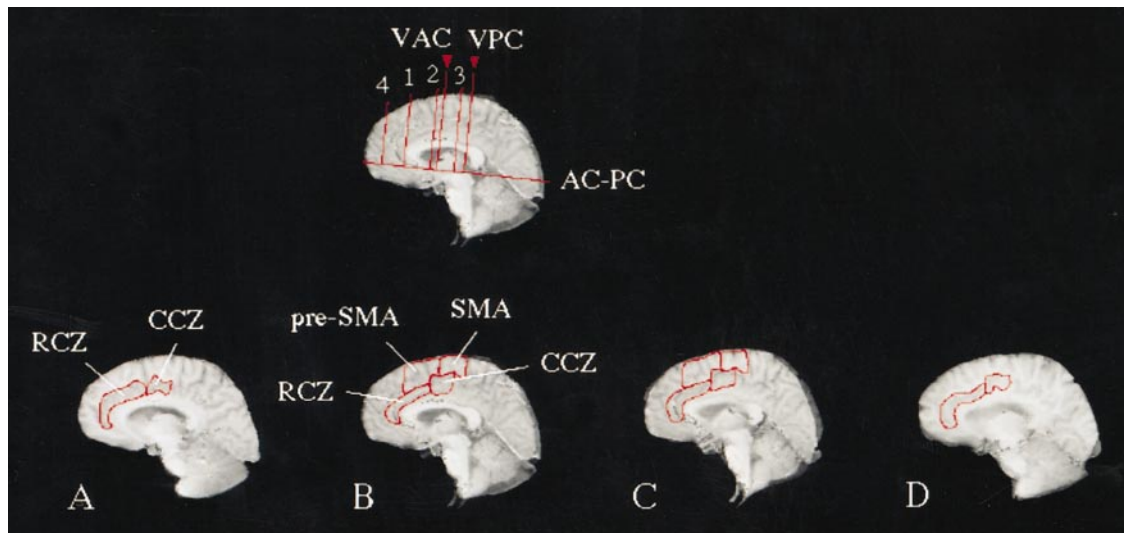


FIG. 1. High-resolution magnetic resonance images from 1 subject: sagittal slices 6-mm thick. *A* and *B*: left hemisphere; *C* and *D*: right hemisphere. Interhemispheric fissure is located between *B* and *C*. The landmarks used to trace the regions of interest (ROIs) are shown on slice *B* (top), according to the scheme of Picard and Strick (1996). Pre-SMA, rostral portion of the supplementary motor area; SMA, caudal portion of the supplementary motor area, corresponding to the SMA proper; RCZ, rostral cingulate zone; CCZ, caudal cingulate zone; AC-PC, horizontal line passing through the anterior and posterior commissures; VAC, vertical line perpendicular to AC-PC, passing through the anterior commissure; VPC, vertical line perpendicular to AC-PC, passing through the posterior commissure; 1, vertical line delimiting the pre-SMA anterior boundary (from VAC, percentage of total anteroposterior brain dimension: 17.1%); 2, vertical line delimiting the CCZ anterior boundary (3.7%); 3, vertical line delimiting the CCZ posterior boundary (9.4%); 4, vertical line delimiting the RCZ anterior boundary (28.6%). Pre-SMA and SMA are traced on the more medial slice in each hemisphere (*B* for the left hemisphere, *D* for the right hemisphere), and RCZ and CCZ are traced on the 2 more medial slices in each hemisphere (*A* and *B* for the left hemisphere, *C* and *D* for the right hemisphere).

smoothing a time-dependent sensorimotor parameter of interest (i.e., a box-car waveform with 0s for rest epoch scans and 1s for movement epoch scans) with a Gaussian kernel of a delay and dispersion of the square root of 8 s, modeling the hemodynamic response function. The time-series fMRI data also were smoothed over observation (time) by use of the same Gaussian kernel as the hemodynamic response function. Thus with the use of matrix notation, the model can be expressed as

$$Y = Xb + e \quad (1)$$

where Y is the observed data matrix after smoothing, arranged with scans in rows, one column per voxel; X is the design matrix with the same number of rows as Y and two columns, one for the reference waveform and the other for the mean of all scans; b is the matrix for unknown parameters (to be estimated), with two rows corresponding to columns of X and one column per voxel; and e is for the error term. The null hypothesis of no activation corresponds to zero amplitude of the reference waveform (i.e., the first row of b equals 0). The resulting statistics are expressed by the t distribution with the "effective degrees of freedom," which is calculated from the number of observations (i.e., number of scans) and the size of the smoothing kernel (Friston et al. 1994a). The t values constituted a statistical parametric map $SPM\{t\}$, which was transformed to a unit normal distribution to give a $SPM\{Z\}$ (Z -score map). To assess statistical significance, a Z -score map was thresholded at 3.09; the significance of the activation detected was estimated by the use of distributional approximations from the theory of Gaussian fields in terms of spatial extent and/or peak height of the fMRI signal (Friston et al. 1994b). Accounting for multiple nonindependent comparisons, an estimated P value of 0.05 was used as the final threshold for significance. A map of the brain regions in which there was significant cerebral activation, composed of voxels for which $Z > 3.09$ and $P < 0.05$, called a cluster map, was produced. Thus a Z -score map and a cluster map were obtained for each subject and each condition.

At the same time, the intensity of the signal in the activated areas

was assessed by measuring the amplitude of the fitted (or modeled) reference waveform at each and every voxel. The fitted reference function was obtained by

$$Y_{fit} = Xb \quad (2)$$

where Y_{fit} denotes the matrix of the fitted reference waveform, with scans in rows, one column per voxel, and X and b are the same as in Eq. 1. Note that b includes the term for the mean across all scans. The percentage of the change in signal intensity (%CSI) at each voxel was calculated by normalizing the amplitude of the fitted reference function to its minimal value

$$Y\%CSI = 100 \times [Y_{fit}(\max) - Y_{fit}(\min)] / Y_{fit}(\min) \quad (3)$$

where $Y\%CSI$ denotes the row vector expressing %CSI at each voxel, and $Y_{fit}(\max)$, or $Y_{fit}(\min)$, is the row vector consisting of the maximal, or minimal, value of the fitted reference function at each voxel (i.e., maximum, or minimum, of each column of Y_{fit}). This estimation is analogically identical to the estimation of a difference between the means of two different conditions in t statistics. Thus a map of the percentage of change in signal intensity (%CSI map) also was obtained for each subject and each condition.

