NeuroImage **10,** 682–694 (1999)
Article ID nimg.1999.0507, available online at http://www.idealibrary.com on IDEAL®

# The Role of Higher-Order Motor Areas in Voluntary Movement as Revealed by High-Resolution EEG and fMRI

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Received February 16, 1999

**In the human motor cortex structural and functional differences separate motor areas related to motor output from areas essentially involved in higher-order motor control. Little is known about the function of these higher-order motor areas during simple voluntary movement. We examined a simple finger flexion movement in six healthy subjects using a novel brain-imaging approach, integrating high-resolution EEG with the individual structural and functional MRI. Electrical source reconstruction was performed in respect to the individual brain morphology from MRI. Highly converging results from EEG and fMRI were obtained for both executive and higher-order motor areas. All subjects showed activation of the primary motor area (MI) and of the frontal medial wall motor areas. Two different types of medial wall activation were observed with both methods: Four of the subjects showed an anterior type of activation, and two of the subjects a posterior type of activation. In the former, activity started in the anterior cingulate motor area (CMA) and subsequently shifted its focus to the intermediate supplementary motor area (SMA). Approximately 120 ms before the movement started, the intermediate SMA showed a drop of source strength, and simultaneously MI showed an increase of source strength. In the posterior type, activation was restricted to the posterior SMA. Further, three of the subjects investigated showed activation in the inferior parietal lobe (IPL) starting during early movement preparation. In all subjects showing activation of higher-order motor areas (anterior CMA, intermediate SMA, IPL) these areas became active before the executive motor areas (MI and posterior SMA). We suggest that the early activation of the anterior CMA and the IPL may be related to attentional functions of these areas. Further, we argue that the intermediate part of the SMA triggers the actual motor act via the release of inhibition of the primary motor area. Our results demonstrate that a noninvasive, multimodal brain imaging technique can reveal individual cortical brain activity with high temporal and spatial resolution, independent of *a priori* physiological assumptions.** © 1999 Academic Press

## INTRODUCTION

The neural basis of voluntary movement in human and nonhuman primates is currently under intense investigation. Recent evidence from different approaches (Marsden *et al.,* 1996; Picard and Strick, 1996; Rizzolatti *et al.,* 1996; Tanji, 1996) suggests the existence of so-called higher-order motor areas, such as the anterior supplementary motor area (SMA) and the anterior cingulate motor area (CMA), separate from cortical motor areas closely related to movement execution which possess the largest population of corticospinal fibers. These areas, the primary motor area (MI), the posterior SMA, and the posterior CMA, are referred to here as executive motor areas. However, it must be kept in mind that these areas also appear to participate in "higher-order" aspects of motor control such as bimanual coordination. Therefore, the distinction between higher-order and executive motor areas is not absolute.

This functional segregation into higher-order and executive motor areas is well established for the motor areas of the frontal medial wall (Picard and Strick, 1996), based on evidence from different approaches, such as human cytoarchitectonic studies, human positron emission tomography (PET) studies, and nonhuman primate studies. According to these approaches, different terminologies have been developed. However, there are some unresolved discrepancies between these different maps of the frontal medial wall. Rather than giving preference to one of these terminologies, we use a descriptive scheme shown in Fig. 2a.

In the CMA an anterior, an intermediate, and a posterior part can be distinguished. The anterior and intermediate parts are preferentially activated by motor tasks, which either demand the selection of movement parameters or are complex in nature, corresponding to their higher-order function in motor control. The posterior part of the CMA can be activated during simple externally triggered movements (Fink *et al.,* 1997) and its cell architecture and connectivity are typical for a motor output area (Braak, 1976; Dum and



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Strick, 1996). The CMA links the limbic system with motor areas (Devinsky *et al.,* 1995) and sustains attention for forthcoming actions (Jueptner *et al.,* 1997). Therefore, it may serve as a motivational–motor interface.

As in the adjacent CMA, also in the SMA a higher-order anterior part can be distinguished from a more executive posterior part based on structural and functional evidence from human and nonhuman primates (Luppino *et al.,* 1991; Matelli *et al.,* 1991; Matsuzaka *et al.,* 1992; Rizzolatti *et al.,* 1996; Tanji, 1996). Recent PET and functional magnetic resonance imaging (fMRI) data indicate that a further, intermediate subarea exists at least in the human SMA (Dettmers *et al.,* 1995; Grafton *et al.,* 1996; Stephan *et al.,* 1995; Tyszka *et al.,* 1994). This area has the remarkable feature to be preferentially activated during movement imagery compared to movement execution (Stephan *et al.,* 1995). When examining the influence of movement peak force on regional cerebral blood flow changes using PET, no such correlation was found for the area corresponding to the intermediate SMA, in contrast to the executive motor areas (Dettmers *et al.,* 1995). These characteristics suggest that the intermediate SMA belongs to the group of the higher-order motor areas, in parallel to the intermediate CMA. However, so far the specific role of the intermediate SMA in motor control remains unknown.

The inferior parietal lobe (IPL) is also a candidate area for higher-order motor function, based on recent results showing a specific motor deficit in movement initiation after IPL lesion (Mattingley *et al.,* 1998) and on the observation of increased activation of the IPL in stroke patients with lesioned primary motor system (Weiller, 1998).

Of special interest is the dynamic aspect of movement-related activity of these areas, which can be investigated by electrophysiological methods such as scalp-recorded EEG and MEG or intracranial electrical recordings. These methods directly detect neuronal activity on a milliseconds scale by measuring electric potential or magnetic field distributions resulting from postsynaptic extra- or intracellular currents. Using these methods in humans it was demonstrated that MI and the posterior SMA show a similar temporal activation pattern during the preparation and execution of a simple voluntary movement (Toro *et al.,* 1993; Shibasaki and Ikeda, 1996; Lang *et al.,* 1991; Rektor *et al.,* 1994).

However, little is known about the time course of movement-related activity in human higher-order motor areas. To study activity in these areas, we examined the Bereitschaftspotential (BP) paradigm (Kornhuber and Deecke, 1964), consisting of a simple self-paced right index finger flexion. Recent PET studies have shown that in addition to executive areas, this specific motor task involves activation of higher-order motor areas in the anterior medial wall and of the IPL (Jahanshahi *et al.,* 1995; Larsson *et al.,* 1996). Therefore, the Bereitschaftspotential paradigm is an attractive tool to investigate higher-order motor area function.

Activity of the medial wall motor areas was not shown in previous MEG studies in healthy subjects. This is due to the fact that MEG is only sensitive to tangential components of the currents of an active neuronal population, as is the case with the primary sensorimotor area sources. For the bilaterally organized sources in the frontal medial wall MEG is silent even for the tangential components because they cancel each other (Lang *et al.,* 1991). Since the investigation of the frontal medial wall motor areas was a major point of interest of our study, we used high-resolution EEG, which is sensitive to both tangential and radial currents and can therefore measure the radial current components of the medial wall sources.

