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Localizing the site of magnetic brain stimulation by functional MRI

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Abstract In order to locate the site of action of transcranial magnetic stimulation (TMS) within the human motor cortices, we investigated how the optimal positions for evoking motor responses over the scalp corresponded to the hand and leg primary-motor areas. TMS was delivered with a figure-8 shaped coil over each point of a grid system constructed on the skull surface, each separated by 1 cm, to find the optimal site for obtaining motor-evoked potentials (MEPs) in the contralateral first dorsal interosseous (FDI) and tibialis anterior (TA) muscles. Magnetic resonance imaging scans of the brain were taken for each subject with markers placed over these sites, the positions of which were projected onto the cortical region just beneath. On the other hand, cortical areas where blood flow increased during finger tapping or leg movements were identified on functional magnetic resonance images (fMRI), which should include the hand and leg primary-motor areas. The optimal location for eliciting MEPs in FDI, regardless of their latency, lay just above the bank of the precentral gyrus, which coincided with the activated region during finger tapping in fMRI studies. The direction of induced current preferentially eliciting MEPs with the shortest latency in each subject was nearly perpendicular to the course of the precentral gyrus at this position. The optimal site for evoking motor responses in TA was also located just above the activated area during leg movements identified within the anterior portion of the paracentral lobule. The results suggest that, for magnetic stimulation, activation occurs in the primary hand and leg motor area (Brodmann area 4), which is closest in distance to the optimal scalp position for evoking motor responses.

Key words Transcranial magnetic stimulation · Functional magnetic resonance imaging · Motor cortex Central sulcus · D wave

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Introduction

Using transcranial magnetic stimulation (TMS) of moderate intensity, it is possible to induce motor-evoked potentials (MEPs) in hand and leg muscles by placing a figure-8-shaped magnetic coil over a relatively broad area on the scalp. If we project this area onto the underlying cerebral cortex, this should span a wide region covering the premotor and parietal cortices in addition to the primary motor area subjacent to the optimal site (Epstein et al. 1990; Meyer et al. 1991). On the other hand, if we reduce the stimulation intensity just enough to yield motor responses over the optimal site, the area would converge into a quite small region, nearly to a point. This optimal position invariably stays over a point just above the anterior lip of the precentral gyrus, as we will show in the present study. While it seems self-evident that MEPs arise from stimulation of the motor cortex, this does not exclude the possibility that they could also arise from outside the motor cortex. If we adopt the broader map as representing the hand motor area, does this imply that TMS can elicit MEPs anywhere within that cortical region via direct stimulation of the descending pathways to the spinal cord or via transsynaptic stimulation of the cortico-cortical fibers? Or should the responses apparently arising from these "extra-primary" motor areas simply be attributed to a current spread into the primary motor area (in this case, activation always occurs in the primary motor area regardless of the coil position)? The site of action within and outside the motor areas are equally possible because anatomical findings in primates have demonstrated the existence of tracts descending to the spinal cord both from the primary motor cortex and the adjoining cortical regions as well as abundant cortico-cortical connections between them (Dum and Strick 1991). These studies raised serious questions about the classical viewpoint that the primary motor cortex is the main source of motor signals in the corticospinal tract and suggested that premotor areas could have the potential to influence the generation and control of movement independently of the primary motor cortex. Some authors have even discussed the possibility, though unlikely, that TMS stimulates other structures, such as the premotor areas and thalamus (Hess et al. 1987).

The exact site at which the electromagnetic field stimulates the motor system bears importance not only for brain topography, but also for understanding the physiology of MEP generation. Multiple successive excitatory efferent volleys are known to occur in a corticospinal axon after direct cortical stimulation, giving rise to an initial D- (=direct) wave followed by several I- (=indirect) waves (Day et al. 1987; Burke et al. 1993; Nakamura et al. 1996). The indirect waves are named I1-, I2-, and I3-waves in the order of their onset latency. Various latencies of MEPs obtained by TMS and transcranial electrical stimulation (TES) are explained by the arrival of different volleys to the spinal motoneurons. It is now generally accepted that the predominant action of TMS is transsynaptic, whereas TES excites the corticospinal neurons directly (Amassian and Cracco 1987; Amassian et al. 1987; Rothwell et al. 1991). Fuhr et al. (1991) showed that latencies of MEPs evoked by the same intensity of TMS tended to be shorter in the center of maps than in the periphery. Moreover, weak stimulation over the optimal position resulted in a progressively longer latency of MEPs than strong stimulation. The earliest responses evoked by stimulation over the optimal site would correspond to the D-waves caused by the direct stimulation of the corticospinal axons. On the other hand, responses with longer latency induced over the periphery or elicited with a weak stimulation intensity over the optimal site could be generated through a chain of multiple synapses. If so, is this entire chain contained within the primary motor cortex (M1), or does it extend from other cortical regions into the main efferent system in M1?

