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RESEARCH ARTICLE

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Functional mapping of human medial frontal motor areas

The combined use of functional magnetic resonance imaging and cortical stimulation

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Abstract Two functional brain-mapping techniques, functional magnetic resonance imaging (fMRI) and cortical stimulation by chronically implanted subdural electrodes, were used in combination for presurgical evaluation of three patients with intractable, partial motor seizures. Brain mapping was focused on characterizing motor-related areas in the medial frontal cortex, where all patients had organic lesions. Behavioral tasks for fMRI involved simple finger and foot movements in all patients and mental calculations in one of them. These tasks allowed us to discriminate several medial frontal motor areas: the presupplementary motor areas (pre-SMA), the somatotopically organized SMA proper, and the foot representation of the primary motor cortex. All patients subsequently underwent cortical stimulation through subdural electrodes placed onto the medial hemispheric wall. In each patient, the cortical stimulation map was mostly consistent with that patient's brain map by fMRI. By integrating different lines of information, the combined fMRI and cortical stimulation map will contribute not only to safe and effective surgery but also to further understanding of human functional neuroanatomy.

Keywords Epilepsy · Brain mapping · Supplementary motor areas · Somatotopy · Mental calculations · Human

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Introduction

Cortical stimulation and epicortical recordings by means of subdural electrodes are the established techniques with which to evaluate surgical candidates with intractable, extratemporal lobe epilepsy (Lüders et al. 1987). To plan effective and safe surgery, chronically implanted subdural electrodes are utilized not only for identifying epileptogenic areas but also for mapping adjacent functional areas. This subdural cortical mapping provides invaluable information to further the understanding of human functional neuroanatomy. On the other hand, subdural cortical stimulation only gives fragmented pieces of the functional brain map, limited by the number and interelectrode distance of implanted electrodes. Hence, because of anatomic alterations due to underlying pathology, cortical stimulation with limited electrode coverage may not detect functionally critical brain areas. Another potential problem is difficulty in the precise coregistration of electrode locations onto the brain.

Functional magnetic resonance imaging (fMRI) visualizes task-related changes in MR signals based on blood oxygen level-dependent (BOLD) contrasts (Kwong et al. 1992; Ogawa et al. 1992). This relatively new, noninvasive tool for human brain mapping allows us to examine an individual's brain using fine anatomic localization. Because of such properties, fMRI is expected to fill in the gaps on the brain maps that have relied solely on subdural electrodes.

In the present study, we tested the feasibility of the combined functional brain maps made by integrating information from fMRI and cortical stimulation. For this purpose, we carried out fMRI on three patients who subsequently underwent cortical stimulation of the medial wall of the hemisphere. This patient selection was in part because it is relatively easy to coregister subdural electrodes on the medial hemispheric wall onto a sagittal slice of an anatomical MRI. Moreover, there are several distinct motor-related areas on the medial hemispheric wall, which can be explored well by cortical simulation. Supplementary motor areas (SMAs), previously regarded as a single motor area occupying the medial part of Brodmann's area 6, are now divided into two subregions: the anterior part, the pre-SMA, and the posterior part, the SMA proper (Picard and Strick 1996). In humans, the vertical anterior commissure (VAC) line, based on the stereotaxic coordinate system of Talairach and Tournoux (1988), serves as an anatomic landmark to discriminate between the pre-SMA and the SMA proper. The SMA proper, located just anterior to the foot representation of the primary motor cortex (M1), has somatotopically organized movement representations, as shown in nonhuman primates (He et al. 1995; Luppino et al. 1991; Matsuzaka et al. 1992; Mitz et al. 1991) and humans (Fried et al. 1991; Yazawa et al. 2000). The SMA proper, tightly interconnecting with the M1 and the spinal cord (Luppino et al. 1993), probably plays an important role in motor preparation and execution. In contrast, the pre-SMA has no clear somatotopy. The pre-SMA has substantial projections to neither the M1 nor the spinal cord, but instead interconnects with the prefrontal cortex and other premotor areas. Not only the anatomic connections but also physiological evidence indicates that the pre-SMA functions in response selection and/or preparation rather than motor execution itself (Matsuzaka et al. 1992). Interestingly functional subareas exist in the posterior part of the pre-SMA, termed the supplementary negative motor areas (SNMAs), where 50-Hz cortical stimulation interferes with ongoing movements of various body parts (Lüders et al. 1987). Listed also as the medial frontal motor areas, cingulate motor areas are represented in the depths of the cingulate sulcus (Picard and Strick 1996).