Most previous EEG source reconstruction studies of self-paced movement-related activity used spatiotemporal multidipole modeling (Böcker *et al.,* 1994; Bötzel *et al.,* 1993; Praamstra *et al.,* 1996; Tarkka, 1994; Toro *et al.,* 1993; Mackinnon *et al.,* 1996). Due to this approach a constraint on the number of sources, i.e., current dipoles, had to be used. In some of these studies additional assumptions about the geometry and location of the sources were made. Further, for the source reconstruction, the individual brain morphology was not taken into account. The number of electrodes used and the spatial resolution achieved in this studies was not high enough to discriminate between nearby areas as it is the case with the SMA and CMA or their subdivisions.

A recent EEG study introduced a new source reconstruction approach: Knösche *et al.* (1996) have used current density reconstruction, i.e., a distributed source model. This kind of reconstruction method has the principal advantage that no *a priori* assumptions about the number or location of the sources are required. This study demonstrated a strong source in the area of the medial wall motor areas. However, due to the low number of electrodes, the suboptimal electrode layout, and the simple spherical source space model used, the spatial resolution of this study was still limited.

In the present study, high-resolution EEG (64 electrodes) was used in an innovative way. The individual brain anatomy from MRI was used for the source space models and for the volume conductor models. As in the study of Knösche *et al.* we also used a current density reconstruction method in order to avoid the problem of *a priori* constraints, but with a higher number of electrodes and using a L1 instead of a L2 norm, which is more focal and of higher spatial resolution than the corresponding L2 solution (Wagner, 1998). Further, the

results from the high-resolution EEG were individually cross-validated using functional MRI, the latter providing information about the metabolic activity resolved into small volume elements. In this way we were able to describe movement-related activity of executive and of higher-order motor areas on an individual basis and with high temporal and spatial resolution.

## MATERIALS AND METHODS

### *Subjects*

Six healthy right-handed subjects (four male, two female, mean age 28 years, range from 24 to 35 years) participated in the experiments after having given their informed consent. All of them had 100% dextrality after a modified Oldfield questionnaire (Oldfield, 1971). The subjects had previous experience with similar experiments.

### *Experimental Paradigm*

For the EEG experiments subjects were seated in an electrically shielded, dimly lit room. The motor task to be performed was a self-paced right index finger flexion carried out at irregular intervals of 12 to 24 s, starting from complete relaxation (Bereitschaftspotential paradigm) (Kornhuber and Deecke, 1964). The subjects were instructed to avoid any other movements and to fix their gaze on a light-emitting diode placed in front of them. The paradigm used in the fMRI experiments was the same, except that the intervals between the finger flexions were shorter (around 3 s).

### *EEG Recording and Source Reconstruction*

Using a 64-channel EEG system (NeuroScan, U.S.A.), electrical potentials (bandpass filter 0–100 Hz; sampling rate 500 Hz) were recorded from 61 scalp positions equally distributed over both hemispheres. The EMG of the right flexor digitorum longus muscle (pars indicis) was recorded and the EMG onset was used as a trigger for the averaging. The EOG was also recorded to reject trials contaminated with eye movements from further analysis. The analysis time was set from 3500 ms before to 1000 ms after EMG onset. A total of 200 to 300 artifact-free trials were averaged and baseline-corrected using the first 500 ms as a baseline.

After the EEG recording the electrode positions and the head contour of the subjects were digitized using a 3D ultrasound localization device (Zebris). The digitized head contour was matched with the head contour from the anatomical MRI using an automatic surface matching technique for the registration of the coordinate systems of the two modalities (Huppertz *et al.,* 1998).

Source reconstruction was performed using nonlinear cortical current density analysis (CCD). The CCD maps obtained in this way show a current flow distribution on the cortex which can account for the potentials measured on the head surface. In contrast to linear CCD implementations minimizing the L2 norm of the reconstructed currents (minimum norm least squares, MNLS) (Ilmoniemi, 1991), the method used here finds the regularized solution with minimal sum of absolute current densities (L1 norm). The regularization parameter $\alpha$ was determined according to the $\chi^2$ criterion, which relies on the assumption that a reasonable variance is inversely proportional to the signal-to-noise ratio of the data. This nonlinear CCD solution is more focal and of higher spatial resolution than the corresponding MNLS solution (Wagner, 1998). Due to the current density approach, no assumptions about the number and locations of sources had to be made, except that sources were constrained to a discretized surface representing the cortical gray matter. Two distinct types of such source surfaces were used: average surfaces with about 4000 locations obtained by spatially filtering the segmented cortices and the segmented cortices themselves with all individual gyri and sulci and about 15,000 discretized locations. The latter models were used to obtain the precise locations of sources within the interhemispheric fissure. Realistic three-compartment boundary element method (BEM) models with about 800 nodes per model were used as the volume conductor models. Image segmentation, volume conductor modeling, source reconstruction, and visualization were performed using the Curry software (Curry 2.1.3, Philips Research, Hamburg, Germany).

The centers of mass of the sources in the CCD maps were determined automatically by computing a weighted average of all reconstructed sources around local maxima that had at least 33% of the strength at the local maximum itself.

The time course of the CCD sources was determined by sequential CCD reconstructions in 10-ms steps from $-150$ to $+150$ ms around movement onset and in 50-ms steps in the remaining periods of analysis time. The CCD was performed independently for each analyzed time point. Between $-3000$ and $-1000$ ms separate reconstructions were made using sliding-window-filtered data (window width 200 ms). Results reported for this time period are based on these sliding-window-filtered data.

Due to the $\chi^2$ criterion used for the regularization, the goodness of fit increased during the premovement period in parallel with the signal-to-noise ratio. For the reconstructions using the smoothed cortex as a source model, the mean goodness of fit for the onset of premovement activity was 73.6% (from 71 to 81%). At the peak of primary motor activity (30–50 ms after EMG onset), the mean goodness of fit for all subjects was 90.7% (from 88.8 to 92.7%). During the peak of the medial sources, the mean goodness of fit was 91.2% (from 89.4

to 93.1%). For the reconstructions using the realistically segmented cortex as a source model, the goodness of fit was similar (for the onset of premovement activity: mean 73.1%; from 71 to 80%).

