Physiological observations validate finite element models for estimating subject-specific electric field distributions induced by transcranial magnetic stimulation of the human motor cortex

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Abstract

Recent evidence indicates subject-specific gyral folding patterns and white matter anisotropy uniquely shape electric fields generated by TMS. Current methods for predicting the brain regions influenced by TMS involve projecting the TMS coil position or center of gravity onto realistic head models derived from structural and functional imaging data. Similarly, spherical models have been used to estimate electric field distributions generated by TMS pulses delivered from a particular coil location and position. In the present paper we inspect differences between electric field computations estimated using the finite element method (FEM) and projection-based approaches described above. We then more specifically examined an approach for estimating cortical excitation volumes based on individualistic FEM simulations of electric fields. We evaluated this approach by performing neurophysiological recordings during MR-navigated motor mapping experiments. We recorded motor evoked potentials (MEPs) in response to single pulse TMS using two different coil orientations (45° and 90° to midline) at 25 different locations (5 × 5 grid, 1 cm spacing) centered on the hotspot of the right first dorsal interosseous (FDI) muscle in left motor cortex. We observed that motor excitability maps varied within and between subjects as a function of TMS coil position and orientation. For each coil position and orientation tested, simulations of the TMS-induced electric field were computed using individualistic FEM models and compared to MEP amplitudes obtained during our motor mapping experiments. We found FEM simulations of electric field strength, which take into account subject-specific gyral geometry and tissue conductivity anisotropy, significantly correlate with physiologically observed MEP amplitudes ($r_{\text{max}} = 0.91, p = 1.8 \times 10^{-5}$; $r_{\text{mean}} = 0.81, p = 0.01$). These observations validate the implementation of individualistic FEM models to account for variations in gyral folding patterns and tissue conductivity anisotropy, which should help improve the targeting accuracy of TMS in the mapping or modulation of human brain circuits.

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Introduction

Transcranial magnetic stimulation (TMS) is becoming a widely implemented tool in neuroscience for modulating brain circuit activity and holds promise for treating some neuropsychiatric disorders (Lefaucheur et al., 2011; Padberg and George, 2009). The use of TMS in research and clinical applications has been somewhat limited by variable outcomes and improvement on its implementation is still required (Padberg and George, 2009; Wagner et al., 2007; Wassermann and Zimmermann, 2012). The basic biophysical mechanism of TMS is that a time-varying magnetic field induces an electric field in brain tissue (Opitz et al., 2011; Wagner et al., 2006). The resulting electric field strength and its spatiotemporal distribution are critical factors influencing the tissue volumes and brain circuits affected by TMS. Thus, accurate methods for estimating these brain volumes are crucial for optimizing TMS coil positioning and circuit targeting strategies. This is especially true when one desires to implement TMS to elicit repeatable physiological and behavioral outcomes.

Various strategies have been implemented to predict the brain regions influenced by TMS. These targeting methods include the use of 10–20 EEG positioning coordinates, group functional Talairach coordinates, or...
MR-guided neuronavigation systems (Sack et al., 2009). The basic premise of these targeting methods is that the volume of the brain stimulated resides directly underneath the center of the TMS coil. Hence, TMS coils are typically positioned such that the desired targeted cortical area resides in the direction of the coil axis (Sparing and Mottaghy, 2008) and that the distance from the coil on the scalp to the cortical area is minimized (Rusjan et al., 2010). Cortical areas stimulated by TMS have also been predicted by projecting the center of gravity (CoG) measured at the scalp onto the cortex (Diekhoff et al., 2011; Weiss et al., 2012) or using spherical models to estimate the electric field distribution (Salminen-Vaparanta et al., 2012; Thielsher and Kammer, 2002). These approaches however, do not take into account critical principles related to tissue specific conductance or boundary effects.

Projection-based methods of TMS targeting rely on the fact that the magnetic vector potential is maximal directly beneath the center of the coil for the most widely implemented figure-eight TMS coils. This is not necessarily the case for the electric field generated by a TMS pulse however. The electric field (\( \vec{E} \)) induced by TMS is composed of two components, where \( \vec{E} = -\frac{\partial \vec{A}}{\partial t} - \nabla \varphi \) with \( \vec{A} \) being the magnetic vector potential and \( \varphi \) being the scalar electric potential. The second component in the equation occurs due to charge accumulation at tissue interfaces. Charge accumulation and conductivity differences in tissues and their borders, for instance skin–skull, skull–cerebrospinal fluid, cerebrospinal fluid–gray matter, and gray matter–white matter interfaces, have been shown to introduce significant distortions to electric fields generated by TMS in the brain (Chen and Mogul, 2010; Salinas et al., 2009; Thielsher et al., 2011; Toschi et al., 2008). These subject-specific electric field distortions are not accounted for by either conventional CoG projection approaches or spherical models. Therefore, although these methods have collectively proven useful for estimating areas of cortex affected by TMS, they can be improved upon. In fact, it has been recently suggested that finite element modeling approaches can offer improved estimates of the electric field generated by TMS by considering distortions unique to an individual (Opitz et al., 2011; Thielsher et al., 2011; Windhoff et al., 2013).

