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Functional magnetic resonance imaging and transcranial magnetic stimulation: Effects of motor imagery, movement and coil orientation

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Abstract

Objective: To compare fMRI activations during movement and motor imagery to corresponding motor evoked potential (MEP) maps obtained with the TMS coil in three different orientations.

Methods: fMRI activations during executed (EM) and imagined (IM) movements of the index finger were compared to MEP maps of the first dorsal interosseus (FDI) muscle obtained with the TMS coil in anterior, posterior and lateral handle positions. To ensure spatial registration of fMRI and MEP maps, a special grid was used in both experiments.

Results: No statistically significant difference was found between the TMS centers of gravity (TMS CoG) obtained with the three coil orientations. There was a significant difference between fMRI centers of gravity during IMs (IM CoG) and EMs (EM CoG), with IM CoGs localized on average 10.3 mm anterior to those of EMs in the precentral gyrus. Most importantly, the IM CoGs closely matched cortical projections of the TMS CoGs while the EM CoGs were on average 9.5 mm posterior to the projected TMS CoGs.

Conclusions: TMS motor maps are more congruent with fMRI activations during motor imagery than those during EMs. These findings are not significantly affected by changing orientation of the TMS coil.

Significance: Our results suggest that the discrepancy between fMRI and TMS motor maps may be largely due to involvement of the somatosensory component in the EM task.

Keywords: fMRI; BOLD; TMS; CoG; Motor cortex; Motor imagery

1. Introduction

Transcranial magnetic stimulation (TMS) is a method that allows for noninvasive stimulation of neurons in localized regions of cortex (Lazzaro et al., 2004). It is widely used as a research tool in neurosciences and therapeutic management of patients with a variety of neuro-psychiatric disorders (Schlaepfer et al., 2003; Tassinari et al., 1990). However, with almost two decades of TMS use since it was introduced by Barker et al. (1985), the exact stimulation site on the cortex remains under debate despite multiple attempts to define it (Epstein et al., 1990; Terao et al., 1998; Thielscher and Kammer, 2002). This stimulation site, or TMS maximum, is the point of maximum electric field, running along the line perpendicular to the center of the figure-of-eight coil (Kobayashi and Pascual-Leone, 2003). Knowledge of TMS maximum is crucial to accurate positioning of the coil in studying normal and pathological cerebral functions.

Functional magnetic resonance imaging (fMRI) has been used to study the cortical effects of TMS noninvasively because of its high spatial and temporal resolution (Brett et al., 2002). fMRI measures the hemodynamic correlates of neural activity (Ogawa et al., 1992) and allows for mapping functional activity and connectivity in humans (Matthews and Jezzard, 2004). In fMRI experiments, fast sequences

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such as echoplanar imaging (EPI) techniques are used to measure changes in the blood oxygenation level dependent (BOLD) contrast as the result of brain activity (Ramsey et al., 2002) and activation maps are derived from the BOLD images.

Functional neuroimaging techniques such as fMRI and positron emission tomography (PET) have been used to examine cortical activity before, during and after the application of TMS. Some investigators used fMRI to localize areas of cortical activation during task performance, then utilized the cortically active areas as markers for positioning a TMS coil (Neggers et al., 2004). Others simultaneously recorded cortical activity by interleaving TMS and fMRI thus revealing the brain's direct responses to TMS as well as intracerebral functional connectivity of the stimulated areas (Bohning et al., 1999; Paus et al., 1997). The long-term effects of TMS on brain activation were investigated using functional imaging immediately post-stimulation which led to empirical insights into functional cortical plasticity (Siebner et al., 2001).

One consistent finding in the studies that combined fMRI and TMS was the discrepancy of the maps generated by TMS targeting the primary motor cortex and fMRI of brain activity during motor movement (Bastings et al., 1998; Bohning et al., 2001; Boroojerdi et al., 1999; Krings et al., 1997a,b). These authors reported a mismatch of 4–22 mm between TMS centers of gravity (TMS CoG) and fMRI activation maximae. The most recent studies which showed the mismatch of 4.14 (Neggers et al., 2004), 10 (Herwig et al., 2002) and as high as 13.9 mm (Lotze et al., 2003) indicated that the cortical sites corresponding to the scalp TMS CoGs were consistently anterior to the fMRI activation maximae.

One plausible explanation for the TMS CoGs to be located anterior to the fMRI activations may be the presence of a somatosensory component in the BOLD activity during overt movements. In a recent review, Lafleur et al. (2002) compared the BOLD activity during imagined movements (IM activation) to that during the executed movements (EM activation), in studies conducted with fMRI, PET and single photon emission computed tomography (SPECT). Many of these studies demonstrated activation of several cortical regions including the primary motor cortex (M1), supplementary and cingulate motor areas and dorsal premotor cortex during both EMs and IMs (Binkofski et al., 2000; Gerardin et al., 2000; Kuhtz-Buschbeck et al., 2003; Naito et al., 2002; Porro et al., 1996). On the other hand, in addition to M1, EMs activated primary sensory (S1) and sensorimotor (SM) areas, whereas in most studies IMs activated only M1 (Lotze et al., 1999; Porro et al., 2000; Roth et al., 1996).

