

# Comparison of representational maps using functional magnetic resonance imaging and transcranial magnetic stimulation

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## Abstract

**Objective:** Comparison of functional magnetic resonance imaging (fMRI) representational maps, that were generated during voluntary thumb abduction, hand dorsiflexion and foot elevation to amplitude maps of motor-evoked potentials (MEPs) elicited by single transcranial magnetic stimulation (TMS) administered to cortical motor representation areas of the muscles of the thenar eminence, extensor carpi radialis and tibialis anterior muscles.

**Methods:** Stimulus locations that produced maximal motor-evoked potential amplitudes were compared to fMRI activation maxima in three-dimensional (3D)-space and in a 2D-projection using a novel technique that allowed fMRI activation sites to be projected onto the surface of the brain.

**Results and conclusions:** When analyzing pooled data from all target muscles, the location of projected fMRI and TMS activation maxima on the cortical surface differed by an average 13.9 mm. The differences in 3D distances were particularly large for representation areas of lower leg muscles. 3D distances between fMRI activation maxima and highest MEP site in TMS correlated significantly with higher TMS thresholds. These observations strongly suggest that higher TMS excitation thresholds and lower MEP amplitudes are largely due to the absolute distance between the stimulation site and the excitable cortical tissue targeting this muscle. After the projection 4 out of 5 representation sites as evaluated by TMS were located anterior to the fMRI activation maxima, an observation which may be due to the orientation of the magnetic field induced by the current in the coil. The representation sites as evaluated with both methods were specific for the type of movement: distances between representation maxima of the same movements were significantly smaller than those within different movements. Nevertheless, fMRI and TMS provide complementary information, which is discussed on the basis of the functional map observed with both methods.

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## 1. Introduction

Both functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) are capable of non-invasive mapping of neural representations of the motor cortex. Nevertheless, qualitative differences between the two methods exist: fMRI maps are assessed during voluntary movements and contraction whereas TMS passively evokes activity in the fully relaxed target muscles. fMRI measures activation areas indirectly by assessing blood oxygenation

level dependent contrast (BOLD). The BOLD-effect is linked to the electrical response of neurons by the increasing demand for oxygenated blood in the vicinity of discharging neurons, an effect that was first demonstrated in craniotomized patients (Jack et al., 1994). In particular, the average response of local field potentials, which results from dynamic interactions of various synaptic and cellular mechanisms, was found to give good estimates of the BOLD-signal (Logothetis et al., 2001). The spatial resolution of fMRI is dependent on the matrix size and slice thickness. A comparison of intraoperative electrical stimulation maps with fMRI-activation maps showed differences in localization ranging from 3 to 10 mm (Yoursy et al., 1995).

Short-duration magnetic pulses delivered to the scalp overlying motor cortical representation areas evoke

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compound motor action potentials (MEPs) in target muscles. To map the spatial properties of motor cortical representation areas, focal transcranial magnetic stimulation is delivered via a figure-of-8 shaped magnetic coil to different scalp positions. Such a coil allows for maximal spatial accuracy (Cohen et al., 1990). The spatial distribution of the magnetic field induced by a single magnetic pulse delivered through a figure-of-8-coil was demonstrated using fMRI by Bohning et al. (1997). As opposed to transcranial electric stimulation of the brain, TMS activates descending pathways primarily by exciting interneurons that target pyramidal tract neurons via I-waves, and to a lesser extent, provides for direct stimulation of descending pyramidal axons (D-waves; Di Lazzaro et al., 1998).

MEP maps can be described by at least 3 variables: first, the highest MEP site represents the stimulus location over the scalp that evokes the maximal motor responses in target muscles; second, the size of the motor representation area is indicated by the number of stimulus locations that evoke MEPs in the target muscle of at least a given amplitude in mV; third, the ‘center of gravity’ (COG) describes the center of all activation intensities within a representational map.