A region-of-interest (ROI) approach was used to describe the results over the nine subjects. On the high-resolution MRI slices, four ROIs were traced on the medial wall of the hemisphere for each subject: pre-SMA, SMA, RCZ, and CCZ (Fig. 1). In each hemisphere, the pre-SMA and SMA regions were traced on the more medial slice, and the RCZ and CCZ regions were traced on the two more medial slices. The regions were delimited according to the analysis of Picard and Strick (1996), who reviewed the results of positron emission tomography (PET) studies on activation in the medial wall of the human brain. First, the anatomic landmarks of Talairach and Tournoux (1988) were drawn on the appropriate high-resolution MRI midsagittal slice: AC-PC line, VAC line, and VPC line. Measurements of the brain were taken (anteroposterior dimension, maximal height from AC-PC plane). ROIs then were traced as follows: pre-

SMA, region rostral to the VAC line, above the cingulate sulcus, extending anteriorly up to 17.1% of the anteroposterior brain dimension; SMA, region between the VAC and VPC lines and above the cingulate sulcus; CCZ, region including the cortex on both banks of the cingulate sulcus, extending rostrally to the VAC line $\leq 3.7\%$ and caudally $\leq 9.4\%$ of the anteroposterior brain dimension; RCZ, region including the cortex on both banks of the cingulate sulcus, adjacent to CCZ and extending rostrally $\leq 28.6\%$ of the anteroposterior brain dimension (Fig. 1). The number of pixels, including both hemispheres, in the four ROIs (mean \pm SD of 9 experiments) was 650 ± 84 for the pre-SMA, 533 ± 95 for the SMA, 775 ± 117 for the RCZ, and 402 ± 70 for the CCZ. [According to Talairach and Tournoux (1988), the brain is 175 mm in total anteroposterior length. Given that measurement, the proportional measurements are determined from the numerical boundaries given in Figs. 4 and 5 of Picard and Strick (1996). The pre-SMA anterior boundary is 30 mm rostral to VAC (i.e., 17.1% of 175 mm, the total anteroposterior brain dimension), the CCZ anterior boundary is ~ 6.5 mm rostral to VAC (i.e., 3.7% of 175 mm), the CCZ posterior boundary is ~ 16.5 mm caudal to VAC (i.e., 9.4% of 175 mm), and the RCZ anterior boundary is 50 mm rostral to VAC (i.e., 28.6% of 175 mm)].

The fMRI images were interpolated to have the same pixel size as the high-resolution MRI. To avoid distortion of the functional images, the high-resolution images were coregistered to the mean of the fMRI time series by use of the algorithm of Woods et al. (1993), and the ROI templates were applied to the Z, cluster, and %CSI images. The ROIs were used for two purposes: a descriptive analysis, in which the results of the individual cluster analysis were reported and which resulted in histograms showing the number of subjects having significant activation in each ROI and each condition and a quantitative analysis of activation differences between conditions, which was performed separately on the extent of activation and on the %CSI during movement versus rest periods. The extent of activation, computed from the Z maps, was expressed as the number of pixels in which $Z > 3.09$. Analysis of the %CSI during movement periods versus rest periods was performed from the %CSI maps on the maximum value within each ROI. For RCZ and CCZ, measurements from the two medial slices within each hemisphere were averaged. Results were analyzed by repeated measures ANOVA, with a Greenhouse-Geisser correction.

RESULTS

Task performance

Intervals between finger taps or intertap intervals (ITIs) and movement frequency are shown in Table 1. No movement was recorded during the control condition (VISUAL), but small-amplitude movements that did not trigger an electrical signal from the glove cannot be excluded. Movement frequency was calculated for each subject in each condition as follows: the number of movements performed in each movement period was computed as the number of ITIs plus 1, and the sum of ITIs gave the movement time (the first ITI corresponding to the beginning of a 30-s rest period to the first movement was always discarded); movement frequency was obtained by dividing the number of movements by the movement time (in seconds). For each condition, the number of movements and the movement time in each of the three movement periods were added, to calculate the movement frequency. SLOW movements were performed at a mean frequency of 0.31 Hz and FAST movements at 0.69 Hz. SEQUENCE movements were performed slightly faster (mean, 0.53 Hz) than FIXED movements (mean, 0.47 Hz), a result solely attributable to the fast movements. The frequencies of the movements in the SI and VT tasks were very similar (SLOW: 0.32 Hz in SI, 0.31 Hz in VT; FAST:

TABLE 1. Intervals between taps and movement frequency

	Fixed		Sequence	
	Self-Initiated	Visually Triggered	Self-Initiated	Visually Triggered
SLOW				
ITI (mean), ms	3,888	3,985	3,564	3,599
ITI (max)	5,050	5,448	4,685	4,815
ITI (min)	2,613	2,674	2,470	2,527
Frequency, Hz	0.30 ± 0.05	0.30 ± 0.05	0.30 ± 0.06	0.32 ± 0.06
FAST				
ITI (mean), ms	1,677	1,747	1,433	1,506
ITI (max)	2,028	2,077	1,834	1,871
ITI (min)	1,373	1,434	928	938
Frequency (mean), Hz	0.64 ± 0.09	0.62 ± 0.08	0.76 ± 0.16	0.73 ± 0.16

Values are means \pm SD.

0.70 Hz in SI, 0.67 Hz in VT). A repeated measures ANOVA, with RATE (SLOW, FAST), MOVEMENT (SEQUENCE, FIXED), and TASK (SI, VT) as within-subject factors, was performed on the movement frequency data. There was a significant effect of RATE ($F = 129.76$, $P < 0.001$) and MOVEMENT ($F = 12.01$, $P < 0.01$) on movement frequency. However, as expected because of the study design, movement frequency was not significantly affected by TASK.

The movements were performed with relative irregularity as shown by the large difference between the maximum and minimum values of the ITIs (Table 1). Accuracy was measured only in the SI mode because of limitations of the study design. No errors were reported in FIXED movements. In SEQUENCE movements, on average, 96.9% of the responses were correct at the SLOW rates and 97.8% were correct at the FAST rates.

Descriptive analysis

Figures 2 and 3 show the results of the cluster analysis in the left paramedial slice of four individual subjects in each condition. The cluster analysis revealed significant activation in the mesial cortex for the movement conditions ($Z > 3.09$, $P < 0.05$), with differing distributions depending on ROIs, hemisphere, and condition. Examination of activity distribution using the ROI approach revealed that location of the activity peak in the mesial cortex was quite variable among subjects and conditions. However, VT movements frequently were associated with maxima of activity in the most posterior mesial regions, i.e., in the SMA or CCZ. In SI sequential movements, the four mesial structures were activated in most subjects, whereas in SI fixed movements, activation was generally less extended and did not always include all four mesial regions. Variability across subjects regarding the mesial activation extent was even higher for VT movements. In addition to the mesial cortex, foci of activity also could be found independently of the movement condition in the visual cortex, cerebellum and thalamus (Figs. 2 and 3). Histograms of the distribution of activation over the nine subjects are shown in Fig. 4. The mesial structures were activated in very few subjects in the control condition, that is, when flashes were presented but no movement