High-resolution simulations using the finite element method (FEM) make more specific predictions about the distribution of the electric field generated by TMS and, compared to spherical models or center of gravity (CoG) estimations, are thought to provide a more accurate estimation of the brain volumes affected by it (Opitz et al., 2011; Thielsher et al., 2011; Windhoff et al., 2013). Since the generation of FEM simulations are time consuming and simulations using them is computationally demanding, broad applications of FEM approaches in clinical neuro modulation and research has been scarce. With increasing automation in model creation, the use of individualized FEM simulations for predicting brain regions influenced by TMS pulses is becoming more feasible (Windhoff et al., 2013). However, FEM simulations have not been validated by physiological investigations aimed at determining their functional accuracy. In the present study we found that individualized FEM simulations can be used to estimate electric field strengths and distributions for accurately predicting the excitation volumes generated by TMS in brain circuits. By comparing our observations to projection-based and CoG approaches, we further show how FEM simulations of electric fields can help to improve the spatial targeting accuracy of TMS by accounting for individual neuroanatomical differences. We anticipate that the broadened implementation of subject-specific FEM field simulations will result in an increased consistency across observations when TMS is used to modulate or map brain circuits.

Materials and methods

Subjects

Five participants (3 males, 2 females, ages 23–36, mean 27.6 yr ± 5.5 yr) provided written informed consent to participate in the study. None of the participants reported any history of neurological or musculoskeletal impairment and all were right hand dominant. All procedures were approved by the Institutional Review Board at Virginia Tech.

Magnetic resonance imaging (MRI)

Functional and anatomical images were collected at Virginia Tech Carilion Research Institute on a Siemens 3T MRI Trio TIM scanner using a 12 channel head matrix coil. A 3D T1-weighted magnetization-prepared rapid acquisition gradient echo sequence (MPRAGE) anatomical scan was acquired for each subject (TR = 2600 ms, TE = 3.02 ms, flip angle \( \theta = 8^\circ \), FOV = 256 × 256 mm, 176 slices, 1.0 mm isotropic resolution, transverse plane). A 3D T2-weighted (TR = 11.990 ms, TE = 93 ms, flip angle \( \theta = 120^\circ \), bandwidth = 219 Hz/Px, echo spacing = 9.34 ms, Turbo Factor = 11, FOV = 256 mm × 256 mm, 2 mm isotropic resolution) sequence was acquired in the sagittal plane. BOLD images were acquired using gradient-echo planar imaging (TR = 2000 ms, TE = 30 ms, flip angle \( \theta = 90^\circ \), FOV = 190 mm, 33 slices, slice thickness = 3 mm). An additional higher resolution gradient-echo planar imaging sequence (TR = 2000 ms, TE = 30 ms, flip angle \( \theta = 50^\circ \), FOV = 200 mm × 200 mm, 20 slices, slice thickness = 1.8 mm) was collected in the transverse plane overlying the motor cortex.

Diffusion-weighted images using a spin echo EPI sequence (TR = 8700 ms, TE = 96 ms, 64 axial slices, voxel size = 2 × 2 × 2 mm\(^3\), GRAPPA acceleration factor 2, 6/8 phase partial Fourier, 2 averages) with 64 diffusion directions with a b-value 1500 s/mm\(^2\) and one b = 0 s/mm\(^2\) image were also acquired.

Behavior

In the MRI scanner, participants were required to perform four movements, which included adduction–abduction of their right index finger. Only the finger movement was used in this study. Movements were self-paced though encouraged to be performed at about 0.5 Hz unless fatigued. Participants were familiarized with the movements and allowed to briefly practice outside of the scanner. Movements were performed in four 40 second blocks interspersed by 40 second Rest blocks. Participants were instructed when to engage in volitional movement and when to rest by visual cues on a projection screen in the scanner.