Functional magnetic resonance imaging (fMRI) has also been used to map the human motor cortex by evaluating the hemodynamic changes in human cortex during motor tasks (Kwong et al. 1992; Connelly et al. 1993; Constable et al. 1993; Kim et al. 1993). These studies have shown that the activated areas largely reflected where regional cerebral blood flow increased during physiological activation such as finger movements. Neuronal activity in the cortex induces the increase in tissue metabolism and a resultant increase in the regional cerebral blood flow, which is determined by the size of the responsive area and the number of active neurons (Fox and Raichle 1986). Therefore, the activated areas in fMRI would correlate well with the density of motoneurons innervating the muscle needed for the motor task. On the other hand, Wassermann et al. (1992) have shown that the MEP amplitude evoked in a given muscle is closely correlated with the number of descending volleys from the cortex following TMS, and this in turn was determined by the density of motoneurons under the area of stimulation. Thus, there should be a general correspondence between the area activated in fMRI and the location where the largest amplitude of MEP is obtained by TMS, because both of these are likely to represent the region where the motoneurons are most concentrated. With the improved spatial resolution provided by fMRI (on the order of several millimeters), we would be able to localize the activation site of TMS more precisely than with PET.

By co-registering the results of TMS with fMRI, we will show in the present study that, regardless of the latency of the MEP, the site of action of magnetic brain stimulation is located within the primary hand and leg motor areas, which is activated in fMRI scans during motor tasks. This site is not far away from the activation site of electrical cortical stimulation, which is presumed to be at the initial segment of the corticospinal axon or its extension in the subcortical white matter. The site of action defined will help us to understand the physiological implication of various experiments performed with TMS.

Materials and methods

Five normal volunteers (four males and one female) participated in this study. The following procedures were approved by the Ethics Committee of the University of Tokyo. Informed consent was obtained from the subjects prior to the experiments.

Mapping of the motor areas by transcranial magnetic stimulation

In order to locate the optimal site for evoking MEPs from the hand and leg muscles, TMS was delivered over various scalp regions in 1 cm increments both anteroposteriorly and mediolaterally. For this purpose, nasion, inion, vertex, and pre-auricular points were located, and then a 1-cm-grid reference system covering the skull was constructed for each subject (Meyer et al. 1991). Lines were drawn between nasion and inion and between the vertex and pre-auricular points on the scalp. Then a grid was made by drawing further lines parallel to these reference lines such that the distance between them was 1 cm. For TMS, we used a thinly covered prototype of figure-8 shaped coil (diameter of each loop 10 cm) connected to a magnetic stimulator (Magstim 200, Magstim, U.K.) to allow close contact with the skin. Motor-evoked potentials were recorded from Ag-AgCl gel electrodes placed over the belly and tendon of the bilateral first dorsal interosseous (FDI) and tibialis anterior (TA) muscles. All subjects were asked to keep their muscles active (10% maximal voluntary contraction) throughout the experiments to allow identification of D-, I1-, I2-, and I3-waves by a procedure described later in this section (Day et al. 1987, 1989). The center of the coil was placed flat and tangential to the scalp surface at each of the grid points with the current flowing in anterior-to-posterior direction at the junction of the coil (thus, the induced current in the brain flowed in the posterior-to-anterior direction).

Mapping of the hand and leg area of motor cortex was performed over both hemispheres. Initially, the intensity of TMS was set at 60–70% of the maximal output of the stimulator, which was well above the threshold intensity over the hand motor areas in all the subjects investigated. With this intensity, 10–20 MEPs were obtained per grid point and the peak-to-peak amplitude was averaged at each site. This allowed us to identify a circumscribed area on the motor areas of both hemispheres over which the amplitude of MEPs exceeded 0.5 mV.

Subsequently, we focused our investigation over a rectangular region just large enough to include this area and whose boundaries were parallel to the main axes of the grid coordinate system. The intensity of TMS was decreased in small steps, i.e. first in 5% decrements and then in 2% decrements of the maximal output of the stimulator, and the mapping procedure was repeated as the stimulus intensity was lowered until it reached a level at which MEPs were elicited only over up to 6–7 grid points and no longer yielded MEPs elsewhere. This final intensity of magnetic stimulator came within 30–60% for all subjects. Additional 10–20 MEPs were obtained over these selected grid points and the optimal site for TMS was defined as the grid point over which TMS elicited the MEP of largest average amplitude. Wassermann et al. (1992) have described a different method of noninvasive mapping of muscle representations in the human motor cortex. They also obtained MEPs over many grid points and, based on the amplitude of MEP over each point, calculated the “center of gravity” in this map, instead of detecting the optimal grid point of stimulation by repeated measures as above. Based on our own results, we also calculated the optimal point using their method. The optimal grid point detected by our procedure was invariably the closest of all the grid points and within 5 mm of the “center of gravity”.