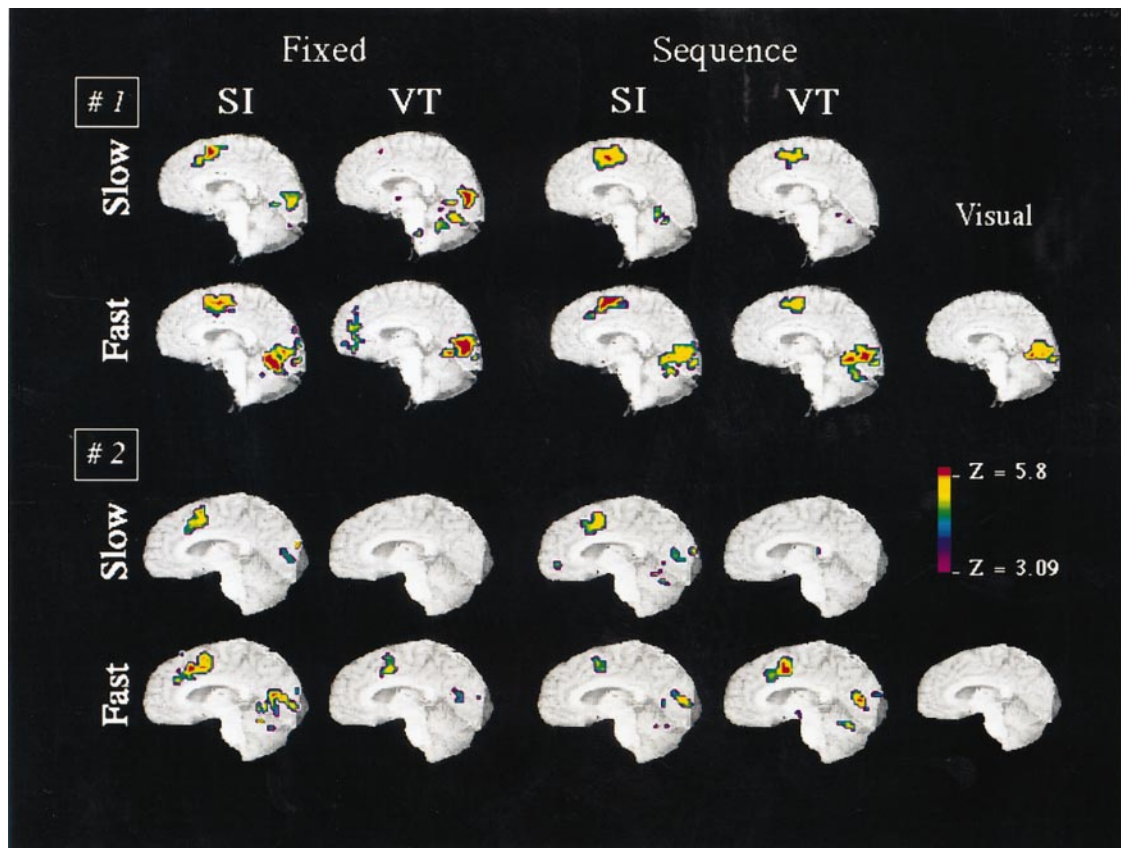


FIG. 2. Cluster maps of significant cerebral activation in 2 subjects, for each condition. 1 (2 top rows): *subject 1*; 2 (2 bottom rows): *subject 2*. For each subject, the clusters are superimposed on the high-resolution magnetic resonance (MR) image of the more medial sagittal slice in the left hemisphere (for *subject 1*, the slice corresponds to *B* in Fig. 1). Cluster maps were obtained by thresholding the Z-score maps at 3.09, and the significance of the activation was estimated in terms of its spatial extent and/or the peak amplitude of the signal, with a final threshold for significance of $P < 0.05$ after a Bonferroni correction. On the color scale, purple represents the lowest Z scores (from 3.09) and red the highest Z scores (>5.8). The brain is reduced in scale in the visual condition for figure clarity. SI, self-initiated condition; VT, visually triggered condition.

was performed (VISUAL). In all movement conditions, subjects showed more constant bilateral activation of the mesial structures with the SI task than with the VT task. The difference in activation between the SI task and the VT task was large in the SEQUENCE, SLOW movements, especially for the contralateral pre-SMA and RCZ, whereas the difference was much smaller in the SEQUENCE, FAST movements. Mesial structures were activated in fewer subjects with the FIXED, SLOW movements than with the other movements. In all conditions, activation in the pre-SMA was usually more ipsilateral than contralateral.

Quantitative analysis

For measurements of the extent of activation and %CSI, two distinct questions were posed: are the movement conditions different from the baseline condition (VISUAL) and how do the movement conditions differ from each other? To answer the first question, we performed a repeated measures ANOVA with CONDITION (8 movement conditions and 1 control condition) as the within-subject factor. We sought to answer the second question by performing a repeated measures ANOVA with the following within-subject factors: ROI (pre-SMA, SMA, RCZ, CCZ), TASK (SI, VT), MOVEMENT (FIXED, SEQUENCE), RATE (SLOW, FAST), and HEMISPHERE (left, right).

EXTENT OF FUNCTIONAL ACTIVATION. The extent of functional activation was assessed as the number of pixels with $Z > 3.09$. In a comparison of movement conditions with the control condition, the extent of activation was significantly affected by CONDITION ($F = 10.66$, $P < 0.001$). Moreover, contrast analysis showed that the extent of activation was significantly larger for the eight movement conditions than for the control condition (56 vs. 4 pixels, $F = 22.37$, $P < 0.001$).

In a comparison between movement conditions, there was no significant effect of ROI and HEMISPHERE. The extent of activation was affected significantly by TASK (SI: 77 pixels, VT: 35 pixels; $F = 19.11$, $P < 0.01$), MOVEMENT (FIXED: 43 pixels, SEQUENCE: 69 pixels; $F = 31$, $P < 0.001$), and RATE (SLOW: 45 pixels, FAST: 66 pixels; $F = 9.48$, $P < 0.05$). There was a significant interaction of ROI and HEMISPHERE ($F = 8.99$, $P < 0.01$), ROI and TASK ($F = 5.43$, $P < 0.05$), and ROI, TASK, and RATE ($F = 4.8$, $P < 0.05$).

A repeated measures ANOVA was performed for each ROI on the extent of activation for the eight movement conditions. The results are shown in Fig. 5 and summarized in Table 2. In the pre-SMA, there was a significant effect of TASK, with more extended activation for SI (116 pixels) than for VT (30 pixels; $F = 25.21$, $P < 0.01$). RATE had also a significant effect, as there was more extended activation with fast movements than with slow movements (85 vs. 61

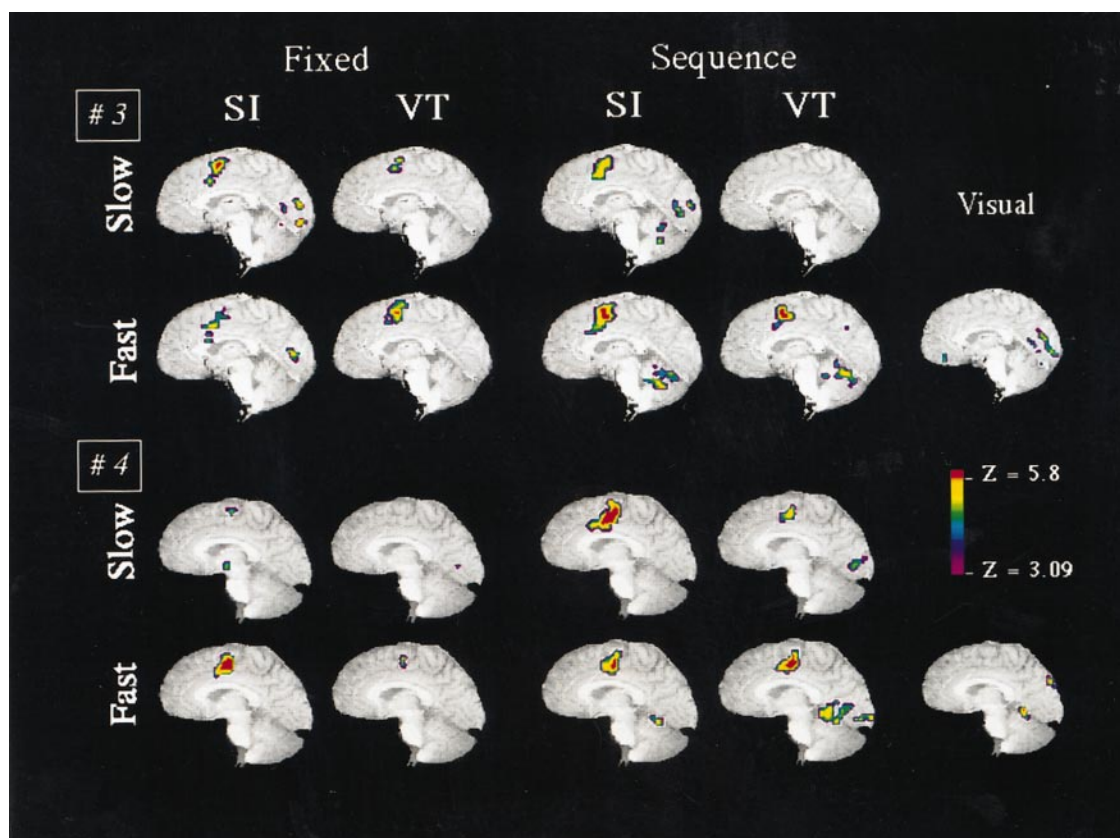


FIG. 3. Cluster maps of significant cerebral activation in 2 subjects, for each condition. 3 (2 top rows): subject 3; 4 (2 bottom rows): subject 4. For each subject, the clusters are superimposed on the high-resolution MR image of the more medial sagittal slice in the left hemisphere. Conventions as in Fig. 2.