Another potential explanation for the mismatch between the TMS and fMRI motor maps may be the influence of TMS coil orientation which determines direction of the induced current with subsequent differential affects on underlying neuronal elements (Lazzaro et al., 2004; Sakai et al., 1997). Changing the coil orientation affects MEP amplitudes and stimulation threshold and therefore can result in different TMS maps (Guggisberg et al., 2001).

In the present study, we compared BOLD activations during IMs and EMs with TMS-evoked MEPs of the first dorsal interosseus (FDI) muscle in order to explicitly examine the contribution of the somatosensory component of EMs. In this study, three coil orientations were used, corresponding to anterior–posterior, posterior–anterior and lateral–medial directions of the induced tissue current, and differences between resultant MEP maps were examined.

2. Methods

Six right-handed healthy volunteers (three males and three females, aged 21–29 years, average 23.2) with no known neurological or psychiatric abnormalities participated in this study. All study procedures were approved by the local institutional review board and written informed consent was obtained from each participant. The study consisted of two parts: an fMRI experiment immediately followed by a TMS experiment.

2.1. fMRI experiment

Block-design paradigms consisting of periods of rest, EM and IM, each lasting 20 s, were used in BOLD scanning. The first scan included six repetitions of EM-rest–IM-rest, the second scan had six repetitions of IM-rest, and the third scan consisted of four repetitions of EM-rest. Prior to scanning, the subjects practiced the paradigm outside the magnet according to instructions on a computer. They were instructed to abduct their right index finger once per second for 20 s and stop when prompted by a cue. Following a 20 s rest, the subjects were instructed to imagine abducting their right index finger by trying to imagine only the motion of the finger as much as possible rather than visualizing or feeling the moving finger. Each subject was required to practice the entire paradigm at least once until he or she was able to perform the task successfully. Two volunteers requested to practice twice. Each subject was closely observed by the investigators to ensure the pace of 1 Hz during EMs and absence of any visible contractions during IMs.

Then the participant's head was fitted with an elastic swimming cap (Speedo® International Ltd, Nottingham, UK) specially equiped by the authors with 45 4 mm vitamin E capsules (BrainLAB, Heimstetten, Germany). The capsules were attached to the left side of the cap corresponding exactly to a 1×2 cm grid of stimulation points which was later used for the motor cortex mapping by TMS. Additional orienting fiducial markers, used for cap measurements and positioning, were affixed to four points on the cap, corresponding to the nasion, bilateral preauricular spaces and inion. Vitamin E capsules are commonly

utilized to indicate standard reference points in MRI. They have been used to project TMS CoG scalp location onto the cortex on MR images (Herwig et al., 2002; Lotze et al., 2003) and coregister image space with physical space in order to navigate a TMS coil to loci of fMRI activity (Neggers et al., 2004). Coordinate points inscribed on the elastic caps have been frequently used to provide the grid reference points for subsequent placing of TMS coils (Bastings et al., 1998; Bohning et al., 2003). Although stretching of the cap varied depending on head size in our study, it remained constant between the TMS and fMRI sessions in each participant and therefore did not affect the accuracy of coregistration. Furthermore, all CoGs were transformed into the Talairach (TAL) space (Talairach and Tournoux, 1988) allowing for inter-subject averaging.

The cap was placed with the vertex fiducial marker matching the vertex of participant's skull, determined prior to the cap placement by measuring distances between the nasion, inion and bilateral preauricular spaces. Following the cap placement, the participant was placed supine on the MRI table. The right hand was stabilized to ensure the sole action of the FDI muscle responsible for abduction of the index finger. The thumb and digits 3–5 were taped to the ventral aspect of the right thigh to minimize movements of these fingers during the index finger abductions.

2.2. Set-up

While inside the scanner, volunteers viewed the computer display via backprojection onto a screen placed on the scanner table. The command sequence was generated by means of a stimulus delivery program (Presentation, Neurobehavioral Systems Inc, San Francisco, CA) which displayed words every 20 s, prompting the participants to either rest, move or imagine moving their right index finger as they did during the practice exercises. The participants were observed during scanning to ensure the proper performance of the task paradigm. Hardware limitations did not allow monitoring of electromyography (EMG) during task performance. Special attention was given to ensure no visible movements occurred in either right or left index finger during the imagined task.