Whereas the highest MEP site is independent of MEP cut-offs, the size of the representation map and the COG is dependent on these. By evaluating COGs, a somatotopical order of representation sites of finger and more proximal muscles of the upper limb has been demonstrated (Wassermann et al., 1992). Determination of COGs improves the spatial differentiation between adjacent target muscles (Borojerdj et al., 1999). More distal muscles show lower excitation thresholds and higher MEP-amplitudes than more proximal ones (Ridding and Rothwell, 1995). Lower excitation thresholds correlate with larger representational areas.

In principle, representational sites of TMS and fMRI activation maxima may be compared by (1) measuring absolute distances between fMRI maxima and scalp positions optimal for TMS in the 3-dimensional (3D) data set obtained by MRI or (2) by projecting the fMRI-activation sites onto a 2D surface on the scalp similar for instance to the 10–20 system of electroencephalographic-references, or (3) by projecting an external marker, indicating the location of the highest MEP site, via a line perpendicular to the scalp onto the nearest point of the cortical surface (e.g. Terao et al., 1998).

While these methods are capable of assessing some aspects of the spatial relationship between TMS and fMRI representation areas, they have two main disadvantages. First, the definition of the perpendicular line from markers to cortex depends, to some extent, on the evaluator and, second, an overview of different locations in a 3D system is difficult to achieve if these locations differ in more than one coordinate. Therefore, the evaluation has to be done by scrolling between slices.

In the present study, we were particularly interested in addressing the following questions: (1) How specific are the representational sites (evaluated in 3D and in the projection to cortex or scalp) for different movements for both meth-

ods? (2) Are there any systematic correlations between 3D-distances from a fMRI-activation site to the highest MEP site and the motor-threshold or the MEP amplitude elicited by TMS? (3) How does the choice of a given cut-off for TMS and fMRI representation areas influence the correlation from using both methods? To address these questions we evaluated fMRI activation maxima in the precentral gyrus and compared these results with locations of highest MEP sites evoked by TMS. Evaluation of distances could be performed in the 3D system but also in the projection of fMRI maps to the scalp or TMS maps to the cortical surface. Furthermore, we compared the map sizes for TMS and fMRI for the muscles of the thenar eminence as the most distal of the investigated muscles, which were assumed to be optimal for this purpose.

## 2. Methods

### 2.1. Subjects

Five right-handed (evaluated by the Edinburgh Inventory of Handedness; Oldfield, 1971) subjects (3 male and 2 female, aged 21–25 years, average 23.2) with no known neurological abnormalities participated in the fMRI and TMS studies. Study procedures were approved by the ethics committee of the University Hospital of Tübingen.

### 2.2. Task and data assessment

#### 2.2.1. TMS

Subjects sat in a comfortable chair with a head rest. The Cz-location was determined and marked with colored ink on the scalp. Focal single-pulse TMS was delivered to the left motor cortex through a poly-foam coated figure-of-8 coil (diameter  $2 \times 70$  mm, 9 turns of wire, peak magnetic field strength 2.2 T, peak electric field strength 660 V/m) that was connected to a repetitive magnetic stimulator (Magstim Rapid, two booster modules, The Magstim Company, Spring Gardens, Whitland, UK). Using surface electrodes, EMG activity was recorded separately from each target muscle (right arm: abductor pollicis brevis; extensor carpi radialis muscle; right leg: tibialis anterior muscle). EMG activity was recorded at a digitizing rate of 5000 Hz using a Toennies electromyography system (Toennies, Myograph II), digitized and stored on a personal computer. During the data acquisition, MEPs were displayed on the oscilloscope screen at a sensitivity of 100  $\mu$ V/div (50  $\mu$ V/div during determination of motor thresholds). Off-line analysis of EMG recordings included digital filtering using a 50 Hz bandstop and a 200 Hz low-pass filter and manual determination of MEP latencies as well as peak-to-peak MEP amplitudes