The present study has appeared as an abstract (Hanakawa et al. 2000a), and electrophysiological findings on the present patients have been reported previously elsewhere, for entirely different purposes (Ikeda et al. 1999a, 1999b, 2000; Yazawa et al. 1998, 2000).

Materials and methods

Subjects

Subjects were three patients with medically intractable, partial motor seizures categorized into SMA seizures on the basis of ictal symptomatology (Morris et al. 1988), associated with organic lesions involving the medial frontal lobe. All patients underwent presurgical evaluation by means of chronically implanted subdural electrodes and subsequent surgery between 1996 and 1998 at Kyoto University Hospital. Patient profiles are shown in Table 1. Before the implantation of subdural electrodes, fMRI studies were carried out at Fukui Medical University for patients 1 and 2 and at Kyoto University Hospital for patient 3. All subjects gave written informed consent according to the study protocol approved by the institutional ethics committee.

Functional MRI

As for fMRI tasks, simple upper and lower limb movements were examined in all subjects. For the upper limb movement task, all subjects sequentially touched the thumb against the tip of the other fingers on each side. The tapping sequence, from the index finger to the little finger, was repeatedly executed during task periods. For the lower limb movement task, patients 2 and 3 performed alternating extension and flexion of all toes on each side. Patient 1 alternated foot extension and flexion at the ankle joint, because she was not able to move the toes only. Movements were auditory-

Table 1 Profiles, lesions, and the outcome of surgery in each patient

Patient	Age (years)	Sex	Onset (years)	Lesions		Outcome	
				Location	Pathology	Deficits	Seizure[a]
1	23	F	7	Rt medial frontal and cingulate gyri	Gliosis	None	Class IIa
2	52	M	47	Rt superior and middle frontal gyri	Astrocytoma (grade II)	None	Class Ia
3	31	F	4	Lt superi or frontal gyrus	Cortical dysplasia	None	Class IId

[a] Seizure control after surgery as classified by Engel and colleagues (1993)

paced at a rate of ~1.7 Hz for patient 1, by utilizing the regular sounds resulting from functional image acquisition as a pacer. Patients 2 and 3 did the tasks at their own pace, since the sounds were no longer adequate as a pacer due to different imaging parameters. Motivated by the several reports on dyscalculia associated with medial frontal lobe lesions (Lucchelli and De Renzi 1993; Tohgi et al. 1995), patient 3 also worked on a mental calculation task in which the subject added a series of 15 single numbers. The numbers were presented in the center of view at a rate of 0.5 Hz. The subject viewed the numbers back-projected onto a screen, through a mirror built into a head coil. After each task period, two numbers, one of which might be the correct answer, were displayed side by side for 2 s. When the subject found the correct sum, she was instructed to briefly move the right or left hand, corresponding to the side of the correct answer. When the subject found no correct answer, she was instructed to move both hands simultaneously. Hence, a probability of responding appropriately by chance was 33%. Before entering the scanner room, the patients were informed about the experimental procedure and allowed to practice the tasks fully.