2.3. Imaging protocol

All fMRI experiments were performed on a 3.0 T whole-body MR scanner (Magnetom Trio, Siemens, Erlangen, Germany). A single-shot gradient-echo EPI sequence was used to acquire T2*-weighted images over 28 oblique axial slices covering the upper two thirds of the brain with a 2000 ms TR, a 35 ms TE, a 90° flip angle (FA), a matrix of 64×64, a 3 mm slice thickness with no gap, a field of view (FOV) of 220 mm, and a bandwidth (BW) of 1816 Hz/pixel. Structural T1-weighted MRI scan was obtained to allow for anatomic overlay with fMRI and three-dimensional (3D) projections of TMS CoGs from the scalp to the cortex, using an MPRAGE sequence (192 contiguous sagittal slices, 2600 ms TR, 3.93 ms TE, 900 ms TI, 256 mm FOV, 8° FA, 256×256 matrix, 1 mm slice thickness and 130 Hz/pixel BW).

In addition, a venogram was collected in each volunteer to determine anatomy of the large draining veins with a gradient echo sequence (64 contiguous sagittal slices, 21 ms TR, 4.12 ms TE, 240 mm FOV, 30° FA, 320×512 matrix, 3 mm thickness with no gap and 188 Hz/pixel BW).

2.4. fMRI Data analysis

Statistical analysis of the activation data, and visualization was carried out using Brain Voyager 4.9 (Brain Innovation, Maastricht, The Netherlands). The raw fMRI data was first preprocessed with 3D motion correction (trilinear interpolation; spatially realigning functional images to the first image of a serial acquisition), temporal data smoothing (high pass filter at the frequency of 1.5 Hz) and slice scan time correction. Activated pixels were identified using the general linear model (Bandettini et al., 1993; Friston et al., 1995) by cross-correlating the hemodynamic response corresponding to the task paradigm and the time course of each pixel to identify pixels exhibiting significant task-related intensity change. Statistically significant differences between the BOLD responses during the task and rest periods were assessed with the threshold of $P<0.01$ (corrected). Locations of the central sulcus and primary motor and sensory cortices were identified from anatomical MR images based on sulcal markers (Ono et al., 1990; Yousry et al., 1997). fMRI centers of gravity (fMRI CoG) were defined by the average of coordinates of the activated pixels in the areas delineated as described above. A paired t test was used to determine whether there was a statistically significant difference between locations of fMRI CoG during IMs (IM CoG) and EMs (EM CoG). Venograms were superimposed on fMRI activation maps, allowing us to rule out activated pixels located in the large draining veins.

2.5. TMS experiment

Following the fMRI experiment, the participant was accompanied to the TMS lab with the cap remaining at its initial location. Before beginning the TMS experiment the 45 fiducial markers were removed from the cap while four orienting fiducial markers were kept in place. Extra care was taken to maintain cap alignment. Removal of the fiducial markers revealed the underlying 1×2 cm grid that served as reference points for subsequent TMS mapping.

To maintain consistent cap placement throughout the experiment, detailed distance recordings were made from the nasion, inion, and bilateral preauricular spaces to the vertex and orienting fiducial markers. These measurements were checked frequently throughout the experiment to ensure absence of cap movement. The grid was referenced

relative to standard landmarks according to the international 10–20 system (Herwig et al., 2003). The choice of grid dimensions was based on the fact that the electric field gradient induced by a figure-of-eight coil in the direction along the coil centers changes more gradually than in the perpendicular direction (Chen et al., 2003; Röricht et al., 1999). The magnitude of the difference between adjacent points is therefore comparable in both dimensions. We adopted this previously-established grid technique to reduce time required to produce TMS maps in three coil orientations in order to avoid subject fatigue and potential increase in MEP variability.

The TMS experimental design and data collection methods were used as described previously (Butler and Wolf, 2003). Briefly, stimulation of the left hemisphere at the motor cortex using a 9 cm diameter figure-eight coil MAGSTIM 200 (Magstim Company Ltd, Whitland, Dyfed, UK) was performed in a systematic fashion at 0.2 Hz). An X-ray of the coil revealed the midpoint of its copper windings to be centered at the intersection of the coil which was important for accuracy of the current direction and therefore TMS maps. The intersection of the coil was positioned depending on its orientation. The coil held with the handle pointing anterior resulted in anterior–posterior (AP) current and electric field (E-field) perpendicular to the central sulcus. The handle pointing lateral resulted in lateral–medial (LM) current and E-field parallel to the central sulcus. The handle pointing posterior yielded posterior–anterior (PA) current and E-field perpendicular to the central sulcus (Brasil-Neto et al., 1992; Kobayashi and Pascual-Leone, 2003). We therefore obtained three separate TMS maps by using the three coil orientations. A 45° coil handle orientation was not used because coil directions parallel to a line drawn on the cap in the AP, PA or perpendicular to AP axes were more reproducible.

One investigator performed the stimulation, while the other monitored the EMG recordings for all sessions. Each investigator performed the same duties throughout the study which has been shown to decrease experimenter variability (Butler and Wolf, 2003). A manual muscle test during abduction of the right index finger was performed to isolate the FDI muscle and subsequent determination of optimal surface electrode placement (Hislop and Montgomery, 1995). Skin surface over the FDI on the right hand was abraded with Lemon Prep® (Faith Medical, Inc., Steedman, MO) and alcohol until an erythemic response appeared. Recording electrodes (Medtronic Adhesive Disposable Surface Electrodes, 7×4 mm) were placed on the skin over the right FDI muscle bellies with their centers approximately 5 mm apart. A ground reference electrode was applied ipsilaterally around the circumference of the elbow joint. Skin impedance between recording electrodes and between each recording electrode and the ground was kept below 2 and 20 kΩ (kilo-ohms), respectively.