Transcranial magnetic stimulation (TMS)

On a separate day, TMS motor mapping was conducted using a MagPro X100 stimulator unit with C860 coil (a figure-eight coil having a 35 mm inner diameter, 75 mm outer diameter, 11 mm winding height, and two layers of five windings for each wing of the coil; MagVenture, Inc., Atlanta, Georgia USA) with a neuronavigation unit (Visor1, ANT, Netherlands). A 5 × 5 grid (1 cm spacing) was generated and centered on the empirically identified motor hotspot using custom Matlab scripts. At each grid point, single biphasic TMS pulses were delivered at an intensity of 120% resting motor threshold (RMT) of the first dorsal interosseous (FDI) muscle. The RMT was determined as the stimulator output that resulted in 5 out of 10 MEPs of at least 50 \( \mu \)V peak to peak. Stimulation at each grid point was performed using two different coil orientations (45° and 90° to midline) during the same recording session. The current direction in the brain induced by the biphasic TMS pulse was AP–PA (first phase–second phase) for the 45° orientation and ML–LM for the 90° orientation. The order of orientation was counter-balanced across subjects. Coil position and orientation were recorded using the neuronavigation system and transformed to the coordinate system of the head models.

Motor evoked potentials were recorded using a Biometrics Ltd. (Ladysmith, Virginia, USA) K800 amplifier and SX230 EMG sensors (1 cm diameter, 2 cm spacing) placed over the longitudinal axis of the muscle belly of first dorsal interosseous (FDI). Data were acquired at 2 kHz using a Digidata 1440A (Molecular Devices LLC, California,
USA), viewed using Clampex 10.3 software (Molecular Devices LLC, California, USA), and stored on a computer for later analysis. Average MEPs were the result of 10 consecutive single biphasic TMS pulses delivered from a particular coil orientation (45° or 90°) every 1–3 s at each grid position. A pulse was delivered only if the coil center was positioned ≤1 mm from the target grid point as assessed by the neuronavigation system (Visor1, ANT, Netherlands). MEP amplitudes and latencies were computed using custom Matlab scripts. MEP maps were generated for each coil orientation from the averaged MEP amplitudes obtained in response to TMS pulses delivered at each grid location.

**Finite element models**

For each subject we constructed an individualized FEM model of the head based on their structural MRI and DTI image data. These FEM models were built using SimNibs as previously described (www.simnibs.org; Windhoff et al., 2013). Briefly, FEM models consisted of around 1.7 million tetrahedron. Mesh resolution was selectively enhanced in GM and WM regions with an average tetrahedron volume of 1 mm³. Electrical conductivities were assigned to different tissue types as previously described (Thielscher et al., 2011) where $\sigma_{\text{skin}} = 0.465$ S/m, $\sigma_{\text{CSF}} = 0.010$ S/m, $\sigma_{\text{WM}} = 1.654$ S/m, $\sigma_{\text{GM}} = 0.276$ S/m, and $\sigma_{\text{skin}} = 0.126$ S/m. Anisotropic conductivity information derived from the DTI data were included using a volume normalized mapping approach as described in Opitz et al. (2011). The vector potential of the TMS coil was calculated by approximating it with small magnetic dipoles, which were placed such that they covered the area of the coil as previously described (Thielscher and Kammer, 2004). For each TMS coil position and orientation studied, the electric field generated by TMS was simulated for all subjects.

**Data analysis**

Functional images were analyzed using FSL Feat (www.fmrib.ox.ac.uk/fsl; Smith et al., 2004) and coregistration between EPI and structural images was performed using FSL Flirt (Jenkinson et al., 2002) and Afni align_epi_anat (Saad et al., 2009).

For each subject and coil orientation, the traditional center of gravity (CoG) was computed and projected on the brain surface (Diekhoff et al., 2011) and the Euclidian distances between the 45° and 90° coil orientation were calculated. Similar to the calculation of the TMS CoG position an electric field “Center of Gravity” ($E_{\text{CoG}}$) was calculated by taking an MEP amplitude weighted sum of the electric field strengths for each node in the mesh over the 25 grid positions, where $E_{\text{CoG}} = \sum \frac{\text{MEP}_i}{\text{MEP}_{\text{total}}} |\vec{E}_i|$, with $\text{MEP}_i$ the mean MEP amplitude of position $i$, $\text{MEP}_{\text{total}}$ the sum of all MEPs and $|\vec{E}_i|$ the absolute electric field strength for position $i$ at the respective node. A combined electric field CoG was computed by multiplying the electric field CoGs of the 45° and 90° coil orientations. The rationale behind this was that the functional relevant regions for TMS yield high field strengths in both orientations and that those areas, which are only co-activated have high field strengths only for one orientation and not the other.

To examine the effects of coil orientation on MEPs, differences of MEP latencies and amplitudes obtained in response to TMS pulses delivered using the same coil position (grid location) for 45° and 90° orientations were calculated. To investigate the influence of the local gyral anatomy, the curvedness of the individual hand knob region was estimated by taking the median over the curvedness of the triangles approximating its shape. The hand knob region was determined by transforming a mask drawn in MNI space back to the individual subject space. Curvedness was calculated as $C = \sqrt{\frac{k_1^2 + k_2^2}{2}}$, with $k_1$ and $k_2$ displaying the principal curvatures (Pienaar et al., 2008).