Functional MRI studies were conducted on a whole-body 1.5-T Horizon MR scanner (General Electric, Milwaukee, Wis., USA) with a standard head coil. BOLD-sensitive, single-shot, blipped, gradient-echo, echo-planar images were acquired using the following parameters: effective repetition time (TR) 3 s, echo time (TE) 40 ms, flip angle 90°, 64×64 matrix, 3.75×3.75×6 mm voxel for patients 1 and 2; effective TR 6 s, TE 43 ms, flip angle 90°, 64×64 matrix, 3.44×3.44×3.5 mm voxel for patient 3. Thirty-eight contiguous axial slices covered the whole brain for patient 3, while 5 and 11 axial slices covered, at least, the medial frontal gyrus and the paracentral lobule for patients 1 and 2, respectively. The subjects lay on the scanner bed with their arms placed beside the trunk and their eyes open. Foam pads and elastic tape were used to minimize head motion. In each scanning session, task periods were alternated in blocks (30 s) with baseline periods, during which the subjects had nothing to do. For the mental calculation task, baseline periods involved a visual fixation task in which the subject fixated on a cross presented in the center of view at a rate of 0.5 Hz. The task periods were repeated five times per scanning session (300 s) for patient 1, twice per session (120 s) for patient 2, and four times per session (240 s) for patient 3. For each session, 100 functional images were obtained for patient 1, and 40 images for patients 2 and 3. Patient 1 underwent two sessions each for the foot movements on each side and a single session for the finger movements on each side. Patient 2 performed three sessions for the limb movements on the left and two sessions on the right. Patient 3 did two sessions each for the finger movements on each side, toe movements on the right, and mental calculations. In all patients, their motor performance was visually inspected by one of the authors (T.H. or T.N.). The difference in the scanning procedure between patients, especially the coverage of the brain, resulted from the technical limitations at the time of each study. For the anatomic coregistration, spin-echo, T1-weighted structural images (0.94×0.94×6 mm voxel) were obtained from the same space as the functional images, in addition to the whole-brain three-dimensional fast spoiled gradient-recalled at steady-state images (0.86×0.86×1.5 mm voxel).

MRI images were transferred to ULTRA2 workstations (Sun Microsystems, Mountain View, Calif., USA). The functional data were analyzed with statistical parametric mapping (SPM96; http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (Mathworks; Natick, Mass., USA). The initial three scans for patients 1 and 2 and the two scans for patient 3 (i.e., initial ~10 s of acquisition) were discarded from the analysis to allow for T1 equilibrium effects. Head motion during the scans was estimated with regard to the first functional image, by using a least-squares method. This resulted in discarding the whole data set of the lower limb movements from patient 1 owing to excessive head motion. The head motion of the other data sets was estimated to be less than 0.6 mm within each session, and then those images were resliced, using an autoregression moving-average method (Friston et al. 1995a). The realigned functional images were coregistered onto the individual's structural MRI and were smoothed with a Gaussian filter of 7-mm full width at half maximum (FWHM). A global difference in MR signals across the images was adjusted by proportional scaling. Boxcar waveforms modeling experimental conditions were convolved with a hemodynamic response function and served as a reference for cross-correlation analysis (Friston et al. 1995b). Low-frequency drifts in MR signals were removed by linear detrending, and temporal smoothing was accomplished by convolving the data with a 4-s FWHM Gaussian kernel. Appropriate linear contrasts to the parameter estimates were tested, producing a statistical parametric map of t-statistics (SPM$\{t\}$). The SPM$\{t\}$ was transformed into a Z-value map, the threshold of which was a Z-value of 3.09 ($P<0.001$ at each voxel level), and further characterized in terms of the number of activated voxels forming each cluster ($P<0.05$, corrected for multiple comparisons).