Prior to each mapping procedure, preparatory measurements were made to determine appropriate TMS parameters for each participant. The hotspot for motor stimulation was defined as the grid location where the motor threshold was the lowest while evoking the largest response (Chen et al., 2003). Stimulus sites were located according to the 1×2 cm grid. Resting motor threshold (RMT) for the hotspot was defined as the minimum TMS intensity required to elicit at least five motor evoked potentials (MEP $\geq$ 50 μV) in 10 consecutive trials and was determined by stimulating over the motor area of the left hemisphere at the frequency of 0.2 Hz according to well-established techniques (Epstein et al., 1990).

In order to reduce unwanted head movement (e.g. head tilting), the investigator placed his hand on the side opposite to the TMS coil to counterbalance its weight. Audio speakers provided feedback to the participant to assure relaxation of the FDI muscle during the mapping procedure. Single TMS pulses at 110% RMT of the right FDI muscle were delivered to the scalp positions according to the $1\times$ 2 cm grid beginning at the hotspot and then proceeding to surrounding grid points. Each scalp position was stimulated 10 times. MEP amplitude for each scalp position was determined as the mean amplitude from 10 recordings. The grid point was considered active if the TMS stimulations resulted in five out of 10 MEPs $\geq$ 50 μV. This procedure was performed in the three coil orientations resulting in three motor maps for the FDI. Every attempt was made to hold the coil tangential to the skull in all three orientations. Each motor map took approximately 35 min, and, with the MT measurements, the average total duration of the TMS session was 2 h.

2.6. TMS data analysis

For each coil orientation, the TMS CoG was determined by the center of mass of the MEP distribution on the grid (Wassermann et al., 1992). TMS CoG has been shown to yield an accurate estimate of the location on the scalp directly overlying the region of maximum neuronal excitability (Boroojerdi et al., 1999; Classen et al., 1998). A paired *t* test was applied to test for differences in CoG coordinates between pairs of coil orientation. Similarly, a paired *t* test was used to assess whether RMTs, measured at the hotspots were dependent upon coil orientation. For all tests, the alpha level was set to 0.05. Because these tests did not show statistically significant differences between scalp CoGs for three coil orientations, subsequent analysis in each participant was based on a centroid (X_c,Y_c) calculated by averaging coordinates of the three CoGs.

2.7. Coregistration of fMRI and TMS maps

Transformation of the scalp TMS CoGs to the imaging space of each subject was achieved based on the 3D anatomic images using Brain Voyager as follows. In each participant, the image space coordinates (x,y,z) of the TMS CoG were established based on its location relative to

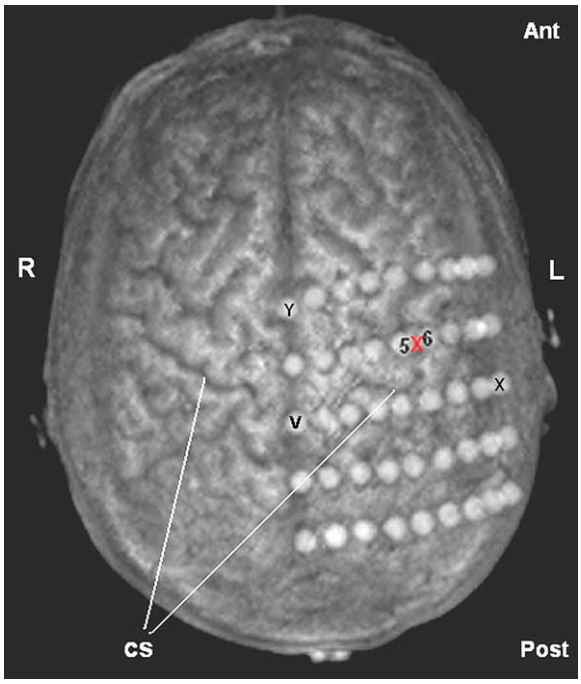

Fig. 1. 3D axial view showing the white fiducial markers arranged in the 1×2 cm grid used for the TMS mapping. Vertex (V) has scalp coordinates (0, 0) and all fiducials are separated by 1 cm along the *X*-axis (*X*) and 2 cm along the *Y*-axis (*Y*). Red cross corresponds to the TMS CoG with the scalp coordinates of (5.5, 1.0) and imaging space coordinates (174, 139, 64) and is located half-way between the bases of the markers 5 and 6 with the scalp coordinates (5, 1) and (6, 1) and imaging space coordinates (172, 139, 61) and (180, 139, 67), respectively. R and L—right and left sides, respectively. CS—central sulcus.

the fiducial markers on the anatomic images. For example, TMS mapping in one participant yielded the TMS CoG at the grid location of (5.5, 1.0) which was half-way between the bases of fiducial markers (5, 1) and (6, 1) as shown in Fig. 1. The imaging space coordinates of the fiducial markers (5, 1) and (6, 1) were (172, 139, 61) and (180, 139, 67), and the coordinates of the TMS CoG were given by their average (174, 139, 64).