pixels, $F = 6.76$, $P < 0.05$). Last, there was a significant HEMISPHERE effect, with more extended activation in the hemisphere ipsilateral to the hand movement (left: 49 pixels, right: 97 pixels; $F = 9.51$, $P < 0.05$). There was a significant interaction between HEMISPHERE and MOVEMENT ($F = 6.74$, $P < 0.05$). In the SMA, the extent of activation was significantly affected by MOVEMENT (FIXED: 57 pixels, SEQUENCE: 104 pixels; $F = 7.28$, $P < 0.05$), and there was a significant interaction of HEMISPHERE and TASK ($F = 6.73$, $P < 0.05$). In the RCZ, the TASK had a significant effect on the extent of activation, with SI (42 pixels) being greater than VT (14 pixels) ($F = 10.1$, $P < 0.05$). In the CCZ, the extent of activation was significantly affected by TASK (SI: 54 pixels, VT: 31 pixels; $F = 51.04$, $P < 0.001$), MOVEMENT (FIXED: 24 pixels, SEQUENCE: 60 pixels; $F = 23.6$, $P < 0.01$), RATE (SLOW: 30 pixels, FAST: 54 pixels; $F = 6.5$, $P < 0.05$), and HEMISPHERE (left: 60 pixels, right: 24 pixels; $F = 15.91$, $P < 0.01$).

PERCENTAGE OF CHANGE IN SIGNAL INTENSITY. The change in signal intensity during movement periods was calculated relative to rest periods as a percentage. Repeated measures ANOVA were performed on the maximum values. In a comparison of movement conditions with the control condition, the %CSI was affected significantly by CONDITION ($F = 3.2$, $P < 0.05$). However, contrast analysis did not show a significant difference among the eight movement conditions and the control condition (0.78 vs. 0.63%, $F = 2.3$, $P > 0.05$).

In a comparison between movement conditions, there was a

significant effect of ROI (pre-SMA: 0.92%, SMA: 0.96%, RCZ: 0.66%, CCZ: 0.57%; $F = 5.41$, $P < 0.05$) and TASK (SI: 0.89%, VT: 0.66%; $F = 7.02$, $P < 0.05$). There were also significant interactions between HEMISPHERE and TASK ($F = 10.78$, $P < 0.05$) and between ROI and MOVEMENT ($F = 4.12$, $P < 0.05$).

A repeated measures ANOVA was performed for each ROI on the %CSI for the eight movement conditions. The results are shown in Fig. 6 and summarized in Table 2. In the pre-SMA, there were significant interactions of HEMISPHERE and TASK ($F = 6.99$, $P < 0.05$) and of RATE and MOVEMENT ($F = 11.56$, $P < 0.05$). In the SMA, none of the within-subject factors had a significant effect on the %CSI. In the RCZ, the TASK had a significant effect (SI: 0.77%, VT: 0.54%; $F = 8.41$, $P < 0.05$). There was also a significant interaction of HEMISPHERE and TASK ($F = 6.74$, $P < 0.05$). In the CCZ, the %CSI was significantly affected by TASK (SI: 0.63%, VT: 0.51%; $F = 11.33$, $P < 0.05$), MOVEMENT (FIXED: 0.5%, SEQUENCE: 0.64%; $F = 29.09$, $P < 0.01$), RATE (SLOW: 0.51%, FAST: 0.63%; $F = 10.18$, $P < 0.05$), and HEMISPHERE (left: 0.63%, right: 0.52%; $F = 17.68$, $P < 0.01$). There were significant interactions of TASK, RATE, and MOVEMENT ($F = 8.28$, $P < 0.05$) and of HEMISPHERE, TASK, RATE, and MOVEMENT ($F = 5.69$, $P < 0.05$).

DISCUSSION

In the present study, we focused on the mesial wall of the cerebral hemispheres to examine the participation of the motor areas in self-initiated movements and movements

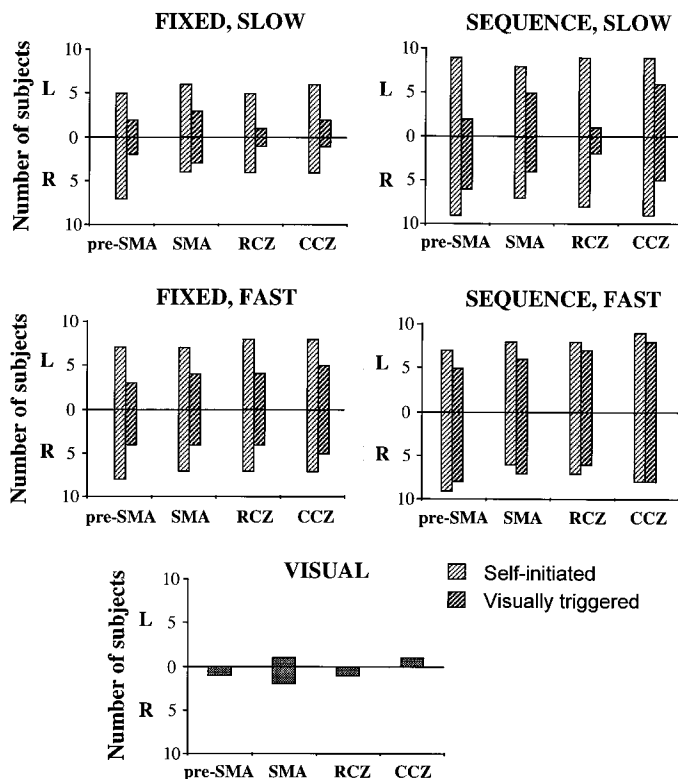


FIG. 4. Histograms of the distribution of activation over the 9 subjects in each condition. Data were obtained from the individual assessment of significant cerebral activation (i.e., from cluster maps; see Figs. 2 and 3). For each subject, the distribution of the significant clusters relative to the ROIs was described with a binary code (1: including a cluster or part of a cluster, 0: not including a cluster or part of a cluster). For RCZ and CCZ, the results were compiled from the 2 slices in each hemisphere (for each subject, hemisphere and ROI: 1 on each slice equals 1; 1 on only 1 slice also equals 1).

triggered by a visual signal. First, we discuss the anatomic basis of our work and describe the technical limitations inherent in this context. Because in humans there is still no absolute identification of separate motor fields in the mesial wall, we elected to use the more recent classification of Picard and Strick (1996), which is based primarily on the analysis of several functional imaging studies. As these investigators anticipated, their work provides a practical framework for studying the role of the medial wall motor areas. They mainly have used data from group PET studies for their analysis, which have in common the reference frame of Talairach and Tournoux (1988). Conversely, our approach is based on individual examination of fMRI images. We have chosen to keep intact as much as possible the high spatial resolution provided by this technique, and thus we have resorted to spatial normalization, which might have been problematic because the brain was only partially sampled. However, we applied the landmarks' conventions of Talairach and Tournoux (1988) in each brain to delimit the anatomic ROIs according to Picard and Strick's (1996) scheme. Our calculations for the ROI boundaries were based on the visual examination of Figs. 4 and 5 in the paper of Picard and Strick (1996) because no numerical measures were provided. We are aware that such an interpretation can lead to some error and that our ROI delimitation in reference to the study of Picard and Strick (1996) is not absolute.