Combined map by cortical stimulation and fMRI

To identify epileptogenic areas and adjacent functional areas, subdural strips with platinum electrodes (Ad-Tech Medical Instrument, Racine, Wis., USA) were chronically implanted in all patients. Each electrode covered 2.3 mm of the cortex, and the center-to-center distance of each electrode was 1 cm. In patient 1, six subdural strips, each containing 1×4 electrodes (i.e., electrode array of one row, four columns) were implanted, four on the medial surface of the right hemisphere and two on the right lateral hemispheric convexity. In patient 2, three subdural strips were implanted, including the one consisting of 2×7 electrodes on the right medial hemispheric surface. In patient 3, one subdural strip with 2×8 electrodes was implanted on the left medial hemispheric surface, in addition to the one with 4×5 electrodes on the left lateral convexity. Methods for cortical stimulation have been described previously (Ikeda et al. 1999a, 1999b, 2000; Yazawa et al. 1998, 2000). Briefly, a ~5-s train of repetitive square pulses (duration, 0.3 ms) of alternating polarity (frequency, 50 Hz) was delivered with a gradual increase in intensity until either reaching the predetermined maximum current (15 mA) or inducing afterdischarges in electroencephalography. The SMA proper was identified by its typical response to the electrical stimuli, consisting of somatotopically organized, predominantly tonic motor responses, either unilaterally or bilaterally. A negative motor response was defined as a cessation of voluntary tonic muscle contractions or rapid alternating movements without a loss of awareness during cortical stimulation. When areas on the medial hemispheric wall showed a negative motor response, they were termed the SNMA and regarded as part of the pre-SMA. To identify the locations of implanted electrodes, a lateral view of the skull X-ray taken after the implantation of electrodes was superimposed onto a nearly midline sagittal view of the T1-weighted structural MRI, by referencing common landmarks (i.e., nasion and inion; Ikeda et al. 1999a, 1999b, 2000; Yazawa et al. 1998, 2000). To obtain more precise coregistration between the two modalities, the T1-weighted structural MRI acquired during the implantation of subdural electrodes was directly used to determine the electrode locations for patient 3. The image coregistration program provided by SPM96 accomplished this. For patients 1 and 2, however, anatomical MRI images with subdural electrodes were not available. The conventional X-ray overlay method works well to coregister the electrodes on the medial hemispheric wall to the sagittal MRI (Lim et al. 1994). We actually compared the two methods for the coregistration of electrodes, using the data set from patient 3. In this particular patient, the maximum discrepancy of the electrode positions determined by the two methods was approximately 1 cm. In all patients, according to the Talairach and Tournoux's atlas (1988), the anterior commissure-posterior commissure line and VAC lines were drawn on a midline sagittal MRI slice as a reference. For this purpose, we also referred to anatomically normalized MRI, which was transformed by using the spatial normalization program implemented in SPM96. Further, we cautiously selected the most appropriate sagittal slice on which subdural electrodes were overlaid. Because