*Functional and Structural MRI*

In the same subjects the activation of the different motor areas was examined by functional magnetic resonance imaging (fMRI) using a 1.5-T Magnetom Vision (Siemens, Erlangen, Germany) in a separate recording session. The blood oxygenation level-dependent (BOLD) contrast was measured with a T2*-sensitive multislice echo planar imaging (EPI) pulse sequence with TR/TE/$\alpha$ = 3500 ms/84 ms/90°. The field of view was 256 × 256 mm using a 128 × 128 matrix at a slice thickness of 4 mm. Each measurement acquired 10–12 slices without an interslice gap. Thus a region of 4–4.8 cm was covered with a spatial resolution of 2 × 2 × 4 mm. Four cycles of rest/stimulation periods (28 s per period) were used, with eight sets of images obtained per period.

All experiments were corrected for motion using a voxel-based cross-correlation algorithm. The first set of images was chosen as reference, because it was used for the spatial registration with the 3D data set. To account for hemodynamic latencies, the rest/stimulation pattern was shifted by one data point (3.5 s). The first two sets of images were omitted because the signal intensity is not yet in a steady-state condition due to saturation effects. After sorting the measurements into stimulation and reference classes, activation maps were calculated pixel by pixel using a one-tailed Student's *t* test provided by Paravision/Xtip software (Bruker, Karlsruhe, Germany). Pixels showing more than 97.5% probability were assigned to an activation map. Because grouped "activated" pixels are more likely to represent a physiological effect than single pixels, the activation map was processed with a cluster detection algorithm (5 of 3 × 3 pixels had to be activated). The number of false-positive voxels due to noise was reduced by this procedure to less than one in the whole brain imaged. The signal time course was evaluated for each of the remaining clusters. Only clusters showing an appropriate hemodynamic delay (one to three images = 3.5–10.5s) and a signal change of less than 9% were considered to result from BOLD contrast due to neuronal activation and not from motion (no hemodynamic delay) or blood flow artifacts in major vessels (signal change >9%).

To transform the final activation map into the coordinate system used for the CCD calculation the first set of EP images was matched onto the 3D data set. As the first set of EPI images provides more contrast due to the different saturation properties of CSF and cortex, it contains the most image information. The registration algorithm we used was a local and elastic matching on the basis of trilinear Bézier splines. The spline defining grid had a mesh size of 16 × 16 × 16 mm leading to a total number of approximately 150 control points within the measured volume. Each control point can be relocated in three dimensions under elastic constraints. This provides a correct warping of echo planar images into FLASH images within margins of error of the pixelsize of the EP images. The resulting transformation was applied to the activation map.

For the structural MRI the 3D data set with full head coverage and 1-mm$^3$ voxels was acquired using a volume-encoded fast low angle shot pulse sequence (FLASH) with TR/TE/$\alpha$ = 40 ms/6 ms/40°. The motor cortices were identified with respect to anatomical landmarks for the primary motor area (Steinmetz *et al.,* 1989; Rumeau *et al.,* 1994; Yousry *et al.,* 1997), for the motor areas of the frontal medial wall (Zilles *et al.,* 1996; Vogt *et al.,* 1995; Wise *et al.,* 1996), and for the inferior parietal lobe (Naidich *et al.,* 1995).

## RESULTS

*Primary Sensorimotor Area Activation*

All subjects showed significant fMRI activation in the left central sulcus along the precentral knob (Fig. 1). This anatomical landmark corresponds to the primary motor hand area (Rumeau *et al.,* 1994; Yousry *et al.,* 1997). All subjects showed a corresponding CCD source just in front of the fMRI activation (Fig. 1). The mean distance between the center of mass of the CCD and of the fMRI sources was 9.5 mm, ranging from 6.7 to 13.0 mm. The main orientation of the CCD source currents was from posterior to anterior (Fig. 1b).

The sequential CCD maps showed MI activity starting typically between 2000 and 1000 ms before EMG onset, slowly rising until approximately 100 ms before EMG onset, followed by a fast rise peaking between 30 and 50 ms after the EMG onset. As an individual variation in the MI activity time course one subject did not show the slow premovement part.

Activity in the primary somatosensory cortex (SI) was found just after the EMG onset reflected in a transient flip of the current orientation from anterior to posterior (Fig. 1c). This was most prominent at about 70 ms after EMG onset.

*Frontal Medial Wall Activation*

All six subjects showed corresponding fMRI and CCD activation in the motor areas of the frontal medial wall with a mean distance between the CCD and fMRI centers of mass of 9.2 mm, ranging from 5.7 to 16.3 mm. On the basis of the fMRI and CCD maps two different medial wall activation patterns could be distinguished (Figs. 2 and 3): an anterior-type activation localized