With a relatively weak intensity of stimulation, such as that used for the mapping sessions, it is known that the latency of MEPs can differ with two different directions of induced currents, i.e. lateromedial and posterior-anterior directions, with the tendency of the former to activate the corticospinal fibers directly and the latter to activate them transsynaptically (Werhahn et al. 1994). Sakai et al. (1997) extended this observation using eight different coil orientations and found that I1-waves were preferentially elicited by induced currents flowing medially and anteriorly, whereas I3-waves were induced by currents flowing laterally and posteriorly. The obtained responses were classified into those mainly produced by D-, I1-, I2-, or I3-waves, according to their latencies. Thus, the latency of D-waves was determined as the latency of MEPs induced by electrical cortical stimulation, which was performed using a Digitimer D180 (Digitimer Ltd., UK) with the cathode placed over the vertex and the anode placed over the hand motor area contralateral to the recorded hand muscle. Magnetically-induced MEPs having a longer latency than this were considered to be produced by I1-, I2-, or I3-waves based on the fact that the latencies of D-waves and each of the successive I-waves are separated by an interval of 1.5–2.0 ms (Day et al. 1989). Thus, the mapping was performed in two subjects with two different coil orientations, with the induced current flowing medially and posteriorly for one subject and anteromedially and posterolaterally for another subject, to see whether the optimal point depended on different current directions (In the first subject, the former current direction elicited D-waves and the latter I3-waves. In the second subject, the former direction elicited I1-waves, and the latter induced I3-waves.)

Co-registration of the optimal point of TMS with MRI and fMRI scans

Thin (2.5 mm), non-gapped slices of magnetic resonance imaging (MRI) of the brain were acquired for each subject with a 1.5 Tesla (T) whole-body scanner (Siemens Vision). These T1-weighted scans were stacked and reconstructed into a 3D image of the brain using software attached to the MRI system, which could be resliced with any given plane. The optimal scalp sites for magnetic stimulation were marked with capsules containing vitamine D3 (Alfarol, Chugai Pharmaceutical), which appeared as high intensity spots on T1-weighed images. The reconstructed image was sliced with transverse, coronal, and sagittal planes including the markers. A line perpendicular to the scalp was drawn through the marker, and the point where it encountered the cortical surface was determined. This position was considered to represent the cortical region activated by TMS, since it was the cortical area closest to the marker and most likely the area where the induced current was maximal.

The subjects were scanned using a 1.5-T whole-body scanner (Siemens Vision) with a circular polarized head coil. Foam pads were placed within the head coil to prevent head movement and minimize motion artefacts. In each scan, 5 axial slices (5 mm in thickness) of T2*-weighted gradient echo-planar images (TR/ TE/ TI/ FA/ matrix/ FOV: 0.96/ 66/ 300/ 90/ 128×128/ 230×230; TR = repetition time, TE = echo time, TI = inversion time, FA = flip angle, FOV = field of view) were collected parallel to the AC-PC line in order to cover the entire extent of the bilateral hand and leg areas of the motor cortices. The changes in image signal intensity due to blood flow and oxygenation-related contrast mechanisms are known to be small (Kwong et al. 1992; Constable et al. 1993; Kim et al. 1993). Therefore, to optimally visualize the signal changes, a sequential task-activation paradigm was used, i.e., the subjects underwent eight alternating scans during test (activation) and resting states. During the test scans, each lasting 30 s, the subjects were required either to oppose the index finger with the thumb (finger tapping) or to perform bilateral dorsiflexion of the foot (foot movement) at 2 Hz, paced by sound. During the control scans, the sound persisted with the same pace, but the subjects were asked to keep their muscles relaxed. These movements were selected because they were presumed to involve predominantly, if not exclusively, the FDI and TA muscles.

Motion correction was performed for the scan data obtained. fMRI data are acquired as a sequence of image volumes, the first of which is termed the *reference* volume (Woods et al. 1992, 1993; Jiang et al. 1995). Subsequent image volumes are aligned with the reference volume by minimizing the ratio-variance algorithm, an iterative process that aligns two sets of images in a pairwise manner by minimizing the variance of ratio of the voxels in the two image sets. Actually, this transformation involves a six-dimensional transformation space (rotation about and translation along each of the three coordinate axes). According to the identified transformation space, a new image sequence is constructed by reslicing each of the original image sets. After the scans were corrected for motion, the time course of MR signal intensity in each pixel was cross-correlated with an idealized box-car reference function derived from the task sequence. The activation foci where blood flow increased significantly during the movement and, thus, which were considered to contain the highest density of neural elements activated during the movement were determined as the pixels with the high correlation coefficients. These pixels were defined as the pixels whose correlation coefficients exceeded 0.3 and were subsequently overlaid onto the corresponding T1-weighted slices. The maps were colored with an orange to red gradient according to the correlation coefficient. The optimal activation sites for TMS and fMRI both have a certain extent in space. The extent can be small or large, depending on the intensity of TMS and according to the correlation coefficient we used as the cutoff value for fMRI. A reasonable way of correlating these two methods would, therefore, be to use the “center” of these two sites. For this purpose, we co-registered the point having the lowest threshold for TMS with the region having the highest correlation coefficient for fMRI.