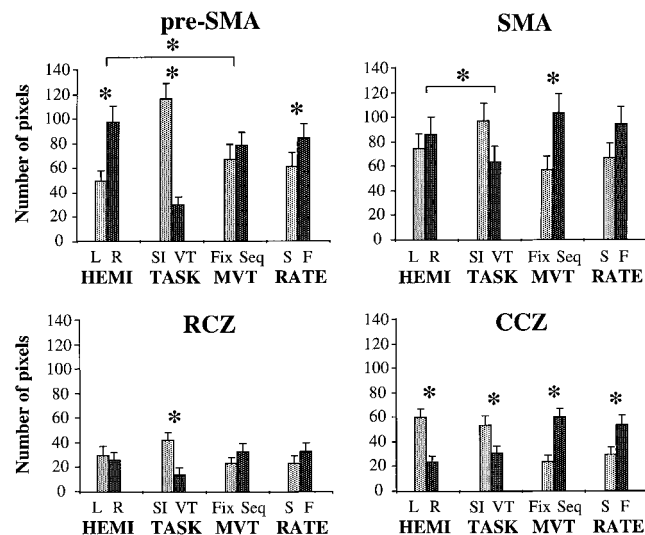


FIG. 5. Mean extent of activation and SEs over the 9 subjects in each ROI for each of the 4 variables: HEMISPHERE (HEMI), TASK, MOVEMENT (MVT), and RATE. Extent of activation is expressed as the number of pixels with $Z > 3.09$. For each variable, the SE value takes into account the variability among the 3 remaining variables, as well as the subjects (e.g., the standard error TASK, SI movements reflect the variability among the variables HEMI, MVT, RATE, and subjects). L: left; R: right; Fix: fixed; Seq: sequence; S: slow; F: fast; asterisks, significant effect; asterisks over the horizontal bars, significant interaction between effects (repeated measures ANOVA performed for each ROI; see text for details).

Motor paradigm and performance

There is abundant literature on changes in regional cerebral blood flow (rCBF) as well as in movement-related potentials in relation to the self decision on a motor response (Deiber et al. 1991, 1996; Frith et al. 1991; Playford et al. 1992; Praamstra et al. 1995, 1996; Touge et al. 1995; Van Oostende 1997). In

TABLE 2. Summary of quantitative analysis

Extent of Activation		Percent Change in Signal Intensity
All data	Task (SI > VT)	ROI (SMA > pre-SMA > RCZ > CCZ)
	Movement (Seq > Fit)	Task (SI > VT)
	Rate (F > S)	<i>Hemisphere × Task</i>
	<i>ROI × Hemisphere</i>	<i>ROI × Movement</i>
	<i>ROI × Task</i>	
pre-SMA	<i>ROI × Task × Rate</i>	
	Task (SI > VT)	
	Rate (F > S)	
	Hemisphere (R > L)	<i>Hemisphere × Task</i>
SMA	<i>Hemisphere × Movement</i>	<i>Movement × Rate</i>
	Movement (Seq > Fix)	
RCZ	<i>Hemisphere × Task</i>	Task (SI > VT)
	Task (SI > VT)	<i>Hemisphere × Task</i>
CCZ	Task (SI > VT)	Task (SI > VT)
	Movement (Seq > Fix)	Movement (Seq > Fix)
	Rate (F > S)	Rate (F > S)
	Hemisphere (L > R)	Hemisphere (L > R)
	<i>Hemisphere × Task × Movement × Rate</i>	

Interactive effects are in italics. ROI, region of interest; SMA, supplementary motor area; RCZ, rostral cingulate zone; CCZ, caudal cingulate zone; SI, self-initiated; VT, visually triggered; Seq, sequence; Fix, fixed; F, fast; S, slow; L, left; R, right.

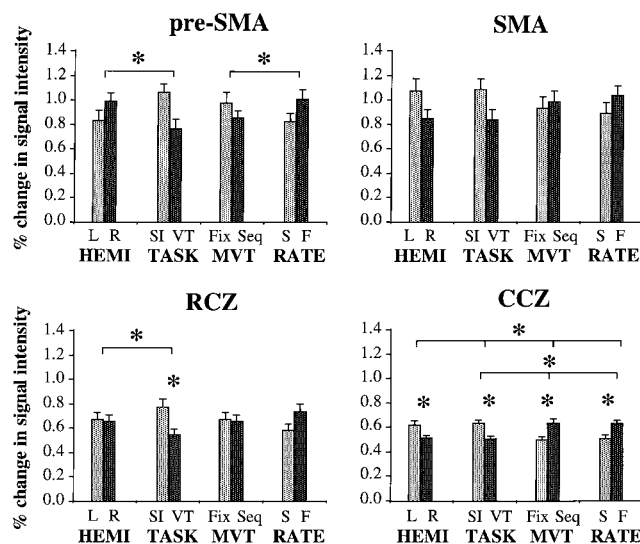


FIG. 6. Mean percentage of change in signal intensity (%CSI) and SEs over the 9 subjects in each ROI for each of the 4 variables: HEMI, TASK, MVT, and RATE. %CSI is expressed as the maximum percentage of change during movement periods relative to rest periods. Conventions as in Fig. 5.

these studies, a free-selection condition, characterized by the subject's own decision about "what to do," generally is opposed to a cued condition, in which the subject is instructed on the movement by a signal; in both conditions, the precise timing of the movements is determined externally by a pacing stimulus or also can be decided by the subject. In contrast, our question related to the effect of the movement initiation mode on brain activation, that is, the aspect of timing or "when to do" something. The movements we tested were all instructed, that is, the subjects knew in advance what to do. Only the way in which they timed their movements was variable: it was either their own decision (self-initiated) or dictated through a visual trigger signal (visually triggered). In the present discussion, we will restrict our review of the literature to studies focused on the initiation mode of instructed movements; this is distinct from the topic of movement selection. In the self-initiated mode, we focused on the volitional aspect of making the movements by asking the subjects to attempt a slightly irregular rate centered around a given value. We wanted to avoid establishing automaticity or rhythmicity that potentially could obscure differences between the SI and VT modes. Moreover, strict regularity in movement performance likely would generate undesirable anticipatory behavior in VT movements, with specific effects on brain activity. In terms of movement frequency, our choice of testing a slow and a fast rate was motivated by the study of Sadato et al. (1996b), which showed a clear difference in SMA blood flow between 0.25- and 1-Hz movements. However, as shown in Table 1, the difference in the frequency of slow and fast movements was smaller than expected, with slow movements performed at ~ 0.31 Hz and fast ones at ~ 0.69 Hz. This observation, along with the fact that only two movement rates were tested, limits the interpretation of the rate effect observed in the present study.