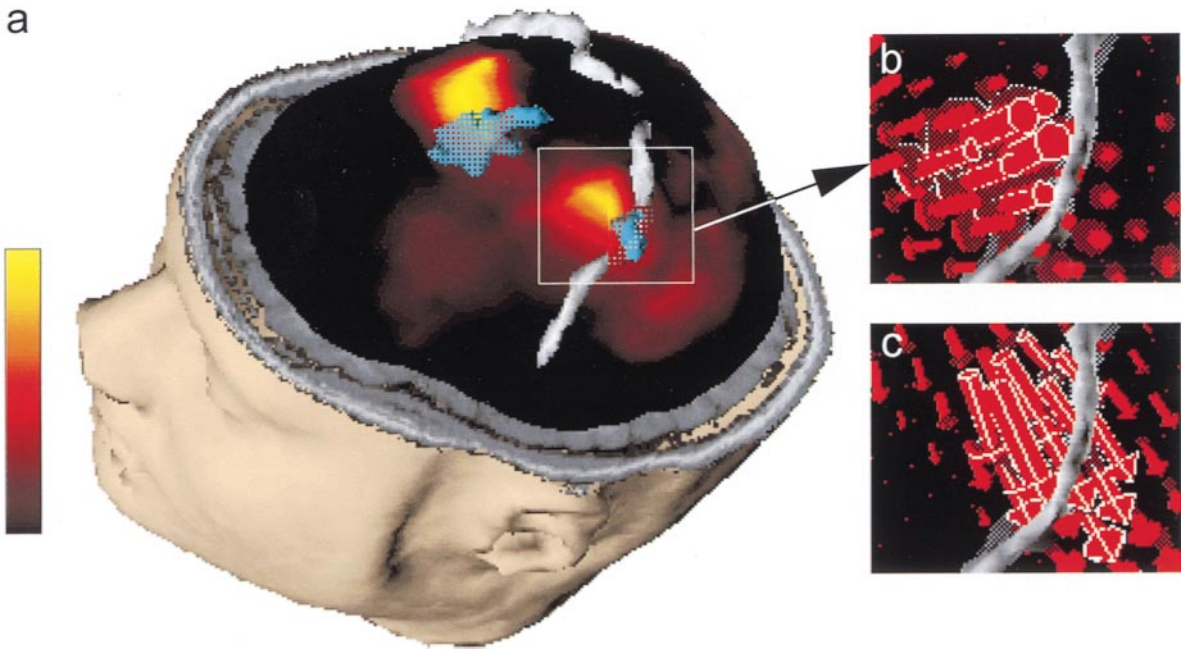


**FIG. 1.** Primary sensorimotor area activation. (a) A rendering of the segmented head of subject 3, view from left and above. The segmented left and right central sulci are shown in gray. Current density map (maximum in yellow, minimum in black, linear scale shown on the left) at EMG onset is shown embedded in the section of the segmented head. fMRI-activated volume is shown in turquoise. The lateral maximum of cortical current density corresponds to the fMRI activation of the hand area of the left primary sensorimotor cortex and the medial current density maximum corresponds to the fMRI activation of the frontal medial wall motor areas. (b) Magnification of the hand area of the left primary sensorimotor area as shown in (a). The individual current vectors of the CCD source are displayed, whereas in the current density map in (a) only the absolute values of the currents are visualized. In their sum they are equivalent to the current density source at EMG onset shown in (a). The currents point in an anterior direction, consistent with activation of MI in the anterior bank of the central sulcus (Kristeva-Feige *et al.,* 1994). (c) Current vectors in the same area as in (b) are shown 70 ms after EMG onset. The currents point in a posterior direction, consistent with activation of SI in the posterior bank of the central sulcus (Kristeva-Feige *et al.,* 1994).

mostly anterior to the vertical anterior commissure plane (VAC plane) and a posterior-type activation localized posterior to the VAC plane.

To describe the location and extend of the activation of the frontal medial wall motor area sources, we developed the following descriptive scheme (Fig. 2a): We defined subareas of the SMA and of the CMA in relation to anatomical landmarks, as was done in previous imaging studies. However, it must be stressed that this scheme is only descriptive. These subareas can not be straightforward equated to the *cytoarchitectonic* subdivisions of the SMA and CMA, because currently no probabilistic cytoarchitectonic map of the medial wall motor areas is available and although the VAC plane is considered to be a cross-landmark for the border between the anterior SMA and SMA proper, the true cytoarchitectonic border between these two subareas may be several centimeters away from the VAC plane (K. Zilles, personal communication).

The *anterior-type* medial wall activation was seen in four of the subjects (Fig. 2a). The anterior-most fMRI activation was found in the depth of the cingulate sulcus, 24 to 36 mm anterior to the VAC plane in the anterior CMA. From here, activation extended through the SMA to the edge of the medial wall ending 6–12 mm posterior to the VAC plane in the intermediate SMA. The total extent of activation typically involved approximately 40 mm of cortex. One subject showed additional activation in the paracingulate sulcus.

The time course of the anterior-type activation revealed by the CCD was characterized by:

- An onset of activity in the anterior CMA approximately 2500 ms before EMG onset.
- A shift of the CCD source location along the fMRI activation from the anterior CMA to the intermediate SMA (Fig. 2c). Activity appeared in the intermediate SMA approximately 2200 ms before EMG onset.
- A sharp drop of the intermediate SMA activity approximately 120 ms before EMG onset, followed by a local minimum around EMG onset and a strong post-movement maximum (Fig. 2d). A strictly reciprocal relation between the intermediate SMA and the contralateral MI activity was found during this period of time.

Figure 2e shows a Bereitschaftspotential recorded at Cz in a subject with anterior-type medial activa-