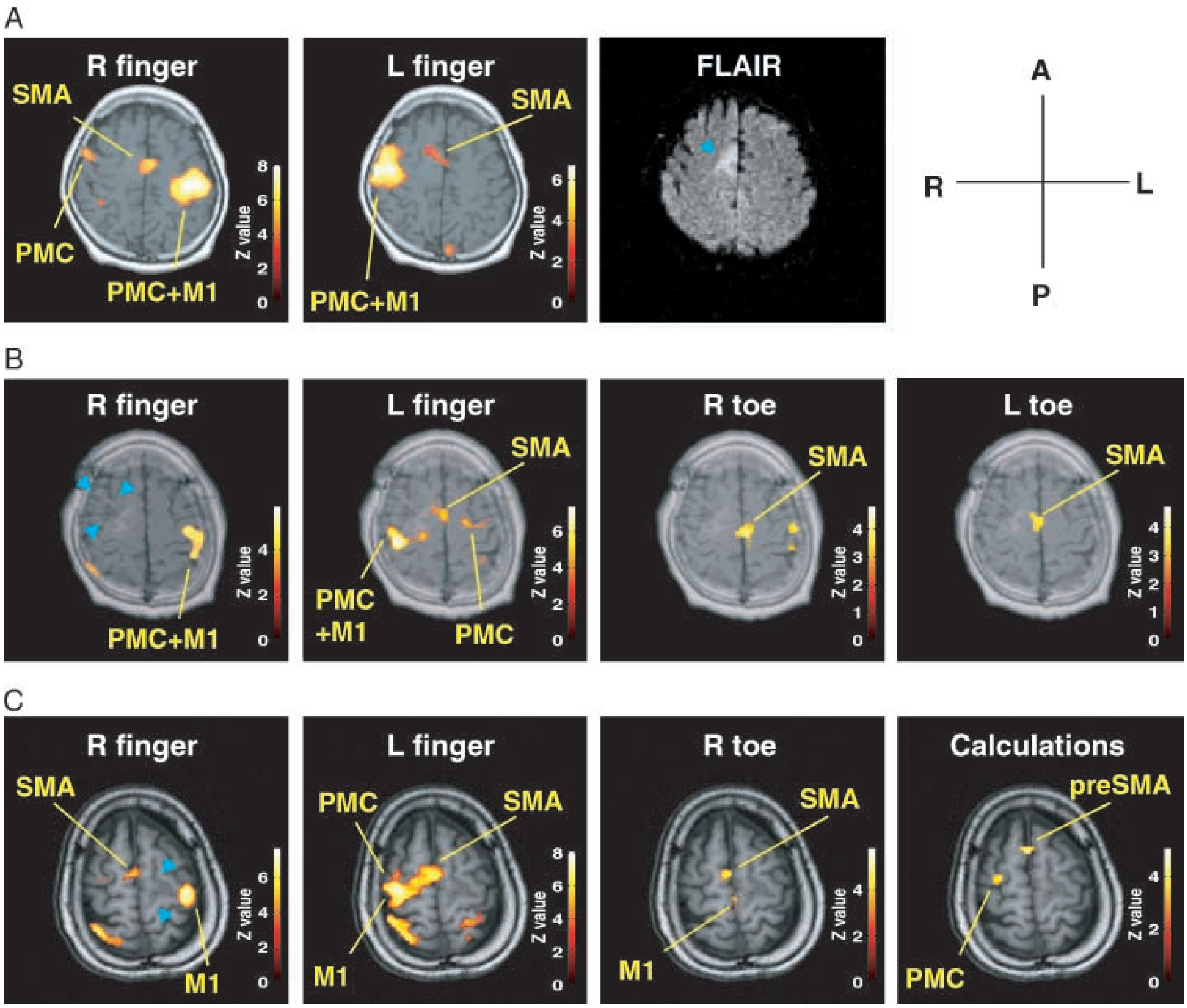

Fig. 1A–C Functional MRI activation in patient 1 (**A**), patient 2 (**B**), and patient (**C**), overlaid onto an axial slice of each individual's own structural MRI. *Blue arrowheads* indicate the site of lesions. Simple limb movement tasks activated the supplementary motor area (*SMA*) proper, in addition to the primary motor area (*M1*) and the lateral premotor cortex (*PMC*). Mental calculations induced the pre-SMA activation in patient 3 (**C**). (*R* Right, *L* left, *A* anterior, *P* posterior, *FLAIR* fluid-attenuated inversion recovery image)

of these, the reference lines as well as the sagittal slices slightly differed from those in our previous reports (Ikeda et al. 1999a, 1999b; Yazawa et al. 1998, 2000). Nevertheless, anatomic nomenclature (e.g. pre-SMA) assigned to each electrode is essentially the same as our previous one.

Results

Behavioral data

Patient 1 was able to keep the externally triggered pace (1.7 Hz for the finger movements and 0.8 Hz for the foot movements) and made no tapping errors at all. The self-paced limb movements of patient 2 resulted in a mean movement rate of 1.2 Hz, 1.4 Hz, 0.8 Hz, and 0.9 Hz for the right fingers, left fingers, right toes, and left toes, respectively. This patient made tapping errors (erroneous double tapping of the same finger) similarly on both sides (5.6% on the right and 4% on the left). The self-paced movements of patient 3 yielded a mean movement rate of 1.3 Hz, 1.5 Hz, and 0.4 Hz for the right fingers, left fingers, and right toes, respectively. Patient 3 made tapping errors (error type not recorded) more frequently on the contralateral side to the lesion (right, 5.3%) rather than on the ipsilateral side (left, 0.05%). In the mental calculation task, patient 3 gave inaccurate responses on all eight occasions, although the patient claimed that she was engaged in mental calculations throughout every task period. This decrease in task performance approached significance (Mann-Whitney's *U*-test, P=0.059) when compared with the mean accuracy of 86% in healthy subjects (26 subjects; mean age 27.3 years) who underwent the same calculation task in our other fMRI study.