The coil was placed tangentially to the scalp with the handle pointing backward and rotated away from the midline by 45°. The current induced in the brain was therefore directed approximately perpendicular to the line of the

central sulcus, a condition optimal for activating the corticospinal system trans-synaptically (Kaneko et al., 1996; Werhahn et al., 1994). The coil was moved over the area of the contralateral motor cortex to determine the optimal position for eliciting the relatively largest MEP amplitudes from the target muscles when stimulating at a given stimulus intensity. This position was marked on the scalp to ensure identical coil placement throughout the experiment. Motor threshold was defined as the stimulus intensity that evoked MEPs of more than 50  $\mu\text{V}$  peak-to-peak amplitude in 3 out of 5 trials. For determination of motor thresholds, evaluated for each of the 3 muscles, stimulus intensities were increased in steps of 1% stimulator output starting from 50% of the maximal stimulator output. We fixated a surgical cap on the head of the subject using rubber bands. The cap had a hole, which was located above the marked point on the scalp indicating the highest MEP site. A grid, printed on an adhesive was pasted on the surgical cap centered around the highest MEP site. For mapping of cortical motor representation areas, single TMS pulses at 110% resting motor threshold of each muscle were delivered to scalp positions 1.5 cm apart in a centripetal, clockwise spiral course beginning at the highest MEP site and then proceeding to the adjacent grid-point. Each scalp position was stimulated 3 times. MEP amplitudes for each scalp position, was determined as the mean amplitude from 3 recordings. If more than two showed an MEP  $> 20 \mu\text{V}$ , the grid-point was evaluated as belonging to the representation map of a given target muscle. Two measurements of cortical representation areas of each target muscle were calculated: (1) the center of gravity (COG) of TMS maps representing the center of MEP amplitudes and (2) the volume of representation area as defined by the scalp positions which showed higher MEPs than 20  $\mu\text{V}$  in 2 out of 3 recordings with a stimulus intensity of 110% above resting motor threshold.

After completion of the TMS study, markers (vitamin E capsules) indicating Cz and the highest MEP sites for each target muscle were fixated on the scalp using EC2 electrode cream (Grass Instruments, Quincy, MA).

### 2.2.2. fMRI

fMRI measurements were carried out immediately after the TMS evaluation. For fMRI data acquisition, subjects lay supine in the scanner with their eyes closed. A subject's head and proximal limbs were secured in order to minimize involuntary movements. Subjects performed right foot (dorsiflexion of the foot in the ankle), thumb (abduction of the thumb) and wrist (hand dorsiflexion) movements paced with an acoustical metronome at a frequency of 1 Hz. The movements were selected in order to maximize similarities in cortical activation patterns during fMRI and TMS. fMRI was performed with a 1.5 T scanner (Siemens Vision) using echo planar imaging (EPI, Matrix  $96 \times 128$ , FOV 250 mm, TE 59 ms, scan time 8 s, repetition time 10 s) of the whole brain with 45 axially oriented slices of 3 mm thickness without gap. Forty-eight measurements (units of 6 measure-

ments each during movement and rest alternating 4 times) were performed per condition. Additionally, a T1-weighted anatomy 3D-dataset containing 128 sagittal slices (effective thickness 1.5 mm; matrix  $224 \times 256$ ; field of view 250 mm; TR 9.7 ms) was measured for each subject prior to the functional data acquisition. Images were acquired with an improved storage system described by Klose et al. (1999).

The statistical evaluation of fMRI data was carried out with the statistical parametric mapping program (SPM96, Wellcome Department of Neurology, London). Within subjects, scans were realigned to the first volume to correct for interscan movement artifacts. Echo planar images of each subject were coregistered to the anatomical datasets by determination of affine transformation, segmentation and coregistering of the images partitions using a rigid body transformation (Ashburner and Friston, 1997). EPI data were smoothed with a Gaussian filter of a full width half maximum of 4 mm. Statistically significant differences between movement and rest were assessed using the delayed box-car model with an intensity threshold of  $P < 0.001$  and an additional correction for false positive responses within the whole brain volume of  $P < 0.05$ . High thresholds were used because we were interested in highly significant responses within the precentral gyrus. Individual image files with thresholded statistical parametric maps were written and were used for further data evaluation in the projection program.