2.8. Projection of TMS CoG onto the cortex

Sagittal and coronal views through the TMS CoG were extracted from the 3D anatomic data. In each view, a line through the CoG and tangent to the contour of the scalp was formed (Fig. 2).

The CoG was then projected towards the cortex for 2 cm along a line perpendicular to the plane defined by the tangential lines in the sagittal and coronal views. The distance of projection was chosen based on previous reports that the TMS affected cortical area, as measured from the center of the coil, was maximally 17–18 mm (Epstein et al., 1990) or 18.1–20.9 mm deep (Rudiak and Marg, 1994) and that TMS sites further than 2 cm from the cortical surface did not produce MEPs (Krings et al., 1997a,b)).

For inter-subject averaging, the fMRI and TMS CoGs of each subject were transformed to his or her own TAL coordinate system. This transformation did not affect the CoG comparisons (EM vs. IM CoG and fMRI vs. TMS CoG) in the same subject.

3. Results

3.1. TMS mapping

There were no systematic changes of the MEP amplitudes during the experiments as the subjects were carefully monitored for any changes in alertness. The TMS experiments indicated individual variations in the maps of the right FDI muscle including RMTs and TMS CoG scalp locations depending on the orientation of the TMS coil (Table 1 and Fig. 3).

The RMT values obtained with the coil in anterior handle position were significantly higher than those with the coil in lateral ($P=0.027$) and posterior ($P=0.007$) handle positions. However, there was no statistically significant difference in the RMT values between the lateral and posterior handle positions ($P=0.17$). The coil in posterior

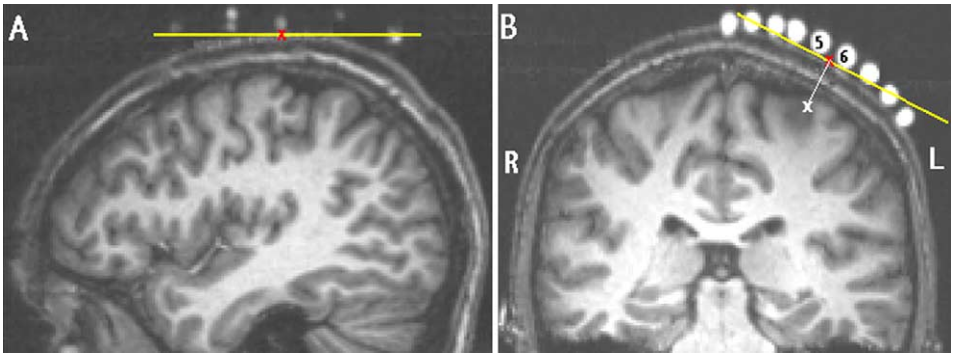

Fig. 2. Sagittal (A) and coronal (B) views showing the lines in two perpendicular planes tangential to the scalp at the TMS CoG (red cross). The TMS CoG with scalp coordinates (5.5, 1.0) and imaging space coordinates (174, 139, 64) is projected towards the cortex for 2 cm along the line perpendicular to the calculated tangential plane which defines the TMS CoG cortical projection point (white cross) with TAL coordinates (162, 140, 74). R and L—right and left sides, respectively.

Table 1
Scalp coordinates (*x*,*y* in centimeters from vertex) of the individual TMS CoGs and their centroids and RMTs (in percent of stimulator output) across all six volunteers obtained by mapping in the three coil orientations with anterior, lateral and posterior handle positions

Volunteer	Anterior handle		Lateral handle		Posterior handle		TMS CoG Centroid
	TMS CoG	RMT	TMS CoG	RMT	TMS CoG	RMT	
1	(5.9, 0.9)	74	(5.5, 1.0)	55	(6.3, 0.6)	53	(5.9, 0.8)
2	(6.0, 1.0)	61	(6.4, 1.3)	55	(6.0, 1.3)	46	(6.1, 1.2)
3	(5.9, 1.0)	58	(5.2, 1.0)	56	(5.5, 0.9)	44	(5.5, 1.0)
4	(5.8, 1.2)	52	(5.1, 1.2)	48	(5.4, 0.7)	38	(5.4, 1.0)
5	(5.4, 1.5)	62	(5.0, 1.0)	48	(5.6, 1.1)	57	(5.4, 1.2)
6	(6.1, 0.8)	52	(6.1, 0.9)	44	(5.2, 0.7)	43	(5.8, 0.8)

handle position elicited significant MEPs at the lowest RMT. The distances between the calculated scalp coordinates of the TMS CoGs among all three coil orientations failed to achieve statistical significance ($P=0.12$, 0.1, 0.09 between anterior–posterior, anterior–lateral, lateral–posterior handle positions, respectively).