Three of the five participants (two males and one female) had also served as subjects of differential I-wave activation in hand muscles with a figure-8 shaped coil (Sakai et al. 1997). This experiment was aimed at correlating the optimal current direction for evoking different descending volleys with the neuroanatomy of sensorimotor cortices. In this study, a relatively weak stimulation intensity was used (30–60% of the maximal output of the stimulator). As stated above, D- or I1-waves are preferentially activated by anteromedially directed current induced in the brain, and I3-waves by posterolaterally directed current. Whether D- or I1-waves are preferentially activated depends on the subject, because the difference in threshold for D- and I1-waves are usually small. We thus correlated the current direction preferentially evoking MEPs of shortest latency (D- or I1-waves) in FDI with the orientation of the portion of the precentral gyrus activated during finger tapping in each subject.

Results

The optimal grid point for eliciting maximal MEPs in FDI was located 3–6 cm lateral to the midsagittal line and 2 cm

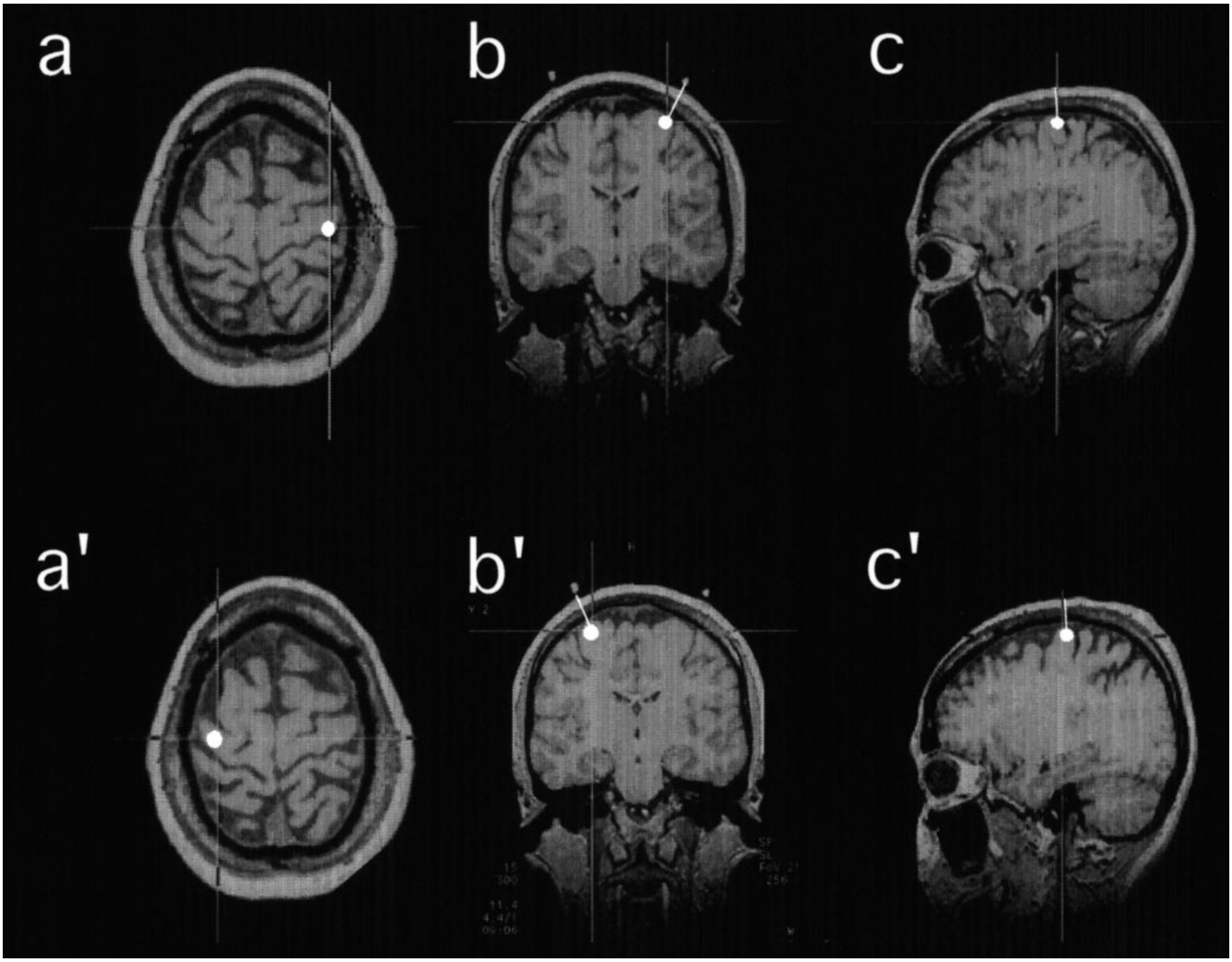

Fig. 1 Optimal site for stimulation of the hand motor area. The optimal scalp site for evoking maximal MEP in FDI was projected onto the crown of the precentral gyrus on transverse (**a**), coronal (**b**), and sagittal (**c**) sections. The *white bright lines* perpendicular to the scalp surface are those used for the projection. The *cursors* show the position of the projected point on the cortical surface. The two *high intensity points* on the scalp in **b** are the markers representing the optimal site for stimulation. When the cursor (not shown) is adjusted to the projected point on the cortical surface, the point having the same x, y, z coordinate is shown on the other two of the three planes simultaneously. The optimal site for TMS was also projected onto the anterior lip of the precentral gyrus also for the right cerebral hemisphere (**a'**, **b'**, **c'**)

anterior to 2 cm posterior to the line joining Cz and the external auditory meatus in the antero-posterior axis. The optimal site remained the same regardless of coil direction for two subjects, in whom mapping was performed with two different current directions, each eliciting MEPs of different latencies.