### 2.3. Measurement of location of activation

For the evaluation of distances with the 2D-projection method, activation maps were superimposed on the 3D-MRI datasets. An ellipsoid was interactively fitted to the individual brain with a multiplane reconstruction program on axial, coronal and sagittal slices. For each point a vector was calculated extending from the center of the brain (between the bottom and the roof of the 4th ventricle) to the surface of the ellipsoid. Intensity values of the anatomic and functional data were averaged along these rays within a shell of 20 mm thickness located at the surface of the cortex. The mean intensity values from the anatomical and functional data were transferred in polar coordinates to form the resulting 2D image (for further details of this method see Lotze et al., 2000). The radius represents the elongation angle theta. So distances along one of the surfaces defined by the ellipsoids can be calculated multiplying the angular distance with the local radius. Another shell of 1 cm thickness was positioned on the scalp surface to project the capsules onto the 2D circle. The intensity of activation (expressed by the  $z$  values between rest and activation) and the size of activation clusters around the central sulcus (number of activated voxels) were evaluated using SPM96 (Wellcome Institute of Cognitive Neurology, London). Activation maxima were assessed as the highest activated voxel in the precentral gyrus. To demonstrate fundamental differences between both methods representational maps of

the same movement within the same subject are demonstrated in Fig. 1. In this figure the fMRI activation map shows two peaks. The white cross demonstrates a center of gravity, calculated by weighting voxels of one cluster above given thresholds with positions within the 2D map.

#### 2.4. Projection of TMS variables to MRI

Absolute distances from activation maxima and capsules over TMS highest MEP site and Cz were determined in the 3D data set. Distances from the projection of the highest MEP site onto the cortical surface to fMRI activation maxima in M1, and distances from the projection of the fMRI activation maxima onto the scalp to the bottom of the capsules were measured with the projection method described above. In addition, the distances from the COG and the projection of the fMRI activation maxima were calculated with the same method. After confirmation of a normal distribution of values with a Kolmogorov-Smirnov test, we tested the following hypotheses: (1) Are there significant correlations between TMS parameters such as map volume, motor resting threshold and amplitude of MEP (Pearson correlation, corrected for 3 comparisons)? Are there correlations between the 3D distance of TMS stimulation sites and fMRI-activation maxima and the TMS motor thresholds (Pearson correlation)? (2) Are there differences between TMS-thresholds between the target muscles (One sided *t* tests; corrected for 3 comparisons)? (3) Is the localization specific for the movement type independent of the method used? Specificity was tested with paired *t* tests between specific (APB, thumb abduction; ECR, hand elevation; TA, foot elevation) and non-specific (ECR to thumb movement; APB to hand elevation; ECR to foot elevation) distances.

Furthermore, the map sizes for the abductor pollicis brevis were compared between the TMS method (MEP amplitude cut-off in steps of 20, 50, 100, 150, 200, 250 to 300  $\mu\text{V}$ ) and the fMRI method (single voxel cut-off  $P < 0.05$ ; 0.01; 0.001) by subtracting the TMS map sizes with the fMRI map sizes with the given cut-off.

### 3. Results

Absolute 3D distances of the TMS highest MEP site and the fMRI activation maxima were about 1 cm larger for the foot than for the upper limb representation sites (see Table 1). For TMS the map total volume and the amplitude of MEP correlated significantly ( $r = 0.67$ ;  $P < 0.005$ ). Motor thresholds for the tibialis anterior muscle were significantly higher than for the muscles of the thenar eminence ( $t(4) = 3.87$ ;  $P < 0.05$ ; Table 1); differences between the tibialis anterior muscle and the extensor carpi radialis showed only a trend ( $t(3) = 3.13$ ;  $P = 0.052$ ). Motor thresholds were positively correlated with 3D distances to fMRI activation maxima ( $r = 0.67$ ;  $P < 0.005$ ).