The perpendicular component of the electric field ($E_\perp$) at the cerebrospinal fluid–gray matter (CSF–GM) interface in M1 was calculated as $E_\perp = E \cdot \hat{n}$, where $E$ was the electric field and $\hat{n}$ was the normal vector of the triangle. In addition, the tangential component of the electric field ($E_\parallel$) was calculated where $E_\parallel = |E - E_\perp|$. Only regions having a BOLD contrast z-score for movement versus rest > 2.3 during voluntary movement of the index finger were taken into account. Similarly the component of the electric field in direction of the first eigenvector of the diffusion tensor at the gray matter–white matter (GM–WM) interface in primary motor cortex (M1) was computed as $E_\parallel = E \cdot \hat{V}_1$, where $E$ was the electric field and $\hat{V}_1$ was the first eigenvector of the diffusion tensor. Furthermore, the perpendicular component was computed as $E_\perp = E - E_\parallel$.

The relationship between the electric field strength in M1 and MEP amplitude was tested with a linear regression model: $\text{MEP}_i = \text{MEP}_{1,i} + \text{MEP}_{2,i} + \text{MEP}_{3,i}$, with the dependent variable $\text{MEP}_i$ set to the mean MEP amplitude of grid point $i$, the explanatory variable $E_{1,i}$ is equal to the mean perpendicular component of the electric field in M1, $E_{i}$ is the mean tangential component of the electric field in M1, $E_{3,i}$ is the mean electric field component perpendicular to the principal diffusion direction in M1 and $E_{2,i}$ is the mean electric field component parallel to the principal diffusion direction in M1 for grid point $i$, respectively. Only grid points with a reliable mean MEP value > 50 μV were taken into account. Regression models were calculated for each subject and coil position separately. To analyze the effect of coil orientation on MEP amplitude and latency, separate two-tailed t-tests were used. The MEP hot spots were empirically derived as the grid location having the highest mean MEP amplitude in response to TMS. The location of this hot spot differed for subjects across coil angles. In some cases, the MEP amplitudes and latencies obtained at these hot spots were compared between subjects. To further study the influence of coil orientation on an individual basis, MEP amplitudes were collapsed across the grid and compared within subjects between coil orientations using paired t-tests. All data shown are mean ± standard deviation and p-values less than 0.05 were considered significant.

**Results**

**Functional imaging**

We examined MRI BOLD contrast maps (finger movement > rest) for volitional right index finger abduction. All subjects exhibited robust BOLD activations at the crown of the left precentral gyrus ($z > 2.3$) that extended deep along the anterior bank of the central sulcus (Fig. 1A) consistent with previous observations (Porro et al., 1996). For each subject, BOLD volumes of the precentral gyrus that exceeded statistical threshold ($z > 2.3$) were used as regions of interest for examining electric fields induced by TMS.

**Comparison of simulation results obtained with finite element and projection models**

We used computer simulations to examine how tilting or rotating the TMS coil would influence the spatial distribution of brain targets and contrasted the results obtained using projection-based approaches with those from FEM models. In these simulations we varied the coil tilt angle by changing its elevation from −30° to +30° in 10° increments at a single grid location. Similarly we modeled the influence of TMS coil orientation by changing its angle with respect to the midline in steps of 45° from 0° to 135°. For each TMS coil condition modeled, we projected the center point of the coil onto the cortical surface using conventional targeting methods (Fig. 1B). We also simulated the electric field using the FEM for each TMS coil condition (Fig. 2). From the simulation data, we calculated the Euclidian distances from the projected...
We observed displacements ranging from 5 to 20 mm between the projection point of the CoG on the cortex and the center point of the coil on the scalp when changes to the elevation (tilt) of TMS coils were modeled (Fig. 1B). Rotation of the coil orientation angle also produced small fluctuations in the distribution of the magnetic vector potential on the scalp (Supplementary Fig. 1). Using projection-based approaches we observed that spatial shifts with respect to the brain areas affected by TMS were more prominent when coil elevation was varied compared to rotation of the coil (Fig. 1B and Supplementary Fig. 1). Interestingly, FEM models predicted somewhat of the opposite where changes to TMS coil rotation would produce more robust shifts of the electric field compared to those elicited by changing the coil elevation. Here changes to the elevation of the coil produced less than 2% of an effect on the spatial distribution of the relative electric field (Fig. 2A), whereas rotation of the TMS coil elicited shifts in distribution of the relative electric field by 23.7 ± 9.6% per 45° change (Fig. 2B).