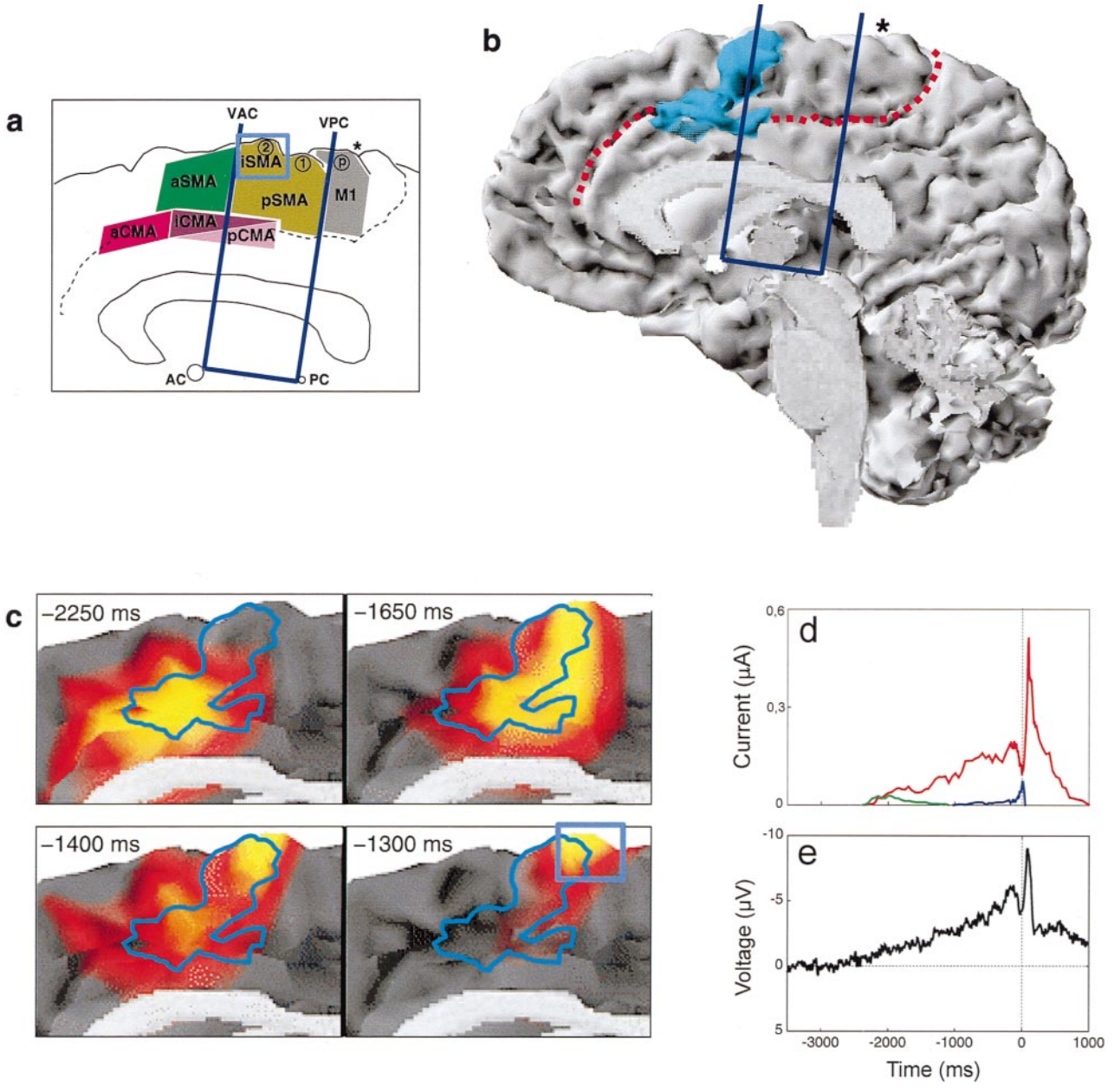


**FIG. 2.** Anterior-type medial wall activation. (a) Schematic illustration of the motor areas of the frontal medial wall, modified after Picard and Strick (1996) and Stephan *et al.* (1995). The ACPC (anterior commissure–posterior commissure) line, VAC (vertical AC) plane, and VPC (vertical PC) plane are marked in blue. The VAC plane is a gross anatomical landmark for the border between the anterior and the posterior SMA (Zilles *et al.,* 1996). The point where the central sulcus meets the edge of the medial wall is marked by an asterisk. The cingulate sulcus is marked with a red dotted line. Both the SMA and the CMA are subdivided into an anterior, an intermediate, and a posterior part. The anterior CMA (aCMA) corresponds to the anterior sector of the rostral cingulate zone of Picard and Strick, the intermediate CMA (iCMA) and the posterior CMA (pCMA) correspond to their posterior sector of the rostral cingulate zone and to their caudal cingulate zone. In the SMA, the anterior SMA (aSMA) was defined as the part of the SMA anterior to the VAC plane, and our intermediate and posterior SMA (iSMA, pSMA) are equivalent to the rostral and caudal posterior SMA of Stephan *et al.,* respectively. The precentral gyrus is marked with an encircled "p," and the first and second gyrus anterior to the precentral gyrus with an encircled "1" and "2," respectively. The area of the intermediate SMA corresponds to the dorsal medial aspect of the second gyrus anterior to the precentral gyrus. This area is marked with a blue box. (b) A median saggital section, showing the medial aspect of the right hemisphere for subject 1. fMRI activation (turquoise) of the CMA and of the SMA. For orientation the same anatomical landmarks as shown in (a) are displayed. (c) Sequential CCD maps corresponding to the fMRI activation shown in (a). The outline of the fMRI activation shown in (a) is marked by a turquoise line. Note the premovement shift of the location of the CCD source from the anterior CMA to the intermediate SMA. In the lower right panel the intermediate SMA is marked by a black box as in (b). (d) Waveforms of the time course of the CCD sources shown in (c): CMA (green); intermediate SMA (red). The time course of activation of the MI contralateral to the movement side of the same subject is shown in blue. Note the reciprocal relation between intermediate SMA and MI activity around EMG onset. (e) Bereitschaftspotential of the same subject recorded at Cz (common average reference). Note the positive deflection just before EMG onset (premotion positivity, PMP), which reflects the drop of source strength of the intermediate SMA shown in (d).

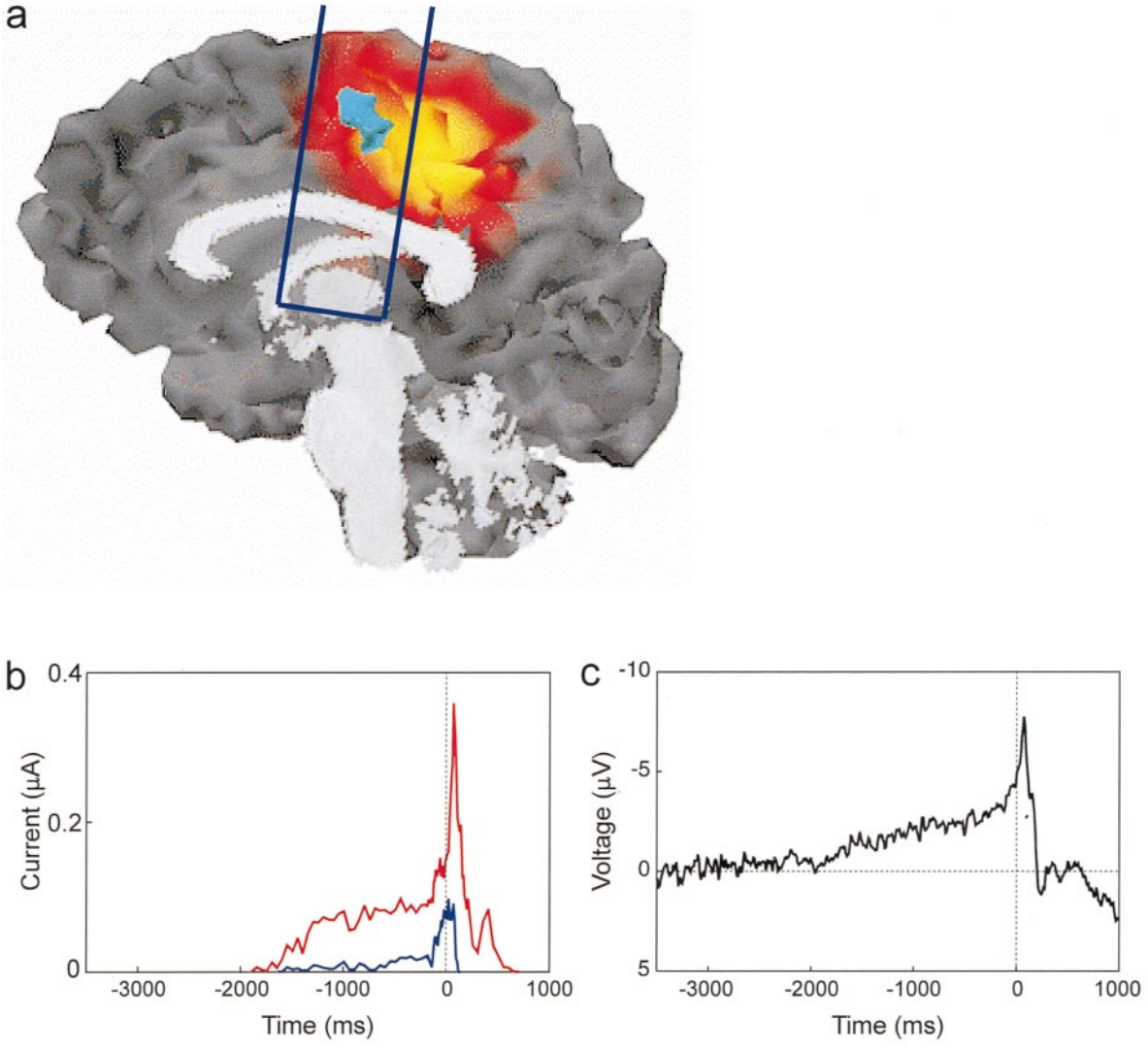


**FIG. 3.** Posterior-type medial wall activation. (a) fMRI activation (turquoise) of the posterior type of medial activation in a median saggital cut, showing the medial aspect of the right hemisphere of subject 5 and corresponding CCD source 1000 ms before EMG onset. All conventions as in Figs. 1 and 2. The fMRI source is located in the posterior SMA. (b) Waveforms of the CCD source (red) shown in (a) and of the MI source (blue) of the same subject. There is no reciprocal relation between the two sources, in contrast to the anterior-type medial activation. (c) Bereitschaftspotential of the same subject recorded at Cz (common average reference) without a premotion positivity in contrast to the BPs of subjects with anterior-type medial activation.

