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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 motormapping 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 motormapping experiments. We found FEM simulations of electric field strength, which take into account subject-specific gyral geometry and tissue conductivity anisotropy, significantly correlated with physiologically observed MEP amplitudes ($r_{max} = 0.91$, $p = 1.8 \times 10^{-5}$ $r_{mean} = 0.81$, $p = 0.01$). 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.

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

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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; Thielscher 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 φ 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; Thielscher 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; Thielscher 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; Thielscher 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 neuromodulation 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 θ = 8°, 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 θ = 120°, 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 echo planar imaging (TR = 2000 ms, TE = 30 ms, flip angle θ = 90°, FOV = 190 mm, 33 slices, slice thickness = 3 mm). An additional higher resolution gradient-echo echo planar imaging sequence (TR = 2000 ms, TE = 30 m, flip angle θ = 50°, 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 C-B60 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 μV 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,