The above comparisons show that electric field distribution is strongly influenced by coil rotation while the projected point of the coil center remains relatively stable since the coil axis does not change with rotation. Thus, projection approaches do not appear sensitive enough to capture differences in the regions of brain affected by changes to the orientation angle of the TMS coil (Supplementary Fig. 1B). To further examine this issue, we analyzed neurophysiological data obtained while recording changes in motor evoked potentials (MEPs) in response to TMS pulses delivered at varied, MR-targeted spatial positions using two different coil orientations in volunteer subjects.

Motor evoked potential variability stemming from stimulator coil position and orientation

Although several observations indicate otherwise (Balslev et al., 2007; Fox et al., 2004; Opitz et al., 2011; Thielscher et al., 2011), it is generally accepted TMS coils should be positioned 45° relative to the midline to achieve optimal stimulation of motor cortex (Brasil-Neto et al., 1992; Mills et al., 1992). We stimulated 25 discrete locations over the cortex using a 5 × 5 (1 cm spacing) grid centered on the FDI hotspot using two different coil orientations (45° and 90° to the midline; Fig. 3).

There were no significant effects of coil orientation angle on the mean latencies of FDI motor evoked potentials (MEPs) across individuals (N = 5; t(4) = 1.54, p = 0.20; 45° MEP latency = 32.40 ± 0.77 ms, 90° MEP latency = 32.01 ± 1.37 ms; Fig. 4A). There was not a significant difference of the mean MEP amplitudes between subjects in response to the 45° and 90° coil orientations (t(4) = 0.92, p = 0.41; 45° FDI MEP = 897.80 ± 257.70 μV versus 90° FDI MEP = 805.40 ± 435.31 μV) likely due to a high degree of inter-individual variability. Within subject comparisons however showed that some individuals responded more robustly to one TMS coil orientation versus another. For example, some individuals exhibited larger MEP amplitudes in
Individuals. Approximately 90% of individuals have a hand knob shape and curvature in the hand region of M1 vary across individuals. Approximately 90% of individuals have a hand knob shape described by an inverted omega (“Ω”), while the remaining 10% of individuals have an epsilon-shaped (“ε”) hand knob (Caulo et al., 2007; Yousry et al., 1997). We thus questioned how the shape of the hand knob with respect to TMS coil orientation angle influences MEP amplitudes observed across the stimulus grid. We observed that subject’s having a hand knob shaped like an epsilon responded preferentially to a 45° coil angle while one subject having a hand knob shaped like an epsilon responded preferentially to a 90° coil angle (Fig. 5).

In order to make a more quantitative assessment of the observation described above, we calculated the curvature of the hand region of M1 for subjects (Fig. 6A). We then compared the median curvature of individual subject’s hand knobs against the difference of their MEP amplitudes evoked at 45° and 90° coil angles across the stimulus grid. We observed an inverted-u-shaped relationship between hand knob curvature and coil orientation preference where subject’s having either weakly curved (<0.22) or strongly curved (>0.25) hand knobs exhibited larger MEP amplitudes in response to a 90° TMS coil orientation angle while subjects with median curvatures > 0.22 and < 0.25 exhibited larger FDI MEP amplitudes in response to TMS pulses delivered from a 45° coil angle (Fig. 6B).

Finite element model simulations of electric fields correlate with physiological observations

Our simulations revealed that electric field distributions in GM and WM vary as a function of the orientation angle of the TMS coil and gyral curvature (Fig. 6C; Supplementary Figs. 2 and 3). Convoluting the E_{\text{Max}} modeled for 45° and 90° coil angles clearly revealed M1 as the primary targeted area irrespective of coil orientation (Fig. 6D). The spatial distribution of the electric field itself however, changed quite dramatically as a function of TMS coil angle. Consistent with recent observations (Opitz et al., 2011; Thielksher et al., 2011), our models indicated that gyri oriented perpendicularly to electric current flow experience high electric field strengths. Our FEM models showed that gyri neighboring M1 experienced high field strengths if they were oriented perpendicularly to the direction of current flow generated by a particular TMS coil angle (Supplementary Figs. 2 and 3). These data illustrate that the direction of current flow with respect to gyral orientation is a key factor for determining the electric field strength generated by TMS pulses. Providing an initial physiological validation of FEM approaches to estimating electric fields elicited by TMS pulses, our modeling observations are in good agreement with our physiological results where FDI MEP amplitudes varied as a function of coil orientation angle (Figs. 4A and 5B) and hand knob curvature (Fig. 6B).