tion. The premovement drop of SMA activity corresponded to a transient positive deflection of the BP, known as premotion positivity (PMP) (Deecke *et al.,* 1969).

A *posterior type of medial activation* was seen in two of the subjects investigated. The fMRI-activated volume was located approximately 15 mm posterior to the VAC plane in the posterior SMA (Fig. 3a). It did not extend over more than 12 mm. In contrast to the anterior type of medial wall activation, the onset time of the posterior SMA source was shorter (approx. 1800 ms before EMG onset) and there was no premovement activity drop (Fig. 3b).

The two subjects with posterior-type medial wall activation had a BP without PMP as shown in Fig. 3c for one of the two subjects.

### *Inferior Parietal Lobe Activation*

Significant fMRI and CCD activation in the IPL were found in three of the six subjects. The activated fMRI volume was located in the left postcentral sulcus, presumably corresponding to Brodmann area 40 (Fig. 4a). The mean distance between the center of mass of the CCD and fMRI sources was 16.8 mm, ranging from 13.1 to 22.5 mm. This parietal activity was one of the main sources of the premovement potential shifts in

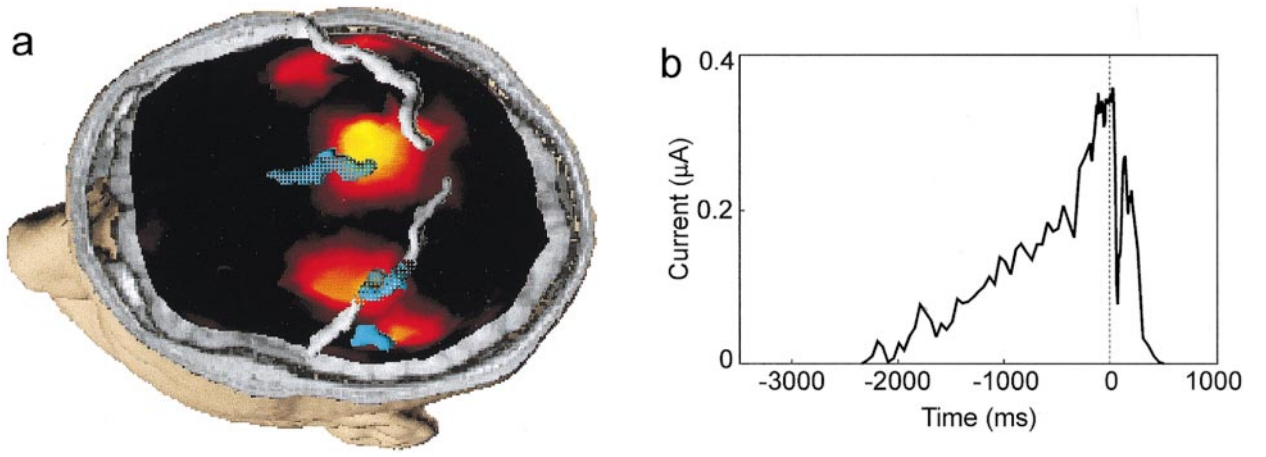


**FIG. 4.** Inferior parietal lobe (IPL) activation. (a) CCD map 100 ms before EMG onset and fMRI activation for S4. Both modalities show a medial source, a contralateral MI source, and a contralateral IPL source. In the CCD map ipsilateral MI and IPL sources can be seen as well. (b) Waveform of the contralateral IPL source shown in (a). Note the early onset of activity and the minimum of source strength occurring 70 ms after the EMG onset.

these subjects. In all three subjects a weaker CCD source was observed in the right IPL as well (Fig. 4a). IPL activation occurred independent of the type of medial wall activation (two of the subjects with an IPL source showed the anterior and one the posterior type). The currents of the IPL CCD source were mainly oriented in a radial direction.

The time course of the IPL source was characterized by an onset time longer than 2 s prior to and a minimum approximately 70 ms after EMG onset, followed by a marked increase of source strength (Fig. 4b). The postmovement minimum of IPL activity occurred during the peak of SI activity.

## DISCUSSION

The present study was designed to investigate the spatiotemporal activation patterns of the cortical motor areas during a simple voluntary movement. For this purpose, high-resolution EEG was analyzed with respect to its neuronal sources taking into account the individual brain morphology. The results were cross-validated using a method with high spatial resolution, fMRI. In this way we were able to describe the activation patterns of the cortical motor areas active before and during a simple self-paced finger flexion with high temporal and spatial detail. The mean distance between the CCD and fMRI sources for MI was 9.5 mm. This constitutes a marked improvement in comparison to the mean EEG–fMRI–coregistration error of 16.5 mm previously reported for MI (Gerloff *et al.,* 1996). The mean coregistration error for the SMA, CMA, and IPL was 12.0 mm.

The discrepancies of about 1–2 cm for "hot-spots" observed between fMRI and EEG techniques are not only due to inaccuracies of both techniques to localize function. We *a priori* do not expect to have the hot spots on one and the same place because the EEG reflects directly the electrical activity of a neuronal population and the BOLD-contrast fMRI at 1.5 T reflects the hemodynamic response in the pial veins related to it. In addition, inaccuracies from both methods must be taken into consideration. Most probably the inaccuracies coming from the EEG method are larger: In addition to deep sources, there are numerous other possible sources of such inaccuracies, for instance, errors in the determination of the electrode position and in the registration to the structural MRI, inaccuracies in the volume conductor model, and inaccuracies in the source reconstruction method itself. Considering all this the discrepancies of about 1–2 cm are not surprising.