The 2D projection of fMRI activation maxima and TMS

highest MEP site onto the cortical surface showed on average a 14 mm smaller spatial difference than the 3D method and 4.2 mm smaller distances as compared to the projections onto the scalp (Table 1). Four out of 5 TMS-representation sites for each movement type were located anterior to the fMRI representation sites. The representation sites as evaluated with both methods seem to be specific for the type of movement: distances between representation maxima (AM and highest MEP site) of the same movements (average distance: 13.81 mm) were significantly smaller than those within different movements (average distance: 25.06 mm);  $t(11) = 2.56$ ;  $P = 0.027$ . This was also observed for intra-limb movements (ECR/hand elevation; APB/thumb abduction);  $t(8) = 2.35$ ;  $P = 0.047$  but not by comparison of distances of each single movement.

The best correspondence of the size of TMS and fMRI representation areas was observed for the fMRI threshold of  $P < 0.001$  and the TMS of 200  $\mu\text{V}$  (difference:  $-29.58 \text{ mm}^2$ ), the second best was fMRI of  $P < 0.01$  and TMS of 150  $\mu\text{V}$  (difference:  $-38.52 \text{ mm}^2$ ) and the third best was observed with a threshold of fMRI of  $P < 0.01$  and TMS of 100  $\mu\text{V}$  (difference:  $-96.28 \text{ mm}^2$ ).

### 4. Discussion

Brandt et al. (1996) demonstrated that if the motor cortex is stimulated electrically with stimulus intensities of 120% MT, the optimal activation sites employed to activate finger flexors coincides with fMRI activation sites observed during finger opposition. Therefore, it seems likely that the representational site, as determined with both methods, actually shares, at least to a large extent, the same neural substrate.

The data about 3D differences in representational sites as evaluated in the present study are comparable to previous reports. In comparison with positron emission tomography (PET; e.g. Wassermann et al., 1996) or fMRI (e.g. Bastings et al., 1998; Bohning et al., 1998; Krings et al., 1997) it has been demonstrated that scalp projections of activation maxima during execution of movement are located about 5–22 mm distant from the TMS highest MEP site of the prime mover. In our study the 3D distances and the TMS thresholds showed positive correlations. This result underlines the findings of Krings et al. (1997) who reported that MEP amplitudes largely depend on the distance between optimal TMS scalp position and fMRI representational sites. This is not surprising as 3D distances between representational sites include anatomical distances between the scalp and the skull and the distance to the stimulated cortical neurons and largest MEP amplitudes have been observed if TMS is performed close to the primary motor cortex (Meyer et al., 1991). Thus, for example, for the tibialis anterior muscle whose cortical representation area resides in the depth of the interhemispheric sulcus, the estimated field strength of the magnetic field induced by non-invasive transcranial stimulation over the optimal scalp position is about