Our FEM results indicated that TMS pulses can induce a robust E_{\text{Max}} in gyral crowns, as well as deeper in the WM regions of brain tissue (Fig. 6D). These FEM data suggest that electric fields generated in response to TMS pulses might be able to activate different neuronal populations located in those areas of high field strength. Further, the results are consistent with fMRI BOLD signals observed in response to volitional finger abduction (Figs. 7A, B). We found the mean perpendicular component of the simulated electric field generated in M1 to be closely related to MEP amplitudes observed in response to a TMS pulse (Fig. 8). A similar pattern emerged for the relationship between the electric field in principal diffusion direction of white matter and the MEP amplitudes recorded during our TMS motormapping studies (Fig. 8). While the field strength of the mean tangential component and the component perpendicular to the principal diffusion direction had higher electric field values, their relationship to the MEPs was similar compared to the other two components (Fig. 8). Finally, there were significant correlations for the regression of the MEP amplitudes against the four electric field components at M1 for each subject’s preferred coil orientation in four out of five subjects (S). The Pearson’s r and p-values for these correlations were as follows: S1 r = 0.82, p = 0.0014; S2 r = 0.91, p = 1.8 × 10^{-5}; S3 r = 0.70, p = 0.052; S4 r = 0.83, p = 3.7 × 10^{-4}; and S5 r = 0.80, p = 0.0048.

Discussion

Measuring MEPs elicited by TMS of the motor cortex represents one of the most commonly employed “biomarkers” for quantifying the effects of a variety of neuromodulation strategies on plasticity.

**Fig. 2.** The TMS-induced electric field in the brain is more prominently affected by changes in coil rotation than coil tilt. A, finite element models reveal that tilting the coil in 10° steps produces a slight anterior–posterior shift in the spatial extent of the electric field as shown. B, modeling rotations of the TMS coil in 45° increments indicated more robust changes in the location of the peak electric field, as well as to its spatial distribution compared to changes in coil elevation. Gyri with high field strengths are determined through the direction of the current flow with respect to the individual gyri.
Transcranial magnetic stimulation of the motor cortex using 45° and 90° coil orientation angles can be used to develop individual motor excitability maps. A, a 5 × 5 stimulation grid (1 cm spacing) is shown centered over the FDI hotspot on a head model for an individual (left). Two different views illustrate a model of the TMS coil positioned at 45° (top) and 90° (bottom) over the motor cortex. B, FDI motor excitability maps generated by stimulating 25 points across the grids shown in (A) using a 45° (top) and 90° (bottom) coil angle are illustrated for an individual. Medial (M), posterior (P), anterior (A), and lateral (L) anatomical orientations of the motor excitability map are indicated. Each pseudo-colored square illustrates the mean FDI motor evoked potential (MEP) amplitude obtained in response to 10 stimuli delivered using TMS pulses at 120% of the motor threshold over every point of the grid. For both coil orientations, individual MEP responses (N = 10) are shown for the FDI hotspot identified using a conventional 45° coil angle.

Motor evoked potential amplitudes vary across individuals as a function of TMS coil orientation angle. A, the scatterplot on the left illustrates the mean latency in milliseconds of FDI MEPs elicited using a 90° (x-axis) and 45° coil angle (y-axis) from the same grid location per subject (indicated by color). The scatterplot on the right illustrates mean maximum normalized FDI MEP amplitudes obtained in response to TMS trials each for a 90° (x-axis) and 45° coil angle (y-axis) at every one of the 25 stimulus grid locations for each subject (indicated by color). Data points falling above the sloped line represent stimulus grid locations which produced larger FDI MEP amplitudes using a 45° TMS coil orientation and data points below the sloped line represent stimulus sites producing larger FDI MEP amplitudes using a 90° coil angle. Some subjects had a majority of their stimulus sites exhibiting larger FDI MEP amplitudes produced by a 45° coil angle (Subjects 1–3) while other subjects exhibited the opposite (Subjects 4,5). B, mean frequency distributions illustrating the spatial jitter of coil placement across all grid positions (N = 25) and orientations (N = 2) for all subjects (N = 5).
This basic approach and several other applications of TMS however continue to suffer from variable outcomes. Minimizing this variability can likely be achieved by increasing our understanding of how to more accurately, consistently, and reliably target brain circuits with TMS. Therefore we investigated the influence of inter-individual neuroanatomical characteristics like hand knob curvature and procedural variables like TMS coil orientation angle, which both affect physiological responses to TMS. We observed that traditional projection-based targeting methods do not sufficiently account for the above anatomical and procedural variables. Using FEM simulations of the TMS-induced electric field to more adequately account for anatomical and procedural variables, in the present study, we found that the strength of the modeled electric field in M1 significantly correlated with MEP amplitudes on an individual basis. These findings validate the use of FEM simulations as a more reliable approach to subject-specific TMS targeting compared to projection-based methods. Our observations further indicate the optimal coil orientation angle used during TMS studies or treatments can be predicted using FEM simulations and should be based upon an individual's specific gyral folding patterns and tissue conductivity anisotropy.