3.2. fMRI activity and comparison of TMS and fMRI maps

Our results demonstrated low intrasubject variation across all six subjects (Table 2), suggesting that the TAL normalization used in this study is consistent across subjects.

The center of the fMRI activity averaged among all volunteers was located in the left precentral gyrus. The TMS CoG cortical projection sites were on average 1.2 ± 1.2 mm medial to the IM CoGs and 9.5 ± 1.2 mm antero-medial to the EM CoGs (Fig. 4). The IM CoGs were registered on average 10.3 ± 1.2 mm anterior to the EM CoGs and closer to the precentral sulcus.

Regardless of the paradigm used (EM-rest–IM-rest, IM-rest or EM-rest) or number of blocks within each paradigm, the locations of IM and EM CoGs remained the same. The IM CoGs were also less robust with the activated area of approximately half the size of the EM CoGs (IM 344 ± 10 vs. EM 714 ± 10 pixels, $t=2.26$, $P=0.027$).

Venograms showed variations in each participant's venous network. However, none of the BOLD signals of interest were located within the large draining veins which would otherwise denote false-positive activation (Rostrup et al., 1995).

4. Discussion

fMRI and TMS maps have been consistently reported to have a 4–22 mm mismatch when fMRI and TMS were performed separately (Herwig et al., 2002; Krings et al., 1997a; Lotze et al., 2003; Neggers et al., 2004; Terao et al., 1998,). The best match (4.14 mm) was reported by Neggers et al. (2004) who used BOLD activity to guide their TMS experiments. Their improved match could be possibly attributed to the bias introduced by TMS mapping around the center of activity predefined by fMRI response as a result of finger movements.

Most investigators attempted to explain the incongruence of fMRI and TMS maps by focusing on some aspects of the TMS mechanisms. Lotze et al. (2003) state that TMS maps have a maximum which decays isotropically while fMRI

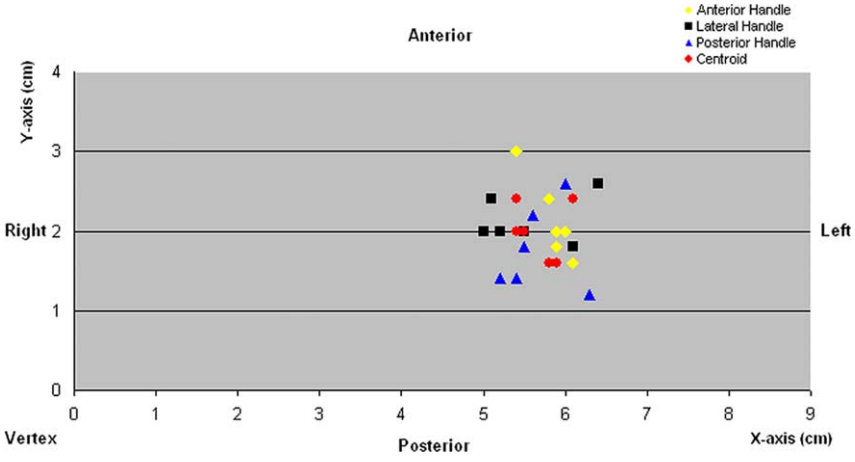

Fig. 3. Graph of the scalp coordinates of individual TMS CoGs and centroids calculated from the MEP maps obtained by TMS mapping with the coil in the three handle positions. *X*- and *Y*-axes are in centimeters with vertex at (0, 0). Orientation is the same as in Fig. 1.

Table 2
TAL coordinates (*x*,*y*,*z*) with their means and standard deviations (SD), of the scalp and projected TMS CoG centroids, EM and IM CoGs and activation peaks

Subject	Scalp TMS CoG Centroid	Projected TMS CoG Centroid	EM CoG	EM activation peak	IM CoG	IM activation peak
1	(−48, −11, 64)	(−35, −12, 54)	(−36, −21, 54)	(−38, −22, 54)	(−35, −11, 54)	(−34, −9, 54)
2	(−46, −11, 65)	(−34, −13, 55)	(−35, −22, 55)	(−37, −23, 56)	(−36, −12, 55)	(−38, −12, 55)
3	(−44, −10, 65)	(−37, −13, 53)	(−38, −21, 53)	(−39, −21, 53)	(−37, −12, 53)	(−37, −11, 54)
4	(−45, −9, 66)	(−35, −10, 55)	(−36, −20, 55)	(−38, −22, 54)	(−35, −9, 55)	(−37, −11, 53)
5	(−46, −10, 67)	(−35, −13, 55)	(−36, −23, 55)	(−37, −24, 55)	(−36, −12, 55)	(−38, −14, 53)
6	(−47, −10, 66)	(−36, −11, 53)	(−38, −21, 53)	(−40, −23, 52)	(−37, −12, 53)	(−38, −14, 52)
Mean ± SD	(−46.0 ± 1.4, −10.2 ± 0.7, 65.5 ± 1.1)	(−35.3 ± 1.0, −12.0 ± 1.3, 54.2 ± 1.0)	(−36.5 ± 1.2, −21.7 ± 1.2, 54.2 ± 1.0)	(−38.2 ± 1.2, −22.5 ± 1.1, 54.0 ± 1.4)	(−36.0 ± 0.9, −11.3 ± 1.2, 54.2 ± 1.0)	(-37.0 ± 1.5, −12.3 ± 1.4, 53.2 ± 1.2)