Because an fMRI study is primarily a single-subject technique, we consider it essential to show how each subject behaved on the different tasks tested. Histograms of the results (Fig. 4) were based on cluster maps, which essentially assert

the significance of activation by its intensity and spatial extent within each task for every subject. The results clearly showed more intense activation for SI tasks than for VT tasks; visual stimulation without any detectable movements was associated with minimal activity. Activation was largely bilateral, with the hemisphere contralateral to the movements generally more activated than the ipsilateral hemisphere, except for the pre-SMA. The difference between SI and VT movements was smaller for sequential movements performed at a fast rate. In a sequence, the decision about the next movement can be made during the interval between movements for both SI and VT tasks. When the sequence must be performed at a fast rate, timing preparation in SI is minimal, and one can argue that for fast sequences, the SI and VT tasks are not very different. This interpretation also should apply to the fixed movements at a fast rate; however, the difference between SI and VT was not so small for those movements. An alternative explanation is that when the movement is sufficiently complex and temporally demanding, as it is in the sequence performed at a fast rate, the difference between the SI and VT tasks tends to disappear because of the additional processing role of the mesial motor areas in movement complexity and high-rate movement production.

Quantitative analysis focused on the extent of activation (Fig. 5) and the percentage of change in signal intensity (Fig. 6). These measurements might correspond to neural recruitment and neural activity rates, respectively, but the relation between CBF and neuronal discharge rates remains too uncertain for us to give any definite conclusion. From a theoretical point of view, one has to be aware that with the use of spatial smoothing, an increase in signal intensity could artificially produce an increase in activation extent, the intensity value of a pixel being smeared to its nearest neighbors. However, considering the increase range of the fMRI signal obtained ($\sim 1\%$ on average, see Fig. 5) and the small FWHM used (5.6 mm in-plane), the effect of the Gaussian filter on data dispersion can be estimated as being negligible. This is supported further by the observation that a motor parameter could affect significantly the extent of activation without affecting the increase in signal intensity (Table 2).

In confirmation of the descriptive approach, the main result of the quantitative analysis is that, compared with the VT movements, the SI movements were associated with a larger extent and intensity of activation in the mesial motor regions. Moreover, significant interaction between TASK (SI vs. VT) and ROI (SMA, pre-SMA, RCZ, and CCZ) was observed for the extent of activation, which means that the effect of the task differed according to the mesial structure involved (Table 2). Additionally, for all regions taken together, the extent of activation was also sensitive to movement type (FIXED vs. SEQUENCE) and rate (~ 0.31 vs. ~ 0.69 Hz), with larger values for sequential movements and faster rates (Table 2).

Pre-SMA and SMA

Our measures showed predominant changes in the extent of activation with no main effect on intensity of activation. Only the pre-SMA was affected significantly by the nature of the task, with SI movements inducing more extended activation than VT movements. The SMA showed a trend for such a differential response, although it did not reach significance. On

the other hand, the SMA was affected by the movement type, with sequential movements associated with a larger extent of activation than fixed movements.

EXPERIMENTAL DATA. Some neurophysiological studies in monkeys have addressed the issue of specificity of the premotor areas in self-initiated versus externally triggered movements, most of which comparing the SMA with the lateral premotor area (Mushiaki et al. 1991; Okano and Tanji 1987; Romo and Schultz 1987). However, their goal differed from ours on a basic point: movement rates in the two modes of selection were not matched. In the self-initiated mode, the monkeys had to “learn” to respond at their own pace within a time window, whereas in the triggered mode, a cue was presented intermittently. In those studies requiring performance of simple motor tasks, both the SMA and the premotor area were similarly active regardless of the generating mode. However, long lead neurons, which are more abundant in the SMA, were observed mainly before self-paced movements (Okano and Tanji 1987). Neuronal modulation in the SMA was found to occur earlier for self-initiated than for externally triggered movements (Thaler et al. 1988). Mushiaki et al. (1991) contrasted a self-initiated task in which the monkeys had to remember a predetermined sequence with a visually triggered task in which the sequence of touch pads was visually guided; the self-initiated mode cannot be considered as purely self-paced because the time to start the whole sequence was cued. Results showed that the SMA was more active in the self-initiated than in the triggered mode, whereas the premotor area showed the inverse behavior. Altogether, the results of the aforementioned studies suggest some preferential participation of the SMA in self-initiated movements, especially when more complex movements are involved. However, the studies were all conducted before the description of the SMA proper/pre-SMA subdivision, and thus no clear parallel can be drawn with our data as to which part of the SMA is concerned.

Recent experimental studies have analyzed the implications of differences between self-initiated and externally guided actions. Thaler et al. (1995) removed the medial premotor cortex, which corresponds to the whole SMA, in monkeys. The animals were poor at performing a simple, learned arm-raise task at their own rhythm, but much less impaired when a tone triggered their performance. The investigators concluded that the medial premotor areas play a crucial role in the performance of self-initiated actions, independently of the nature of the movements (simple or sequential). Chen et al. (1995) further analyzed the role of the tone in externally triggered tasks and showed that animals with lesions of the medial premotor cortex performed better when given external cues because the cues acted as instructions. In other words, the authors interpreted the impairment of the monkeys with a mesial area 6 lesion in terms of a lack of retrieval of the appropriate action. Our own findings suggest that the role of mesial area 6, and more specifically the pre-SMA, is rather related to the timing of the self-initiated response; i.e., that the impairment of lesioned monkeys could be interpreted as a default in timing the response.

HUMAN ELECTROPHYSIOLOGY AND FUNCTIONAL IMAGING. Studies of movement-related potentials preceding movements show that these potentials indeed are modulated by the mode of motor initiation. Papa et al. (1991) recorded the Bereitschaft

potential occurring before wrist movements in self-paced and externally cued conditions. The Bereitschaft potential was present only in self-paced conditions, suggesting different cortical areas for the generation of self-paced and stimuli-triggered movements. Jahanshahi et al. (1995) confirmed the absence of Bereitschaft potential in externally triggered movements when the rate of presentation of the trigger stimulus was very variable. With more regular trigger presentation, the amplitude of the Bereitschaft potential was smaller for externally triggered than for self-initiated movements. If the Bereitschaft potential mainly reflects SMA activity (Deecke and Kornhuber 1978; Ikeda et al. 1992; Lang et al. 1991), then its absence or reduced amplitude in externally cued movements suggests minor activation of the SMA in this type of movement, which is consistent with our data. However, different components can be distinguished in the Bereitschaft potential, and their cortical generators remain an object of debate (Böcker et al. 1994; Bötzel et al. 1993; Neshige et al. 1988; Toro et al. 1993). Moreover, the spatial resolution of scalp-recorded electrical potentials is too weak to achieve definite distinction between the pre-SMA and the SMA proper.

A few studies have used either PET or fMRI to compare self-paced and externally triggered movements (Jahanshahi et al. 1995; Larsson et al. 1996; Rao et al. 1993; Remy et al. 1994; Tyszka et al. 1994; Wessel et al. 1997). However, the results from these studies have been divergent, possibly because of different paradigm designs. We will review the available data and draw parallels with our own findings as far as possible.