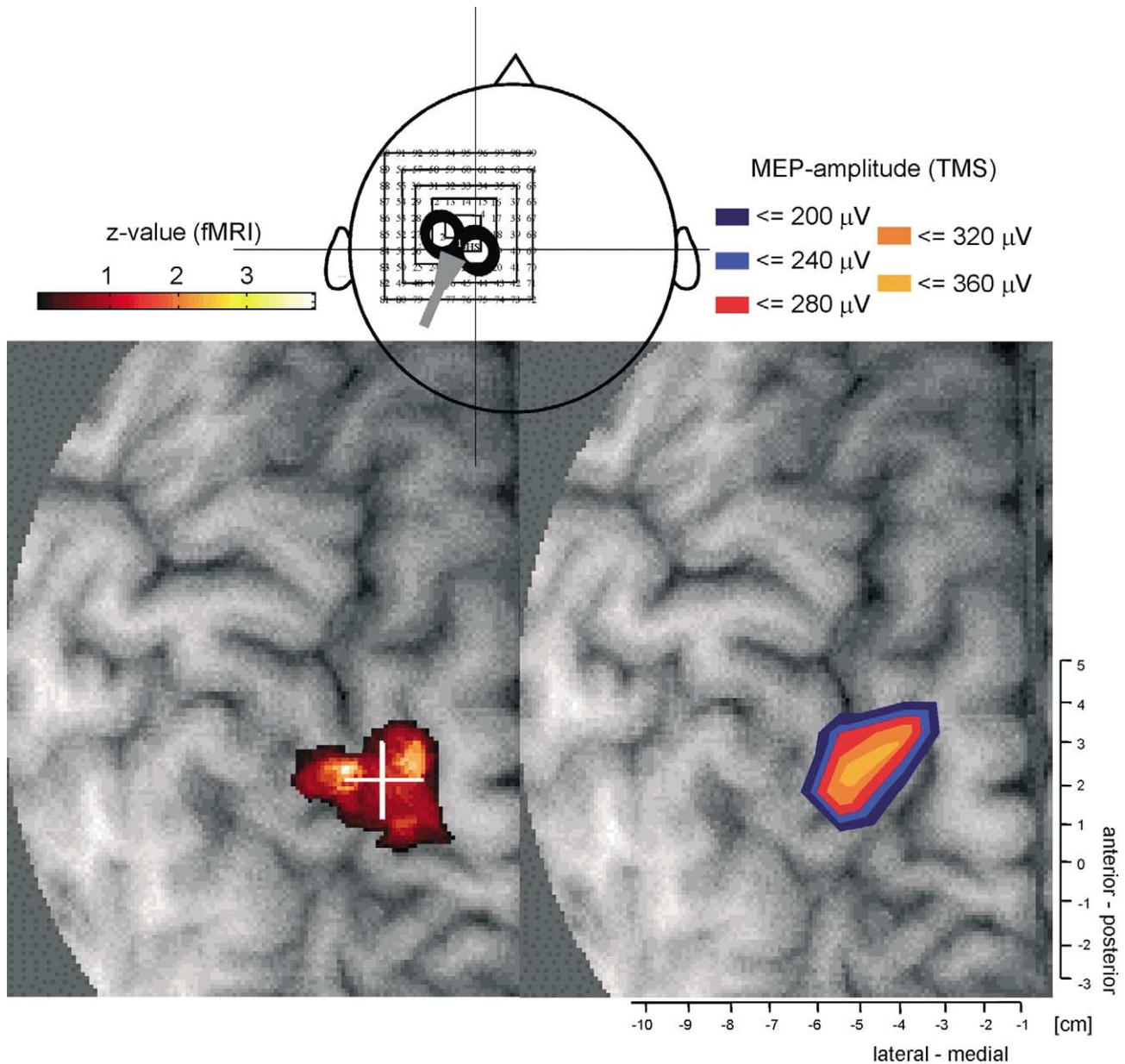


Fig. 1. Comparison of map-sizes: example of one subject showing the fMRI-map size with a cut-off of  $P < 0.001$  (left) and the TMS-map size (right) with a cut-off of  $200 \mu\text{V}$  of the thumb movement (abductor pollicis brevis). The white cross indicates the center of gravity of the fMRI representational area. Top demonstrates the mapping procedure for TMS (circular clockwise from the highest MEP site) and the corresponding MEP amplitude (color coded).

20% of the maximum field strength in the vicinity of the coil junction (Eaton, 1992). As a consequence, TMS motor thresholds are higher and MEP amplitudes are smaller in these muscles compared to recordings from more distal hand muscles such as the extensor carpi radialis or the abductor pollicis brevis.