Spherical models predict electric field strengths at gyral crowns that remain spatially stable across varied TMS coil orientation angles. Conversely, FEM simulations indicate that electric field distributions experience prominent spatial shifts when the TMS coil orientation angle changes (Thielscher et al., 2011; Supplementary Figs. 2 and 3). Consistent with the predictions made by these FEM simulations, our physiological observations indicate that the efficacy of TMS depends mainly on coil angle (Fig. 5) with respect to the orientation and curvature of an individual's gyri (Fig. 6). Additionally, the strength and shape of the TMS-induced electric field are dependent on specific brain tissue electrical properties, which cannot be captured by spherical models or projection approaches. Thus compared to these conventional projection-based predictions, we conclude that FEM simulations of the electric field represent a more precise estimate of brain regions targeted by TMS. While these FEM-simulated electric field distributions do not predict discrete cellular points of stimulation, their more realistic estimation of the brain regions impacted should enable us to more confidently unravel the biophysical mechanisms of action underlying the ability of TMS to modulate brain circuit activity.

Fig. 5. Individual hand knob shape influences the preferred TMS coil orientation angle for obtaining maximal FDI excitation. A, volume-rendered three-dimensional reconstructions of structural MRI data indicating the hand knob region (red square) of the precentral gyrus are shown for three subjects (left). On the right, higher magnification images of the hand knob region (red square) are shown superimposed with the orientation of the two coil angles (45° and 90°) used to map the excitability of the FDI muscle across the stimulus grid. Note that the top two panels show subjects having inverted omega (Ω) shaped hand knobs while the subject shown in the bottom panel has an epsilon (ε) shaped hand knob. B, pseudo-colored motor excitability maps illustrate the mean FDI MEP amplitudes in microvolts (µV) in response to 10 stimulation trials delivered at each location across the stimulus grid with a 45° (left) and 90° (right) TMS coil angle. Note that the individuals possessing an inverted omega shaped hand knob exhibit a marked decrease in the FDI MEP amplitudes across the grid for a 90° versus a 45° coil angle, while the individual possessing an epsilon shaped hand knob displayed the opposite relationship.
Possible limitations of our study are that while different conductivity domains are determined individually, fine scale differences in conductivity within an individual (for example, within GM or WM) are not presently taken into account. Such differences do not change our interpretations since it has been demonstrated that slight changes in conductivity between domains do not significantly alter the electric field distribution (Thielscher et al., 2011). Similarly, Opitz et al. (2011) recently demonstrated modeling results are stable for different conductivity mapping approaches. Gross alterations in tissue conductivity under pathological conditions like stroke however can induce distortions and alter the spatial distribution of the electric field induced by TMS (Wagner et al., 2006). In our study we used healthy participants, so potential consequences of pathologies are unlikely. Future studies may wish to consider the variability of intra-individual tissue conductivity when implementing TMS across individuals of different ages or disease states. An additional potential source of error in our study could be related to the placement and recording of TMS coil positions using the neuronavigation system. While the jitter at each coil position was generally 1 mm or less, the algorithms mapping these recorded positions to MRI coordinates have a limited resolution resulting in measurement inaccuracies of about 3–5 mm (Ruohonen and Karhu, 2010). It is unlikely that these measurement inaccuracies exceed the 1 cm grid spacing employed in our mapping strategy and thus we feel confident in our ability to reliably distinguish individual grid positions.

In the present study we chose to implement biphasic pulses since they are known to have lower thresholds for generating MEPs compared to monophasic pulses (Kammer et al., 2001). The physics of TMS falls in the quasistatic domain, so the spatial and temporal domains can be decoupled from one another. Based on observations by others regarding pulse parameters required to induce plasticity on
long timescales (minutes to hours; Ziemann et al., 2008), the low number of TMS pulses delivered to any one grid location was not likely to elicit robust long-lasting plasticity in our study. Perhaps a limitation to our study however, we used single pulse TMS having inter-trial intervals $\leq 3$ s. Since TMS-evoked MEP amplitudes have been described to be affected to varying degrees when using an inter-trials $\leq 10$ s (Chen et al., 1997; Julkunen et al., 2012; Pascual-Leone et al., 1994), we cannot exclude the possibility that short-term plasticity may have influenced some of our observations. As fundamental properties of brain circuitry any such short-term physiological plasticity would likely be due to conventional synaptic mechanisms, such as receptor saturation, receptor trafficking, changes in channel gating kinetics, synaptic vesicle pool depletion, and dynamic regulation of neurotransmitter release probability, which have all been well-studied at corticocortical and corticothalamic synapses between pyramidal neurons, interneurons, and thalamic relay neurons (Sanes and Donoghue, 2000; Thomson, 2003; Zucker and Regehr, 2002). It is nearly impossible to determine which, if any, of these aforementioned mechanisms may have contributed to the trial-to-trial MEP variability we observed since it is not known with any certainty to what degree specific neuronal