maps consist of several activation foci with an fMRI CoG located between them. They also argue that TMS activates cortical circuits within the volume of tissues affected by the induced current, whereas fMRI measures BOLD response in capillaries adjacent to neuronal firing. However, these arguments do not explain the large discrepancy between fMRI and TMS maps since the above factors could only cause a difference of a few millimeters. Terao et al. (1998) hypothesized the mismatch between fMRI and TMS CoGs might be due to orientation of the magnetic field induced by the current in the coil. However, our experimental data revealed that there was no significant difference between

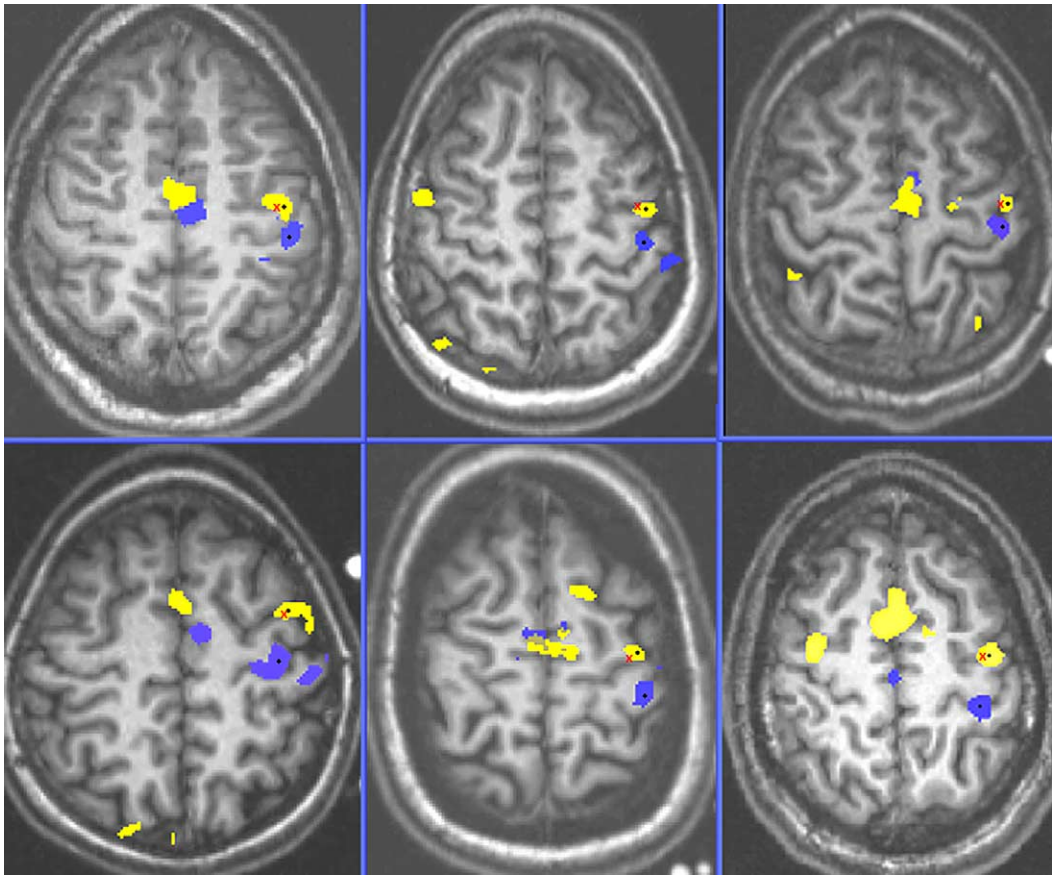

Fig. 4. Representative same-level axial anatomic slices of the superimposed EM and IM activation maps in all six participants (A–F). Blue and yellow activations correspond to the BOLD maps during EMs and IMs, respectively. Red crosses represent the TMS CoG cortical projection points. Black dots denote the EM and IM CoGs. In the first subject (A), the TMS CoG is 1 mm medial to the IM CoG and 9.3 mm antero-medial to the EM CoG. In the second subject (B), the TMS CoG is 1.8 medial to the IM CoG and 9.1 mm antero-medial to the EM CoG. In the third subject (C), the TMS CoG is 1 mm medial to the IM CoG and 8.3 mm antero-medial to the EM CoG. In the fourth subject (D), the TMS CoG is 0.9 mm postero-medial to the IM CoG and 10.2 mm anterior to the EM CoG. In the fifth subject (E), the TMS CoG is 1.9 mm medial to the IM CoG and 10 mm antero-medial to the EM CoG. In the sixth subject (F), the TMS CoG is 1 mm medial to the IM CoG and 10.4 mm antero-medial to the EM CoG. L, R, Ant and Post—left, right, anterior and posterior sides, respectively, in all figures.