Figure 1 shows the optimal site for obtaining motor responses in FDI and the projected point onto the left cerebral hemisphere. A line perpendicular to the scalp surface (the white lines in the figure) was drawn through the marker placed at the optimal site. This projection line encountered the cerebral cortex at the crown of the precentral gyrus. Since this line was slightly slanted, it encountered the cortical surface in a plane somewhat anterior to the coronal plane including the marker. When the cursor (not shown in the figure) was adjusted to the projected point on the coronal plane (Fig. 1b), the point having the same coordinate was automatically displayed in the transverse and sagittal planes (Fig. 1a and c). The optimal site for TMS was also projected onto the anterior lip of the precentral gyrus for the right cerebral hemisphere (Fig. 1a', b', c'). Using the same procedure, the markers on the scalp over both hemispheres were projected onto the anterior lip of the precentral gyrus just before it bent down into the central sulcus in all subjects studied.

Figure 2 (right) shows where significant blood flow increase occurred when a subject performed finger tapping bilaterally at 2 Hz. The area was located on the anterior lip of the precentral gyrus, where the optimal scalp region was also projected (Fig. 2, left).

There was a strong correlation between the site on the cerebral cortex projected from the marker and the activat-

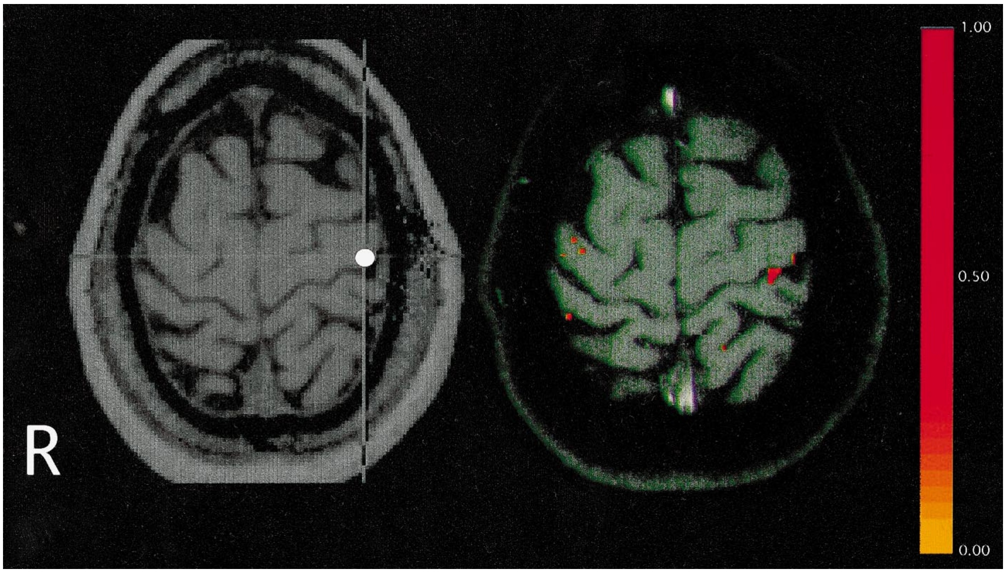

Fig. 2 Areas activated by finger tapping in fMRI. On fMRI scans, the areas exhibiting blood-flow increase during finger tapping at 2 Hz were identified over a discrete region on the lip of the contralateral precentral gyrus (*right figure*), which coincided with the projected site from the optimal scalp site for stimulation (*left figure*). The time course of MR-signal intensity in each pixel was cross-correlated with a box-car reference function derived from the task sequence. Only pixels with correlation coefficients >0.3 are shown. *R* Right