Activated area in fMRI

In the finger movement task, all subjects showed contralateral M1 activation in the central sulcus, extending anteriorly into the lateral premotor cortex. Except for the right finger movements of patient 2, the simple limb-movement task consistently activated medial area 6 (Fig. 1). In patient 1, when the activation of medial area 6 on the lesion side (right side) was compared with the one on the intact side, the right-sided activation seemed weaker and shifted anteriorly by the lesion (Fig. 1A). In both patient 2 and patient 3, the medial area 6 activation on the lesion side was situated just medial to the pathologic lesion. As for the lower limb movements of patient 2, the activation of medial area 6 by the left toe movements was situated posterior to the one by the left finger movements, but the two activated areas partly overlapped in the intermediate zone. In this subject, the activation probably corresponding to the foot M1 was separately found in the right central sulcus, approximately 5 mm lateral to the midline (data not shown). In patient 3, the toe movement task activated the medial part of the paracentral lobule that probably included both M1 and SMA proper. Judging from the fMRI results only, these medial area 6 activations associated with the simple limb movement task most probably represented the SMA proper.

The mental calculation task activated two foci in medial area 6: the posterior locus overlapping the medial area 6 activation by the finger movement task (i.e., SMA proper), and the anterior one presumably corresponding to the pre-SMA (see Fig. 1C). Other mental calculation-induced activation involved the right lateral premotor cortex, Broca's area, left superior temporal cortex, bilateral posterior parietal cortex, and left cerebellum.

Combined functional brain maps by cortical stimulation and fMRI

In patient 1, the stimulation of electrode A3 stopped ongoing movements of the left hand (negative motor response), and the stimulation of electrode A2 elicited abduction of the left arm (Fig. 2A). Electrode A3, anterior to the VAC line, was judged to be on the pre-SMA, and electrode A2 was on or close to the left upper limb representation of the SMA proper (Ikeda et al. 1999b; Yazawa et al. 2000). The fMRI activation associated with the left finger movement encompassed electrode A2 and, marginally, electrode A3, both related to motor responses from the left upper limb.

In patient 2, electrodes 3 and 4 were considered on the SMA proper because of positive motor responses. Electrode 3, which elicited both upper and lower limb movements, was actually situated within the probable SMA region activated by both finger and toe movements, as observed by fMRI (Fig. 2B). This implied that this electrode was on the intermediate zone between the upper limb and lower limb representations of the SMA proper. The stimulation of electrode 1, situated anterior to the VAC line, caused a cessation of ongoing movements of the bilateral upper and lower limbs, eyes, and tongue. Hence, this electrode was judged to be on the pre-SMA (Ikeda et al. 1999b; Yazawa et al. 2000).

In patient 3, by stimulating electrode 4, tonic contraction of the left lower trunk muscles was elicited