### *Comparison with Previous Electrophysiological Studies*

*Primary sensorimotor area.* Concerning the primary sensorimotor area, the results of our study are in line with those of previous intracranial recording (Shibasaki and Ikeda, 1996; Rektor *et al.,* 1994), EEG (Urbano *et al.,* 1996; Praamstra *et al.,* 1996), and MEG studies (Kristeva-Feige *et al.,* 1994; Kristeva *et al.,* 1979, 1991; Lang *et al.,* 1991). The fast component of MI activation described here corresponds to the so-called "motor potential" identified in the EEG and to the "motor field" in MEG considered to reflect the final corticospinal outflow to the target muscle.

The transient flip of the current orientation from anterior to posterior at about 70 ms after EMG onset corresponds to the "movement-evoked potential one" and "movement-evoked field one" previously described in EEG and MEG studies, respectively (Kristeva-Feige

*et al.,* 1994; Kristeva *et al.,* 1991; Toro *et al.,* 1993), which is thought to mainly reflect feedback from the periphery (Kristeva-Feige *et al.,* 1996).

*Frontal medial wall and IPL.* Deecke and Kornhuber suggested already 1978 that besides MI "probably the supplementary motor cortex and perhaps the cingulate gyrus" (Deecke and Kornhuber, 1978) were generators of the scalp-recorded BP. However, when source reconstruction techniques became available to analyze high-resolution EEG with respect to its neuronal sources, some of the first studies failed to show frontal medial wall activation (Böcker *et al.,* 1994; Bötzel *et al.,* 1993). It was argued that the SMA, although active, did not contribute significantly to the scalp-recorded potentials. Although since then a growing number of studies have shown sources located near the medial wall motor areas (Knösche *et al.,* 1996; Mackinnon *et al.,* 1996; Praamstra *et al.,* 1996; Tarkka, 1994; Toro *et al.,* 1993; Urbano *et al.,* 1996), this question could not be settled completely. Our results show EEG sources in the medial wall motor areas in all six subjects investigated, and these results could be individually cross-validated using fMRI. These findings further confirm that the medial wall motor areas significantly contribute to the scalp-recorded EEG.

Of considerable interest is the sequence of premovement activity in the different motor areas. This is due to the assumption that if the cortical motor system is organized in a hierarchical fashion, the motor areas may become active in a sequential way before a self-paced movement, corresponding to their hierarchical level, with the higher-order motor areas preceding the executive motor areas. On the other hand, motor areas on the same hierarchical level can be expected to show premovement activity of similar latency.

Intracranial recordings during the BP paradigm have so far concentrated on MI and the posterior SMA (Rektor *et al.,* 1994; Shibasaki and Ikeda, 1996) showing activity with a similar latency in both areas, in agreement with the spatiotemporal activation pattern of MI and the posterior SMA as described in our study in the two subjects with posterior type of medial wall activation and consistent with the assumption that both areas have mainly executive functions on the same hierarchical level in motor control.

In our study, five of the subjects investigated showed activation of higher-order motor areas (anterior CMA, intermediate SMA, IPL) in addition to the executive motor areas (MI, posterior SMA). In all these subjects activity in the higher-order motor areas started earlier than in the executive motor areas. Further, in all subjects, the duration of premovement activity of the higher-order motor areas was longer than 2 s, and of the executive motor areas shorter than 2 s. This suggests that when a subject prepares to perform a self-paced finger movement, higher-order motor areas indeed become active before the executive motor areas.

The relation of the source strength of medial and lateral sources has also not become clear from previous EEG studies. Some of the authors think that the lateral sources are stronger than the medial sources (Toro *et al.,* 1993); others think that medial and lateral sources contribute in the same order of magnitude (Praamstra *et al.,* 1996). Several authors suggest that the medial sources contribute more to the scalp potentials than the lateral sources (Tarkka, 1994; Knösche *et al.,* 1996; Mackinnon *et al.,* 1996). In some of the subjects we examined, the medial sources were stronger than the lateral sources, while in others the medial source was weaker. These differences may be caused by the individual location and geometry of the active brain areas and at the same time may be the reason for the contradictory findings of other studies.

Concerning IPL activation, to our knowledge neither EEG or MEG nor intracranial recordings have described the time course of movement-related activation in this area so far.

### *The Premotion Positivity*

It is known since more than 20 years ago that the BP occurs in two variations, with and without a transient positive deflection preceding the movement, known as PMP (Deecke *et al.,* 1969). However, the exact generator site of the PMP, its functional significance, and reasons why it is seen in some subjects, while in others not, could not be established so far.

In our study four of the subjects investigated showed a drop of the source strength of the intermediate SMA just before the movement. The same four subjects also showed a PMP. The two remaining subjects lacked both a PMP and activation of the intermediate SMA. Therefore, our results suggest that the main generator of the PMP may be the intermediate SMA. This assumption is in line with recent results based on surface Laplacian estimates (Urbano *et al.,* 1996) suggesting that the frontomesial region is the main origin of the PMP. However, this kind of analysis could not precisely identify the generator site of the PMP.

The assumption that the generator site of the PMP is in the medial wall motor areas is consistent with the fact that the PMP is not seen in MEG (Kristeva-Feige *et al.,* 1994; Kristeva *et al.,* 1991), which is silent for these areas.

### *SMA and Movement Initiation*

Among the different functions discussed for the SMA (for a review see Passingham, 1996), several lines of evidence suggest that the SMA is important for the initiation of voluntary movement (Eccles, 1982; Goldberg, 1985): electrical stimulation of the SMA can elicit

an urge to perform a movement (Fried, 1996), a lesion in SMA leads to akinesia, and Parkinson's disease is associated with impaired activation of the SMA (Passingham, 1996).

Before the advent of source-reconstruction techniques, Deecke *et al.* (1973) proposed on the basis of BP studies that the PMP reflected processes related to movement initiation, but were at the time unable to assign the PMP to a specific anatomic structure.

Here we show that the main generator site of the PMP is the SMA, specifically its intermediate part, and that the drop of source strength reflected in the PMP is strictly reciprocal to the increase of MI activity. Direct electrical stimulation of the frontal medial wall motor areas, especially of its anterior parts, can inhibit ongoing voluntary motor activity or prevent a movement to be executed ("supplementary negative motor area") (Ikeda *et al.,* 1993). Thus we suggest that the premovement activation in the anterior-type medial wall activation described in this study may be essentially inhibitory and that the premovement drop of the strength of anterior medial wall activation represents a release of inhibition leading to the reciprocal increase of MI activity and the start of the movement.

Such an essentially inhibitory/disinhibitory function of the intermediate SMA would offer an explanation for the preferential activation of this area by imagining movements, because this specific task requires the inhibition of overt movement.

This hypothesis is consistent with results from time-resolved fMRI and from single neuron experiments in monkeys. Richter *et al.* (1997) used time-resolved fMRI with a temporal resolution of 200 ms per image in a delayed cued finger movement task and found SMA regions more active during preparation than during execution of a movement sequence in three of nine subjects. Unfortunately, the exact location of these regions within the SMA was not discussed although evident from the figures.