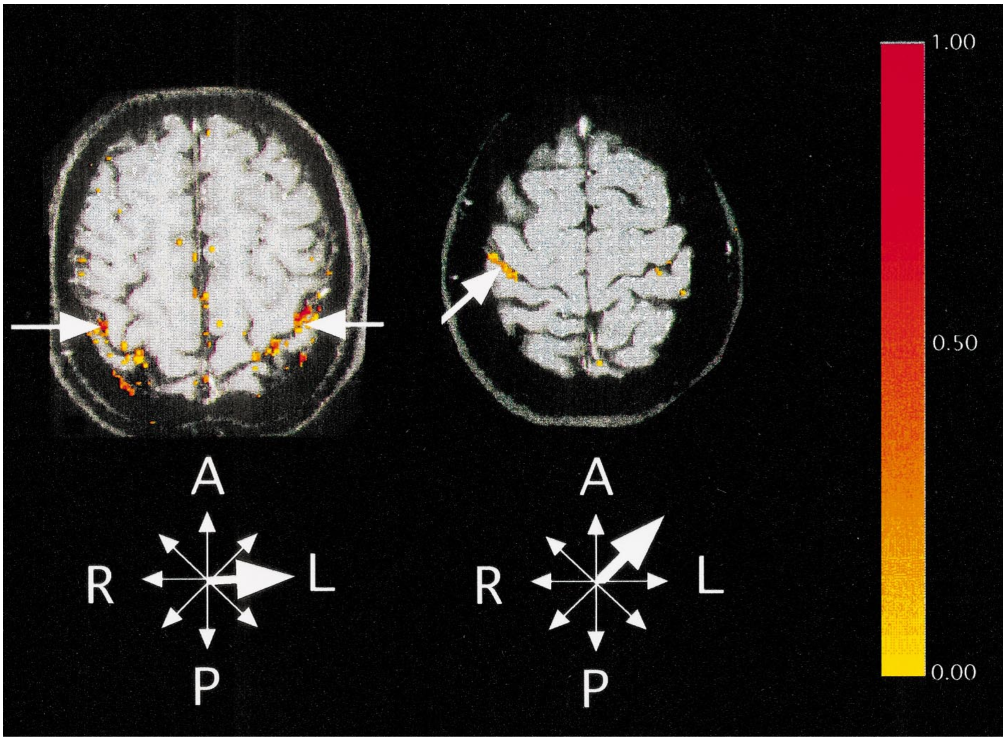

Fig. 3 Optimal current direction for eliciting MEPs of shortest latency. *Thick arrows* in the *lower figures* depict the direction of induced current that preferentially elicited MEPs with the shortest latencies in two subjects. In one subject, the optimal current direction for evoking D-waves was medial and the precentral gyrus coursed in the postero-anterior direction bilaterally. In another subject, the optimal current evoking I1-waves, the MEP of shortest latency in this subject, flowed in the anteromedial direction, which was again perpendicular to the course of the central sulcus at this site. The current directions were nearly at right angles to the courses of the activated regions in the primary motor cortex during finger tapping (*upper figure*). Only pixels with correlation coefficients >0.3 are shown. The activation site in fMRI extended over 4–5 contiguous slices in these subjects. The slices shown were adopted because they included the pixel with the highest correlation coefficients. The area posterior to the postcentral gyrus, which looks like an activation site in the *left figure*, is probably an artefact due to veins. *A* Anterior, *P* posterior, *R* right, *L* left

ed area in fMRI in all the subjects studied. The marker for TMS was invariably projected into the activated area at the anterior lip of the precentral sulcus. The distance between the pixel with the highest correlation coefficient and the projected point onto the cortical surface of the marker was 3.3±0.8 mm for the right hemisphere and 2.3±0.8 mm for the left hemisphere. This indicated that the cortical region projected from the scalp marker corresponded to the portion of the precentral gyrus *functionally* involved in finger tapping.