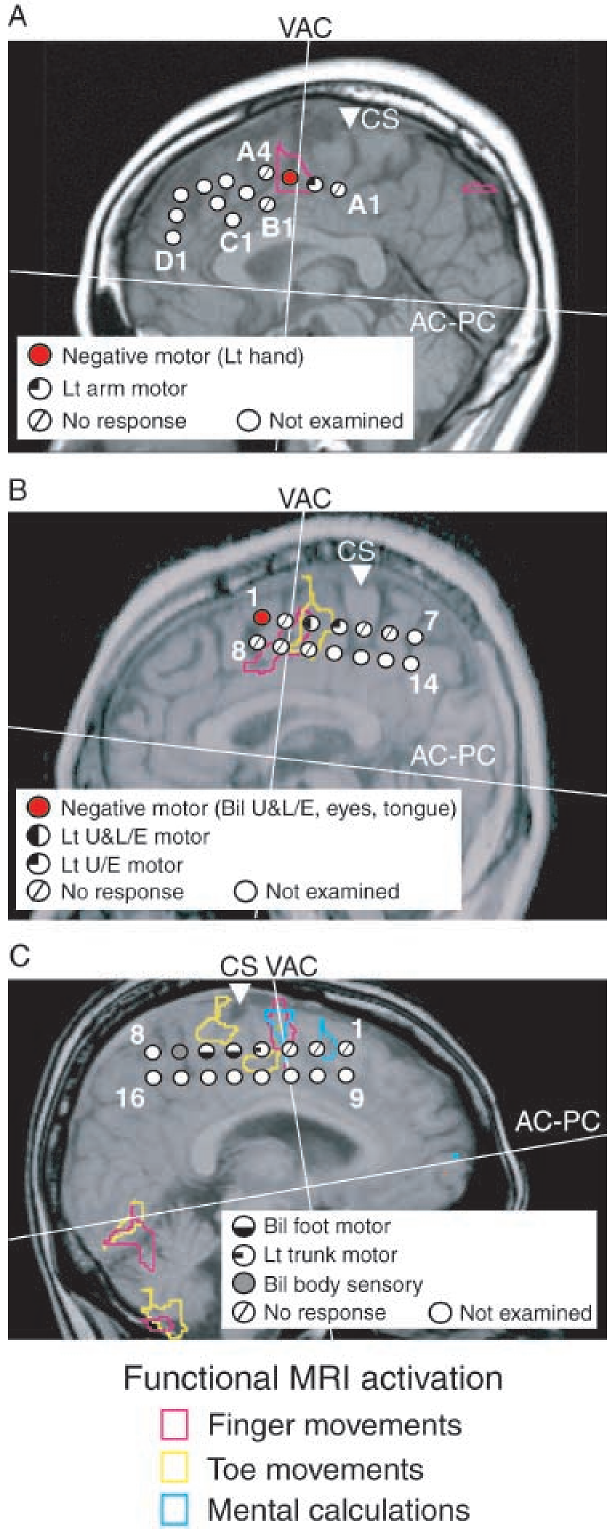

Fig. 2A–C The combined functional brain maps for patient 1 (**A**), patient 2 (**B**), and patient 3 (**C**), overlaid onto a midline sagittal slice of the structural MRI. The activated area of the functional MRI is shown in task-specific colors: finger-tapping task (*magenta*), toe movement task (*yellow*), mental calculation task (*cyan*). *Icons* indicate the cortical stimulation mapping, which are mostly consistent with the functional MRI mapping. In patient 1, the most superior electrodes of each *B-D* subdural strip are not shown for simplicity. (*VAC* the line vertical to the anterior commissure-posterior commissure line (*AC-PC*) through the AC, *CS* central sulcus, *Rt* right, *Lt* left, *Bil* bilateral, *U/E* upper extremity, *L/E* lower extremity)

(Fig. 2C), and thus this electrode was judged to be on the SMA proper. The stimulation of electrodes 5 and 6 induced tonic abduction of the bilateral feet, more marked on the left (Ikeda et al. 2000). In fMRI, the right toe movements activated the area situated just superior to electrodes 5 and 6, showing a good correspondence of the two methods. Another area activated by the toe movements extended into the depths of the cingulate sulcus, probably corresponding to one of the cingulate motor areas. In the mental calculations, out of the two activated foci in the medial frontal lobe, the anterior one partially overlapped electrode 1, presumably located on the pre-SMA.