Two studies failed to replicate the classic picture of the association between self-paced movements and larger activation of the SMA, namely the studies of Remy et al. (1994) and of Jahanshahi et al. (1995). Remy et al. (1994) observed with PET that acoustically triggered movements, but not self-paced movements, activated the SMA. The region they referred to as the SMA covered mainly the SMA proper and extended into the pre-SMA. An unequal number of subjects performed the self-paced and cued conditions (10 and 3, respectively), which renders a proper comparison between the two modes difficult. In the self-initiated task, subjects were asked to move at their own “automatic” frequency, which suggests that the movements might have been performed at a relative regular pace. The movement rate in the cued condition theoretically was yoked to the self-paced condition. However, the calculation of movement frequency in the self-paced condition was based on visual examination by an experimenter, suggesting that only the total number of movements, but not the actual rhythm, was monitored. As a result, it is likely that the self-paced and cued conditions were performed at distinct rhythms, with a potential bias toward a more regular rate in the cued condition. By such a hypothesis, the SMA activation observed in the cued condition could be due to anticipatory and preparatory behavior, rather than to the initiation mode. Jahanshahi et al. (1995) observed that externally triggered movements activated the same areas activated by self-initiated movements but less extensively. They found no difference in rCBF in the mesial structures between self-initiated and externally triggered movements, the rate of both types of movement being accurately yoked. These authors insisted on a regular movement production in the self-initiated mode. As they themselves recognized, it is possible that, because of the regularity and predictability of the trigger, stimulus anticipation and motor preparation had

occurred in the externally triggered condition, leading to activation of the SMA and thus blurring a potential difference with the self-initiated condition. This reasoning supports the hypothesis that movement rhythmicity could have a significant impact on cerebral activation.

Movement rhythmicity remains an unclear issue in the PET study by Larsson et al. (1996). In the self-paced task, the authors required “rhythmic movement” of the fingers at the same rate as previously used in a visually triggered task, in which subjects were asked to respond to changes in screen luminance occurring randomly at 250–2,000 ms. This wide range of trigger intervals appears incompatible with production of rhythmic movements, and indeed the mean movement frequency varied by 37%. Results of the self-initiated task compared with a no-movement condition are compatible with ours, showing activation in the SMA (including both SMA proper and pre-SMA, as deduced from activation coordinates) and rostral cingulate motor area. Activation in these mesial motor regions was significantly larger in the self-paced condition than in the visually triggered condition. On the other hand, there was no significant difference between the visually triggered condition and the reference condition. A parallel could be drawn between this finding and the observation by Jahanshahi et al. (1995) that the Bereitschaft potential was absent before the movements in a triggered condition with high variability of trigger occurrence.

In the PET study of Wessel et al. (1997), short self-paced finger sequences were to be produced every 4–6 s (i.e., ~48 touches/min), thus intermingling the regularity of the sequence performance with some variability in the sequence initiation. The metronome-triggered task differed in that the movements were performed continuously at a regular rate of 2 Hz (120 touches/min). The difference in rate makes it difficult to properly compare the two types of movements, as the authors recognized. Interestingly, the focus of maximal activation in the SMA during self-paced movements was more anterior (at pre-SMA coordinates) than during metronome-paced movements (at the anterior commissural line, that is, in the rostral part of the SMA proper). Although there were fewer movements, the pre-SMA and rostral cingulate motor area, along with prefrontal and inferior parietal cortex, were more active in self-paced than in cued movements. These findings agree with our observations of the mesial structures. Moreover, the results of both studies provide additional information about the predominance of task effect over rate effect in the pre-SMA. Indeed, Wessel et al. (1997) found a task effect despite the slow performance rate, whereas we observed a rate effect of the type “fast rate > slow rate,” which did not hamper the task effect.

Rao et al. (1993) and Tyszka et al. (1994) have examined the mesial motor structures with fMRI, but their results provide only partial information to the present concerns. Tyszka et al. (1994), using self-paced sequential movements of undetermined rate, identified three distinct sites of activation caudal to the VAC within the SMA proper or the adjacent cingulate cortex. No comparison with cued movements was carried out. Rao et al. (1993) studied six subjects while they performed self-paced simple or sequential finger movements with the right or left hand. Activation was more widespread with sequential movements than with simple movements, and included the SMA and bilateral premotor cortex in addition to the contralateral motor cortex. However, the sequential move-

ments were performed at a slower rate than the simple ones (2.2 vs. 2.9 Hz), thus introducing a potential confounding factor. In a 2-Hz metronome-cued condition performed by two subjects, no functional activation was detected for the simple movements, but for the sequential movements, activation was generally less with the metronome-paced movements than with the self-paced movements. The unequal number of subjects performing the self-paced and cued movements reduces the validity of the comparison between the two modes.

In the present study, subjects specifically were instructed not to generate regular movements. Our findings support the hypothesis that movements initiated on a variable, as opposed to a regular mode, activate the mesial area 6 more extensively than movements triggered at a yoked pace by an external stimulus. In pursuing a special effort to resolve the two regions within mesial area 6, we further suggest some functional specificity in this area, although it is relative rather than absolute: the pre-SMA is especially concerned with the mode of movement initiation, whereas the SMA proper is implicated in the type of movement.

The role of the human pre-SMA and SMA proper in sequential movements is complex. The results of some electrophysiological and rCBF studies suggest that the SMA is involved especially in sequential finger movements (Catalan et al. 1998; Deiber et al. 1991; Jenkins et al. 1994; Lang et al. 1992; Roland et al. 1980; Shibasaki et al. 1993), whereas others found no difference in SMA activity between simple and sequential hand movements (Colebatch et al. 1991; Fox et al. 1985; Sadato et al. 1996a). It is probable that many factors are implicated in regulating SMA activity. In particular, human ablation and lesion studies have shown an absence of difficulty in performing single joint movements in contrast with long-lasting deficits in bimanual coordination, sequencing multiple movements, and retrieving correct movement or motor sequence from memory (for a review, see Tanji 1994). Data from our present study suggest that the SMA proper, but not the pre-SMA, is more responsive to relatively simple sequential finger movements as opposed to repetitive single-finger movements. This finding also could be related to the preparation process, which is supposedly more demanding in a motor sequence involving a different target digit each time than in a single digit movement (Deiber et al. 1991; Simonetta et al. 1991).

Recently several experiments have examined the effect of movement frequency on cerebral activation and have demonstrated frequency-dependent changes in the contralateral sensorimotor cortex, higher activation being associated with higher movement rates (Blinkenberg et al. 1996; Jenkins et al. 1997; Sadato et al. 1996b; Schlaug et al. 1996). In terms of the SMA, however, the findings have been inconsistent. Sadato et al. (1996b) tested three frequencies (0.25, 0.5, and 0.75 Hz) and observed peak activation of the SMA proper at 0.5 Hz, followed by a decreasing response at higher frequencies, ending with a plateau between 2 and 4 Hz. Blinkenberg et al. (1996) began with a frequency of 0.5 Hz, observed peak activation of the SMA proper at 1 Hz, and, as in Sadato et al. (1996b), noted a decreasing response at higher frequencies of ≤ 2 Hz; however, a second and higher peak of activity was observed at 4 Hz. Using fMRI, Schlaug et al. (1996) also showed a significant positive dependence of the contralateral sensorimotor cortex with movement rate (1, 2, and 3 Hz were tested) but only a covariant trend for positive dependence of

the SMA. Jenkins et al. (1997) used joystick movements at frequencies ≤ 1 Hz and showed that the rCBF changes in the SMA proper correlated strongly with the frequency of movement, with a nonlinear trend as the frequency reached 1 Hz. Sadato et al. (1996b) used an index-to-thumb opposition task similar to our FIXED task, and their Fig. 2A showed a nearly identical response in the SMA proper at the two frequencies we tested (0.30 and 0.63 Hz) for our fixed movements, slow and fast rates, respectively. Therefore our observation on the absence of a rate effect on the SMA proper at the two frequencies we tested is in accordance with their data. However, we noted a rate effect on the pre-SMA, which neither Sadato et al. (1996b) nor Jenkins et al. (1997) had observed. The reasons for such a discrepancy are unclear. However, the rates we tested in our study originated primarily from a self-initiated decision constrained through the instruction to generate movements at a variable frequency, whereas the aforementioned studies studied strictly controlled acoustically cued rates. An important point of our study is that no interactive effect of TASK and RATE was found in any of the mesial areas, which means that, for the two frequencies tested, the effects of movement initiation mode were independent of the frequency of execution.