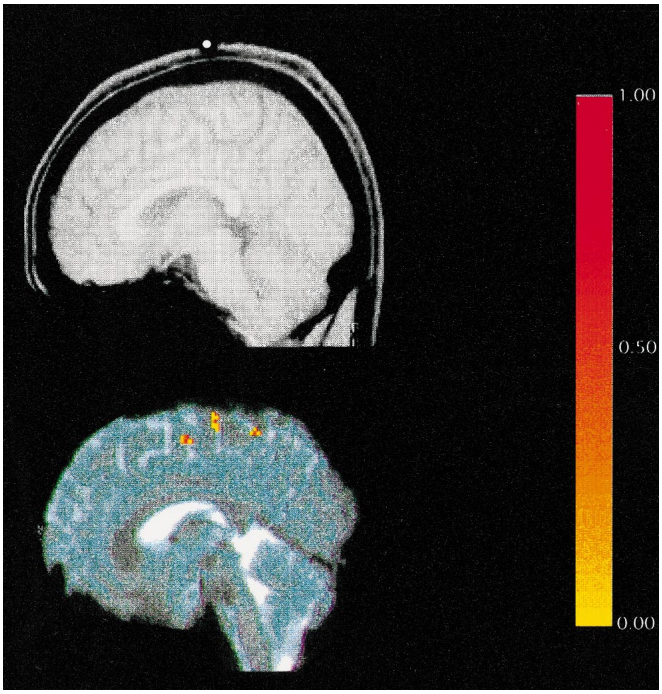

Fig. 4 Cortical areas where blood flow increased during leg movements. The marker (*upper figure*) appeared as a high intensity *spot* on the optimal scalp site. In the *lower figure*, the cortical areas where blood flow increased during leg movements in fMRI studies are overlaid onto the corresponding T2*-weighted MRI image. The optimal site was just above the activated area in the anterior half of paracentral lobule, which was considered to represent the primary leg motor area. Two additional areas are identified, one in the posterior half of the paracentral lobule and another in the medial aspect of superior frontal gyrus, probably representing the primary leg sensory area and the supplementary leg motor area, respectively. Only pixels with correlation coefficients >0.3 are shown

According to the methods of Sakai et al. (1997), eight different coil orientations relative to the antero-posterior direction in 45° steps were tried in order to find out the current direction optimal for evoking MEPs of the shortest latency in three subjects. In the study of Sakai et al., TMS inducing anteromedial current was most effective in eliciting short latency MEPs, such as D- and I1-waves, in 5 out of 6 subjects studied. In two subjects in our study, the optimal current was also in the anteromedial direction, while the course of the central sulcus ran in the posteromedial to anterolateral direction, which was almost perpendicular to the optimal current direction (as shown in Fig. 3, right). In another subject (Fig. 3, left), on the other hand, the optimal current direction for evoking D-waves was medial and the central sulcus at the activated region on fMRI scans ran in the anteroposterior direction. Therefore, the optimal current direction for D-waves flowed nearly perpendicular to the long axis of the hyperperfused precentral gyri on fMRI scans. In all three subjects studied, the mean angle formed between the optimal current direction and the line drawn perpendicularly to the course of precentral sulcus at the site of maximal activation was less than 10° (5.0±2.7°).

The optimal stimulation site for eliciting MEPs in TA was located 0–2 cm lateral and 0–1 cm posterior to Cz in all the subjects. In these subjects, the capsules marking the optimal site came above the anterior half of the paracentral lobule, which also corresponded to one of the areas identified on fMRI scans during leg movements (Fig. 4). Two additional areas were also activated, one within the superior frontal gyrus and one within the posterior half of the paracentral lobule (Fig. 4, lower figure). Taking their locations into consideration, we considered the region just below the marker to represent the leg area of the primary motor cortex (see Discussion).

Discussion

The relation of the scalp map for hand-motor area to the underlying cortical topography has been explored by TMS in many different ways, and consensus seems to have been reached on its location either in or near the motor cortex (Epstein et al. 1990; Meyer et al. 1991). Some positron emission tomography (PET) studies have proceeded to relate the site of action of magnetic stimulation functionally with cortical areas dedicated to hand movements. Wassermann et al. (1996), for example, showed that the magnetic-stimulation site projected inward onto the cerebral cortex encountered the surface of the brain at the anterior lip of the precentral gyrus, which came within 5–22 mm of the PET activation site during finger movements. Our study confirmed earlier observations in that the hand motor responses were optimally evoked when the center of the coil was placed over a scalp position at a minimal distance from the anterior lip of the precentral gyrus (Meyer et al. 1991; Wassermann et al. 1996; Sakai et al. 1997). The same position was always projected into the region involved in finger tapping identified on fMRI scans, which functionally represented the hand area of the primary motor cortex. At first sight, differences in the spatial resolution of fMRI (on the order of several mm) and TMS (on the order of 0.5–1 cm) apparently make it difficult to co-register the optimal locations obtained with these two techniques. However, previous work using TMS, in which coil positions were moved in small increments and the amplitudes of MEPs obtained at each site were interpolated, has attained a mapping accuracy of 0.5 cm (Brasil-Neto et al. 1992a, b; Wilson et al. 1996). We also moved the magnetic coil in small increments (1 cm) and detected the grid point nearest to the optimal site for TMS through repeated mapping procedures, thereby locating the motor cortex within several millimeters. Thus, we concluded that the optimal site for TMS corresponded quite well with the fMRI activation site, which were both on the anterior lip of the precentral gyrus.