Discussion

In the present study, the functional brain maps obtained by fMRI generally agreed with the more conventional brain maps obtained by cortical stimulation, albeit in the limited number of patients. For the best example, the fMRI of patient 2 disclosed the intermediate zone where the finger and toe movements yielded the overlap activation in medial area 6. By stimulating the electrode lying on this intermediate zone, both upper and lower limb movements were actually elicited. The present results agree with attempts to compare fMRI with cortical stimulation on the M1 during surgery (Jack et al. 1994; Yousry et al. 1995).

Under physiological conditions, there is a functional coupling of neural activity with metabolic demands and regional cerebral blood flow; for instance, regional blood flow increases shortly after direct cortical stimulation (Jueptner and Weiller 1995). Because positive BOLD signals measured by fMRI properly follow cerebral blood flow changes with a minimal delay (Yang et al. 2000), the two functional maps, obtained by fMRI and cortical stimulation, ideally correspond well to each other. However, we have to admit the technical and interpretational limitations of the present combination map. The most significant factor would be the coregistration of subdural electrodes onto anatomical MRI. Another technical limitation includes effects of large draining veins, which may affect the precise localization of fMRI activation (Ogawa et al. 1998). Furthermore, the interpretational limitations primarily result from the pathologic conditions of the patients. In patient 1, the fMRI activation corresponding to the left finger representation of the SMA included the electrodes judged to be on the pre-SMA (SNMA for the left hand) and, marginally, the SMA proper (left arm). This possibly reflects either functional reorganization or miscoregistration, or both, taking into account that the simple, sequential finger-to-thumb tapping task normally activates the SMA proper but not the pre-SMA (Tyszka et al. 1994). The functional reorganization here means that, in patients who have suffered from epilepsy since early in life, their functional neuroanatomy may be aberrantly organized. Another concern related to the pathologic conditions is that vascular responses adjacent to the lesions might not be normal, which possibly affected the fMRI maps.

Despite several limitations, the present study provides information about functional neuroanatomy of the medial frontal motor areas in humans, which is substantiated by the combination of the two brain-mapping methods. In both patient 2 and patient 3, the fMRI activation related to the toe movements was basically located posterior to the one related to the finger movements. These findings fit quite well with the known somatotopy of the SMA proper that represents upper limb movement in its anterior part and lower limb movement in the posterior part (Fried et al. 1991; Yazawa et al. 2000). However, we have no clear explanation about the fact that the stimulation through electrode 3 elicited upper limb movements, though the stimulation through more anterior electrode 4 did both upper and lower limb movements.

The mental calculation-induced activation of patient 3 was quite similar to the findings from our own study on 16 normal subjects (Hanakawa et al. 2000b) and also from the previous reports (Dehaene et al. 1996; Rueckert et al. 1996). Accordingly, the patient is judged to have engaged in arithmetic operations throughout the task periods, despite her poor performance. Out of the two medial frontal activation loci, the anterior locus presumably corresponds to the pre-SMA. In the vicinity of this activation, electrodes 1 and 9 (see Fig. 2C) revealed epicortical potentials time-locked to instruction cues in a go/no-go choice reaction task (Ikeda et al. 1999b). This is a crucial property of the pre-SMA neurons, rather than those of the SMA proper (Matsuzaka et al. 1992). The role of the pre-SMA in mental calculations probably relates to verbal working memory (Dehaene et al. 1999), especially executive components rather than inner speech (Hanakawa et al. 2000b).

From the clinical point of view, epilepsy surgery should be performed in a way to maximize seizure control and minimize functional deficits. Damage to the SMA causes various motor deficits, for example, a disturbance of bimanual motor acts (Laplane et al. 1977). Since such deficits are not always transient, particularly in higher-order motor control rather than in gross muscle strength, unnecessary injuries are not justified. This idea demands clinicians to carry out functional mapping at or adjacent to the epileptogenic zone as precisely as possible. In this regard, the combined use of the two different methods is favorable, because one method is expected to make up the disadvantages of the other. Additionally, the combined functional brain map allows us to integrate information from two different techniques with different spatial and temporal resolutions, which will contribute to a further understanding of human functional neuroanatomy.

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