TMS CoGs obtained with different coil orientations, demonstrating that coil orientation did not account for the large mismatch between TMS and fMRI.

In consistency with previously reported results, our study also demonstrated a discrepancy between the EM and TMS CoG, with the former 1 cm posterior to the TMS CoG. In contrast, the IM CoG which was 1 cm anterior to the EM CoG, closely agreed with the TMS CoG. This result strongly suggests that the previously reported discrepancy between fMRI and TMS may be due to the somatosensory component of the EMs although this remains to be systematically tested. Most authors reporting the discrepancy failed to account for the sensory contribution in their paradigm, which might have resulted in the posterior shift of EM CoG towards the sensory areas (Bastings et al., 1998; Boroojerdi et al., 1999; Lotze et al., 2003; Neggers et al., 2004; Terao et al., 1998). Krings et al. (1997a,b) reported a somatotopic shift of the fMRI activations relative to the TMS maps of the FDI and flexor carpi radialis (FCR) muscles, however, these authors did not indicate the magnitude of the shift and whether it was statistically significant. Herwig et al. (2002) discussed the somatosensory involvement in the BOLD activation as one of the possible contributors to the mismatch without actually demonstrating or measuring such involvement in their study.

One of the plausible explanations for a good match between the IM and TMS CoGs in our study is involvement of subliminal muscle contractions during the IMs. Subliminal contractions could not be ruled out directly in our study since EMG was not performed inside the scanner due to hardware limitations. To address this issue, task paradigms with different likelihood of subliminal muscle contractions were used in the fMRI experiments, and the resulting consistency of the activation for these paradigms indirectly suggests an absence of subliminal contractions.

All projected TMS CoGs lie within the left precentral gyrus and on average slightly anterior to the hand knob. We hypothesize that TMS might activate several neuronal populations within the primary motor cortex. According to prior reports (Geyer et al., 1996; Kawashima et al., 1995; Roland and Zilles, 1996; Scheiber, 2001) there are several somatotopic zones within the primary motor cortex that can represent the limb areas. Specifically Schieber (2001) reviewed studies with cortical surface stimulation and intracortical microstimulation which showed that each finger could be excited in several areas of the precentral gyrus including those anterior to the hand knob. Geyer et al. (1996) described two histophysiological zones within the motor cortex of the precentral gyrus—Broadmann areas 4a (anterior) and 4p (posterior). They performed a PET study including imagined and executed movements of the fingers and found the IM and EM activations to be in the 4a and 4p areas, respectively. Therefore, it is possible that TMS in our experiments stimulated the FDI muscle via cortical somatotopic zones anterior to the hand knob.

TAL normalization allowed us to summarize the results in all subjects in a common coordinate system. Limitations of TAL normalization are well known and may lead to errors in inter-subject averaging in this study. While the errors can be potentially large, the fact that the TAL fMRI and TMS CoGs of all subjects exhibited negligible variation provides support for the validity of the normalization. It is also worth noting that the normalization is not needed in data processing and CoG comparison in individual subjects, and the conclusions arrived based on inter-subject averaging could also be drawn, semi-quantitatively, from CoG comparisons in individual subjects without the normalization. Another potential source of error may arise from the B0-inhomogeneity induced spatial distortion in EPI images, which could be much more severe than that in T1-weighted anatomic images. Fortunately, in the sensorimotor cortex, B0 is highly homogeneous and spatial distortion in EPI is relatively small.

While calculation of the tangent plane in our projection method was somewhat subjective, the main factor that affected the accuracy was the definition of tangential lines in the coronal and sagittal images. In our work, this task was performed by a single investigator to maintain consistency and reduce inter-observer variability. Therefore, we believe the evaluator dependence is negligible. While some authors have used automated techniques such as Brainsight frameless stereotaxy (Fernandez et al., 2001) and neuronavigation (Herwig et al., 2002; Neggers et al., 2004), many authors used projection methods not based on automated techniques, in comparing TMS and fMRI motor maps (Erb et al., 1999; Lotze et al., 2000, 2003; Nickerson et al., 2001; Terao et al., 1998). Since our results comparing EM and TMS CoGs agree with those previously obtained with (Herwig et al., 2002; Neggers et al., 2004) and without (Lotze et al., 2003; Terao et al., 1998) automated techniques, such techniques do not appear to be critical in the type of study comparing TMS and fMRI motor maps.

In conclusion, our results demonstrate that IM CoG closely matches cortical site of projected TMS CoG while EM CoG is shifted posteriorly probably as the result of somatosensory signal. These findings are not significantly affected by changing TMS coil orientation or improvement in spatial specificity.

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