Fig. 7. Relationship of the electric field center of gravity, BOLD signal and perpendicular and tangential component of the electric field in gray and white matter. A, the fMRI BOLD contrast signal obtained in response to volitional index finger movement is shown at the left for one subject. On the right the calculated $E_{\text{cog}}$ is shown for the same subject. B, the fMRI BOLD contrast signal in (A) is shown at a higher magnification (top) and the MEP weighted perpendicular electric field (EF-perpendicular, upper left) and the MEP weighted tangential electric field (EF-tangential, upper right) in gray matter. The MEP weighted electric field along the principle direction of diffusion (EF-DTI-parallel, lower left) and the MEP weighted electric field perpendicular to the principle diffusion direction (EF-DTI-perpendicular, lower right) in white matter are shown for the same subject. Cool colors indicate low electric field strengths or BOLD signals and warm colors indicate high electric field strengths or BOLD signals. The sizes of the spheres shown are scaled by field strength, where larger spheres indicate higher electric field strengths. Electric fields in gray and white matter are scaled to the same maximum, respectively.
elements are affected by the electric field induced by TMS. Future studies should however begin driving towards using high-resolution modeling to investigate how different time components of electric fields mediate physiological outcomes (including plasticity) induced by TMS across different timescales. This is a difficult but important and seemingly tractable problem if simulations can include faithful models of neuronal and synaptic populations which react differently to time varying pulse shapes and sequences. Such studies should shed light on the temporal behavior of TMS-induced electric fields while more accurately detailing the mechanisms of action across different embodiments of TMS.

One of the main objectives of the present study was to compare and contrast neurophysiological observations with the results from FEM simulations of TMS-induced electric fields. Comparisons of TMS CoG with the fMRI BOLD CoG have been recently reported (Diekhoff et al., 2011). Using similar approaches we found fMRI BOLD signals in response to voluntary index finger movement to be localized to primary motor and, of course, premotor and supplementary motor cortex. Comparing the fMRI BOLD CoG with the TMS-induced electric field center of gravity ($E_{\text{CoG}}$), we found that the TMS-induced electric fields were concentrated on the primary motor cortex, as well as surrounding gyri during motormapping. Further, we found the normal component of

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**Fig. 8.** Scatterplots illustrating raw MEP amplitudes correlate with the strength of the perpendicular (A) and tangential component (B) of the electric field in gray matter and the parallel (C) and perpendicular (D) component of the electric field in direction of the principal diffusion in white matter. Field strengths (V/m) are shown for a rate of change of current flow in the coil of 1 A/μs.
the modeled electric field in these regions to be correlated with the amplitudes of TMS-elicited MEPs (Fig. 8A). An underlying physiological explanation might be that a current flowing perpendicular to a gyrus is optimally oriented to directly activate pyramidal neurons, which are mainly oriented horizontally in the sulcal wall. This interpretation is further supported by a correlation of the electric field strength along the principal diffusion direction of white matter and the MEP amplitudes (Fig. 8C), since the principal diffusion direction estimates a first-order approximation of the direction of the axons and high field strengths in this direction is a prerequisite for eliciting action potentials (Roth and Basser, 1990). On the other hand, the tangential component of the electric field at the GM/CSF interface also correlated with the MEP amplitudes (Fig. 8B). Perhaps best explained by a high intercorrelation with the tangential electric field at the GM/CSF interface, the component of the electric field perpendicular to the principal diffusion direction was similarly correlated with MEP amplitudes (Fig. 8D). At the top of the gyrus (GM/CSF interface), the tangential electric field is the predominant component and more directly supports hypotheses regarding the indirect trans-synaptic activation of pyramidal tract neurons via interneuron stimulation by TMS (Di Lazzaro and Ziemann, 2013). Yet from our observations we cannot reliably conclude a predominant site of action for TMS in evoking MEPs. Our results rather illustrate that the TMS-induced electric field magnitude explains approximately two-thirds of the MEP variability obtained across motor maps without specifying a particular site of action. Moreover, different mechanisms of action underlying the effects of TMS are still being debated (Salvador et al., 2011). By expanding our understanding of TMS action, both the spatial and temporal properties of the resulting activation can be optimized. For example, FEM simulations will enable the development of specific approaches intended to maximize the effects of TMS on targeted brain circuits in individuals. In conclusion our observations show that such personalized FEM models for targeting TMS are justified given the unique features of our individual brains.

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Conflict of interest

The authors have no financial conflicts of interest related to the research conducted in this study.

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