The hemisphere of activation of the SMA relative to unilateral movements is not easily resolved in group PET studies. Indeed, the spatial smoothing used in the analysis of group data usually precludes a definite conclusion about the exact location of SMA activity, and a single focus of activation standing on the midline generally is interpreted as bilateral activation of the SMA. Single-subject fMRI can improve this spatial limitation. In the present study, we found, for the first time, a significant preponderance of the ipsilateral rather than the contralateral response in the pre-SMA. In monkeys, Tanji et al. (1988) examined the neuronal activity of the SMA related to ipsilateral, contralateral and bilateral hand movements. They found that, contrary to motor cortex activity, SMA neuronal activity did not code the activity of muscles per se: instead, changes in SMA activity occurred in relation to movement only when movement of one limb was coupled with the other in a bimanual action or only when the limb operated alone. In the primary motor cortex, the cells always showed modulation before movement of the contralateral limb, regardless of whether it was coupled with a bimanual movement. These findings suggest a complex interhemispheric distribution of activity in the SMA. Such an hypothesis is supported by a recent fMRI study (Hikosaka et al. 1996), which showed that the pre-SMA was active unilaterally in relation to learning sequential procedures (on either the left or right side, according to the subject). In a purely motor paradigm, Shibasaki et al. (1993) showed that the increased rCBF tended to be greater in a complex sequential task than in a simple one in the ipsilateral SMA. Although region designation differs among studies, this observation is consistent with our report of a significant interactive effect between movement type and hemisphere of activation in the pre-SMA. Specifically, we found that sequential compared with simple movements are associated with more pronounced dominance of the ipsilateral response over the contralateral one.

Rostral and caudal anterior cingulate cortex

In contrast with the pre-SMA and the SMA, for which the extent of activation was more sensitive than the magnitude of activation, both variables were affected similarly in the RCZ

and CCZ. Consequently, activation in the cingulate cortex is discussed with reference to the extent and intensity together. In both RCZ and CCZ, self-initiated movements induced greater activation than did visually triggered movements, and activation was consistently larger in the left hemisphere (contralateral to the movements). In addition, in the CCZ, sequential movements and faster movements were both associated with more activation.

In monkeys, Shima et al. (1991) found two distinct movement-related foci in the cingulate cortex that were associated with self-paced and signal-triggered movements. Using a simple key-press task and matching the execution rate of the two types of movements, they found that more neurons responded to the self-paced motor task in the anterior than in the posterior cingulate cortex. Long-lead type of activity (500 ms to 2 s before movement) was observed mainly before the self-paced movements and was more frequent in the anterior cingulate cortex. According to Picard and Strick (1996), the anterior cingulate cortex described by Shima et al. (1991) is equivalent to the rostral cingulate motor area and would correspond to the RCZ in humans, whereas the posterior cingulate cortex is equivalent to both dorsal and ventral cingulate motor areas and would correspond to the human CCZ. Our data showed that both parts of the human cingulate cortex were more active in self-paced than in triggered movements. No direct comparison was made between the rostral and the caudal zones to determine whether, as suggested by Shima et al. (1991), the RCZ has a greater role in self-paced movements.

In most of the functional imaging studies that have examined the effect of the movement initiation mode on brain activation, the boundaries of the anterior cingulate cortex were not clearly delineated, and little attention was given to this mesial structure (Rao et al. 1993; Tyszka et al. 1994). Remy et al. (1994) defined an "upper anterior cingulate cortex" region whose anteroposterior coordinates covered both RCZ and CCZ. They did not report any significant changes of activity in this region with different modes of movement initiation. Wessel et al. (1997) observed that, as in the pre-SMA, activation in the RCZ was significantly larger with the self-paced than with the metronome-paced task. They found a converse result in the CCZ, but the movement rate was faster for the metronome-paced task than for the self-paced task. In view of our own results, which show higher activity in the CCZ with the self-paced movements as well as with the faster rate, it is possible that the effect of rate is predominant over the effect of movement initiation mode (self-initiated versus visually guided) in the CCZ, in contrast with the pre-SMA (see *Pre-SMA and SMA*).

There are very few studies in which the activity of the anterior cingulate cortex is examined in relation to the complexity and rate of motor tasks. Shibasaki et al. (1993), contrasting a simple finger sequence with a more complex finger sequence, executed at a self-paced rate of 2 Hz, found no difference in rCBF in the anterior cingulate cortex. Our finding of an effect of movement type in the CCZ by contrasting a sequence movement with a single repetitive movement suggests that the critical factor is the sequential nature of the movement, and not its intrinsic complexity, as studied by Shibasaki et al. (1993). Recently, Picard and Strick (1997) examined 2-deoxyglucose uptake in the mesial cortex of monkeys during the performance of remembered simple sequences of reaching movements. The arm areas of the pre-SMA and

SMA proper showed radioisotope uptake, but it was the dorsal cingulate motor area, which is equivalent to the CCZ in humans, that showed the most intense and extensive 2-deoxyglucose uptake. These results further suggest that this region is involved more than any other medial area in the preparation and execution of highly practiced, remembered sequences of movements. Concerning movement frequency, Sadato et al. (1996b) observed a peak of activity in the region we termed the CCZ at very slow movement rates (0.25 and 0.5 Hz), which correlated with the activity in the SMA proper, and a monotonic decrease in rCBF at higher repetition rates. Because we only tested relatively slow rates, it is difficult to draw any parallel with our study.

It is interesting to note that, of all the mesial regions we studied, the CCZ is the only one with a significant response to every variable tested in the present study, that is, TASK, MOVEMENT, and RATE. Furthermore the signal increase contralateral to the movements was significantly larger than the ipsilateral one. The CCZ is likely to correspond to the dorsal cingulate motor area in the monkey (Picard and Strick 1996), which projects directly to the spinal cord (Dum and Strick 1991; He et al. 1995). The dorsal cingulate motor area is the only cingulate motor area in the monkey that lacks interconnections with the dorsolateral prefrontal cortex (Lu et al. 1994), an observation that correlates in humans with the dissociation observed between activation of the CCZ and that of the prefrontal cortex (for a review, see Picard and Strick 1996). Those propositions suggest that the CCZ might be functionally closer to the executive motor system than to a supramotor center, which might explain why the signal there is so responsive to each of the relatively simple motor features tested in this study, without preference for any of them. Our analysis also revealed that the CCZ was the region in which the intensity of signal change was the smallest, suggesting both a low threshold and low magnitude for the correlations reported. The other mesial regions showed more selectivity in their activity. Self-initiated movements induced larger activation in the more rostral mesial areas, that is, the pre-SMA and the RCZ. The movement type was the only variable that affected the SMA proper, with sequential movements inducing larger activation than simple repetitive finger movements.

The authors thank Dr. S. P. Wise for comments on an earlier version of this manuscript and B. J. Hesse and D. G. Schoenberg for skillful editing.

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Received 20 July 1998; accepted in final form 11 February 1999.

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