After 2D projection the radial part of the distance differences is completely eliminated and only the tangential part is observed. The tangential part may include effects of the relative coil and neural fiber orientation and therefore also the 2D-representation site is not in complete spatial coherence. It is obvious that the cortex projection provides smaller differences in distance than the scalp projection since

given the angular separation between TMS and fMRI maxima, the larger radius of the scalp results in larger distance differences after the projection. After projection 4 out of 5 TMS-representational sites were located anterior to the fMRI activation maxima. This systematic difference between both mapping methods has been observed previously: Terao et al. (1998) measured largest MEP amplitudes when stimulating the scalp overlying the anterior lips of the precentral gyrus, i.e. slightly anterior to the somatotopic height of the fMRI-activation maxima. They hypothesized that this topographical difference in the location of activation maxima may be due to the orientation of the magnetic field induced by the current in the coil which

Table 1  
Distances between representational sites evaluated with TMS and fMRI in mm and TMS results

	Tibialis anterior foot elevation	Extensor carpi radialis hand elevation	Abductor pollicis brevis thumb abduction	Average
3D <sup>a</sup> : HS to AM	35.4	24.5	23.9	27.9
2D <sup>b</sup> (cortex): HS to AM	9.9	15.3	16.6	13.9
2D <sup>b</sup> (scalp): HS to AM	14.2	21.5	18.6	18.1
2D <sup>b</sup> (scalp): COG to AM	12.1	19.0	18.8	16.6
TMS motor threshold (%)	56.8	32.5	34	
TMS MEP <sup>c</sup> ( $\mu$ V)	155.8	124.3	211.8	
TMS area <sup>d</sup> (cm <sup>2</sup> )	14.3	21.9	15.1	

<sup>a</sup> Absolute distances evaluated in 3D-space between TMS highest MEP site (HS) and the fMRI activation maxima (AM).

<sup>b</sup> Distances after projection of the TMS HS or center of gravity (COG) onto the cortical surface or the scalp to fMRI AM.

<sup>c</sup> Amplitude of MEPs elicited with TMS at the hot spot.

<sup>d</sup> Area size of the whole map elicited with TMS (cut-off: 50  $\mu$ V).

may more effectively stimulate fibers running parallel to the magnetic field. This systematic distance between both methods induced by maximal effect of coil position in relation to neuronal structures has also been described by Herwig et al. (2002) using a neuronavigational system. By usage of such a system in patients with mass lesions near the central sulcus, distances between the peak parenchymal fMRI activation and the cortical area where TMS elicited the maximum MEPs ranged between 0 and 1.2 cm (Krings et al., 2001).

Representation sites between the same types of movements were significantly smaller than those between different movements. This fact showed also to be true for intralimb representation sites but – probably due to the small sample size – specificity of mapping localization was not significant if each movement type was tested for its own distance differences.

Whereas the location of maximal MEP has a functional relevance and together with localization on the patients MR imaging is especially attractive for presurgical mapping, the evaluation of map sizes with TMS seems to be a somewhat artificial parameter. The maps obtained with TMS have a maximum which is roughly coincident with their center and shows progressively degrading responses 360° around the center. As shown in Fig. 1 this is not the case with fMRI: maps may consist of several activation maxima and the COG may be located in between these. TMS is activating all excitable circuits within the volume reached by the induced current, whereas fMRI measures increased oxygen supply in capillaries adjacent to neural firing. A direct comparison of map sizes between both methods – as is possible with our method – is therefore not practically relevant.

In conclusion, motor cortical representational sites as assessed by TMS and fMRI are located close to each other but are not identical. Our findings support the notion that fMRI and TMS provide complementary information as to the status of the motor cortex. In particular, the present study demonstrated that TMS variables such as motor thresholds and maximum MEP amplitudes depend, to a large extent, on the absolute distance between the excitable

motor cortex tissue and the site of stimulation in 3D space. A 2D comparison of somatotopic representation maps as assessed by fMRI and TMS within the EEG-reference system can be performed by the method described here. Since reorganization mechanisms have been observed in these two methods together (Macdonell et al., 1999), the combination of both may be of benefit.

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