In the monkey, a homologue to the human intermediate SMA is not known so far. However, Rizzolatti *et al.* (1990) described neurons in the pre-SMA, located in the anterior region of the monkey SMA, which were active during the preparation of reaching–grasping movements and became inactive during movement execution. They have speculated that this finding reflected a disinhibitory mechanism involved in movement initiation.

A remaining question is how movements were initiated by the two subjects with activation restricted to the posterior SMA. Results from previous studies and from our study show that the posterior SMA activation is parallel to the MI activation. Both areas are reciprocally connected by corticocortical projections. The posterior SMA is part of the corticostriatothalamocortical loop, and associative and limbic cortex has access to this loop via the striatum. It has been proposed that the premovement SMA activity is build up through reverberations in this loop (Romo and Schultz, 1992). However, this remains speculative, and it is not clear in which way the actual movement could be finally initiated according to this concept.

At the present stage of investigation it is not clear what could be the functional differences between the anterior and the posterior type of activation and why the subjects showed these different types of activation, although performing the same motor task. For this purpose it would be necessary to compare different motor tasks to determine whether a specific movement parameter is responsible for the anterior and the posterior type of medial wall activation. Furthermore, one should take into consideration that, as mentioned above, the defined subareas of the SMA cannot be straightforwardly equated to the cytoarchitectonic subdivisions of the SMA, because currently no probabilistic cytoarchitectonic map of the medial wall motor areas is available (K. Zilles, personal communication). Therefore, the different patterns of activation of SMA do not allow a global conclusion of the SMA role in the motor task studied.

### *CMA, IPL, and Initial Motor Preparation*

It is a longstanding question which area of the brain is activated first before a movement executed at a freely chosen point in time. Until now, the discussion on this matter focused on the relation between MI and the SMA. Here we show that across subjects the first detectable activity before the movement occurs in the anterior CMA and in the IPL.

The finding that the anterior CMA is involved in initial motor preparation is consistent with results from single-unit recordings from area 24c (Shima *et al.,* 1991), the presumed monkey homologue to the human anterior CMA. In this area numerous neurons active long before a simple self-paced key-press task were found. It was concluded that the anterior cingulate was closely related to self-paced movements.

Concerning the function of the CMA, in a PET study the effect of the so-called "attention to action" (Posner *et al.,* 1988) was evaluated. Two experimental conditions were compared for this purpose: an automatized movement sequence and a movement sequence, where subjects were instructed to think about the next movement in the sequence (Jueptner *et al.,* 1997). The CMA showed stronger activation related to the attention task. It has also been demonstrated that attention modulates the scalp-recorded premovement potentials, with larger potentials at midline electrodes in spontaneous voluntary movements compared to unconscious movements (Keller and Heckhausen, 1990).

In contrast to the assumption that the CMA is involved in information processing related to attention

to action as a form of "motor awareness," the IPL is generally assumed to be involved in "sensory awareness." This assumption is based on the fact that neglect, which constitutes an attentional rather than a sensory deficit, is most commonly found after lesions of the IPL (Driver and Mattingley, 1998). A recent study demonstrated also a motor deficit in IPL-lesioned patients (Mattingley *et al.,* 1998). These patients showed an "intentional" deficit in initiating movements toward visual targets on the contralesional side in addition to their perceptual impairment. Single neuron recordings in monkeys also suggest that the parietal association cortex is related to specific motor intention (Snyder *et al.,* 1997).

An association between attention, or awareness, and initial motor preparation has been proposed in another context as well: Crick and Koch (1995) have conjectured that visual awareness has its place in the synergism of higher-order visual and motor processes, providing visual information to the motor system. They proposed that visual awareness should be closely linked to initial motor planning. As a substrate for this motor planning they suggested the prefrontal and the premotor cortex. Driver and Mattingley (1998) discussed their findings on a motor deficit after IPL lesion in the context of the proposal of Crick and Koch, pointing out that the IPL meets the criteria of being involved in higher-order sensory and motor processes as well as in attentional processes. Here we have shown that the IPL indeed is active during initial motor planning, together with the CMA, even in a paradigm requiring no visual processing to achieve the motor task. However, our results do not allow us to make a global conclusion about the role of IPL in the motor task studied because the IPL was active only in three of the six subjects investigated.

### *How Individualized Are Movement-Related Cortical Responses?*

Based on the clear intraindividual correlation of the fMRI and CCD activation maps, the constellation of active areas could be reliably evaluated for each subject. This revealed that besides the primary sensorimotor cortex, which was active in all subjects, the subjects showed activation of different sets of secondary motor areas. Remarkable interindividual variability of movement-related brain activation has recently been reported also by others (Schlaug *et al.,* 1994; Stephan *et al.,* 1995; Richter *et al.,* 1997; Cui *et al.,* 1999). This intersubject variability may be interpreted as resulting from different strategies used by the subjects to perform the motor task.

One aspect of intersubject variability in our study concerned the frontal medial wall motor areas, which showed either an anterior or a posterior type of activation. We have linked these variations to the variations of the BP which occurs either with or without a PMP, as known since more than 20 years ago. It is an interesting question whether subjects which showed one type of medial wall activation could possibly perform the same motor task through the other type of activation as well, for instance, by subtle changes of movement parameters or by paying more or less attention to their motor performance.

Based on the observation that multiple motor areas are involved in different types of motor tasks, Larsson *et al.* (1996) put forward the view that most or all motor areas were active during most movements and that different functional demands only led to changes in the relative contribution of these areas and of their internal processing. In contrast to this view, accumulating evidence for a general intersubject variability of the task-specific recruitment of motor areas indicates that the cortical motor system is not generally activated in a global way, but that even during one motor task, in different individuals different subsets of cortical motor areas team up to perform the task, while others remain silent.

The temporal activation patterns of the CMA, intermediate SMA, and the IPL were found to be different from the well-known temporal activation pattern of MI and the posterior SMA: they showed a longer duration of premovement activity, and they did not show a peak of activity during movement execution. These temporal activation patterns were reproducible for the single motor areas and showed distinctive features, resulting in a unique spatiotemporal activation pattern for each of these areas. It can be speculated that these consistently observed activation patterns may be the signatures of the specific functions of the motor areas.

## ACKNOWLEDGMENTS

The authors thank J. Dietterle for experimental help and Dr. A. Stancak and Professor M. Greenlee for comments on the final version of the manuscript. The authors are indebted to Dr. M. Fuchs for constructive suggestions and help. This study was supported by DFG Grant KR 1392/7-1.

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