TMS results from "electrical" activation of neurons underneath the coil, whereas fMRI detects the hemodynamic changes during "physiological" activation. This can lead to some theoretical misregistration of fMRI and TMS. Using fMRI, Brandt et al. (1996) demonstrated that the site of action of TES, i.e., the region of blood-flow increase elicited by serial TES with a stimulus intensity of 120% motor threshold, was just beneath the stimulating electrode (anode) at the crown of the primary motor cortex exactly where blood flow increase was observed during finger opposition. The area of blood-flow increase during finger opposition was greater than and included the region of blood-flow increase elicited by TES. In the same manner, the electrical field induced by TMS is presumed to be strongest at the cortical region directly underneath the junction of the loops of the figure-8-shaped coil (Eaton 1992) and, in our study, the scalp site for optimal stimulation was always projected into the activation site of fMRI. Therefore, the misregistration due to the mode of activation should also be relatively small for TMS and fMRI. Moreover, the direction of current preferentially evoking D-waves crossed the central sulcus nearly perpendicularly at this site, which strongly suggests that the cortical structure responsible for MEP generation has a configuration in close relationship to this direction. A plausible candidate for such neural structure is the corticospinal fibers running horizontally in the motor cortex where they bend down into the central sulcus, because there is abundant evidence that these fibers are aligned perpendicularly to the main axis of the motor cortex. Thus, we concluded that the site of magnetic brain stimulation was at the anterior lip of the precentral sulcus, which corresponds to the primary motor cortex (Brodmann area 4) regardless of the latency of obtained MEPs, and that, if the coil at some distance from the optimal position evokes an MEP, it should take place primarily as a result of current spread into M1, rather than via direct "stimulation" of the cortical region just beneath the coil.

In two subjects, cortical regions involved in leg movements were identified on the fMRI scans in the anterior portion of the paracentral lobule just beneath the optimal scalp site for evoking MEPs in TA, which probably corresponded to the primary leg motor area. Here again, the site of action in magnetic stimulation was suggested to be localized in M1. The relevant site is 3–4 cm deep from the scalp surface, where stimulation occurs despite the rapid decay of magnetic stimulus with distance. The site of action for leg muscles may appear too deep for TMS, because Epstein et al. (1990) have localized the site of TMS for finger muscles in the gray matter-white matter junction at the crown of the precentral gyrus, which was approximately 2 cm underneath the scalp surface. With a sufficient stimulus intensity, however, it is quite likely that a neural structure at this depth can be stimulated. Eaton (1992) calculated the electrical field in a spherical volume conductor induced by a figure-8-shaped magnetic coil placed on its surface. The magnetic field, and hence the induced eddy current, was maximal just beneath the junction of the loops and rapidly diminished with distance from this point (both tangentially and perpendicularly to the skull surface), but a considerable strength of field was still present at 3–4 cm depth (approximately 20% of the maximum).

Two additional regions were identified, one within the posterior portion of the paracentral lobule and one within the medial aspect of superior frontal gyrus. The former area would correspond to the primary leg sensory area reflecting reafference from the moving foot and the latter area to the supplementary motor area. Leg movements as simple as bilateral dorsiflexion of the feet presumably should require more elaboration than does finger tapping and lead to an additional activation of supplementary motor area (SMA) in the superior frontal gyrus. Thus, for both the hand and leg muscles, the optimal site for magnetic stimulation resides over the functionally activated area in the primary motor cortex.

Most remarkable in the present study was the finding that regardless of the direction and position of the magnetic coil, quite limited cortical regions in the primary hand and leg motor areas seemed to give rise to the MEPs. The site of activation would be determined not only by the intensity of the induced electrical field, but also by the cortical organization. The selective activation would then be understood if we take the cytoarchitechtural organization specific to this area into consideration (Douglas et al. 1990). The hand area of the primary motor cortex (Brodmann area 4) predominantly consists of pyramidal cells sending monosynaptic inputs to the spinal motoneurons and typically lacks a distinct small cell layer, whereas the adjoining sensory cortex and much of the surrounding association cortices contain varying populations of granular and pyramidal cells and few, if any, large corticospinal neurons. The situation, however, is much more complex for the leg motor area. Histologically, corticospinal neurons projecting to lower lumbosacral segments abound in the caudal portion of the SMA as well as in the primary leg motor area, with no obvious borders existing between these two regions that exhibit an obvious change in the density of corticospinal neurons (He et al. 1995). Using subdurally implanted electrodes, Allison et al. (1996) found that foot motor responses were also evoked by stimulation in the superior frontal gyrus, where they were unable to detect a foot region of the SMA distinct from the foot motor area. Therefore, it is conspicuous that methods used in the present study successfully distinguished the primary leg motor area from the leg area of the SMA. Although both of these areas seem to have direct access to the spinal cord and consequently the potential to generate MEPs, the distinction between the leg areas of the SMA and the primary motor cortex might thus depend on the slight difference in density of corticospinal neurons directly projecting to the lumbospinal segments or on an organization finer than this. Approximately 5% of the neurons in the SMA were known to send projecting fibers down the corticospinal tract, which innervate both proximal and distal muscles bilaterally in a manner different from the corticospinal fibers from the primary motor cortex (Brinkman and Porter 1979; Dum and Strick 1996; Wise 1996).

Addendum While the manuscript of this paper was under review, Krings et al. reported the correlation between fMRI and TMS maps and compared them with the results of direct electrical cortical stimulation (Neurology 48:1406–1416, 1997).

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