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PET-Based Confirmation of Orientation Sensitivity of TMS-Induced Cortical Activation in Humans

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Abstract

Background—Currently, it is difficult to predict precise regions of cortical activation in response to transcranial magnetic stimulation (TMS). Most analytical approaches focus on applied magnetic field strength in the target region as the primary factor, placing activation on the gyral crowns. However, imaging studies support M1 targets being typically located in the sulcal banks.

Objective/hypothesis—To more thoroughly investigate this inconsistency, we sought to determine whether neocortical surface orientation was a critical determinant of regional activation.

Methods—MR images were used to construct cortical and scalp surfaces for 18 subjects. The angle (θ) between the cortical surface normal and its nearest scalp normal for ~50,000 cortical points per subject was used to quantify cortical location (i.e., gyral vs. sulcal). TMS-induced activations of primary motor cortex (M1) were compared to brain activations recorded during a finger-tapping task using concurrent positron emission tomographic (PET) imaging.

Results—Brain activations were primarily sulcal for both the TMS and task activations ($P < 0.001$ for both) compared to the overall cortical surface orientation. Also, the location of maximal blood flow in response to either TMS or finger-tapping correlated well using the cortical surface orientation angle or distance to scalp ($P < 0.001$ for both) as criteria for comparison between different neocortical activation modalities.

Conclusion—This study provides further evidence that a major factor in cortical activation using TMS is the orientation of the cortical surface with respect to the induced electric field. The results show that, despite the gyral crown of the cortex being subjected to a larger magnetic field magnitude, the sulcal bank of M1 had larger cerebral blood flow (CBF) responses during TMS.

Keywords

TMS; Cortex; PET; MRI; Orientation; Cerebral blood flow

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Conflicts of interest: none.

Introduction

Transcranial magnetic stimulation (TMS) can non-invasively activate neurons in the brain [1,2]. It has both clinical and research applications including psychiatric therapy [3,4], brain mapping [5], rehabilitation [6–8], and cognitive neuroscience studies [9,10], to name a few. Despite its growing popularity over the past 25 years, there is still a lack of firm understanding of the mechanisms that result in cortical activation in response to TMS. Some identified factors that influence the cortical response to TMS are the magnetic field magnitude (intensity, sub- vs. suprathreshold) [11,12], the direction and path of white matter tracts [13], the TMS pulse duration [14], pulse shape [15,16], and pulse firing frequency (e.g., fast, slow, burst, interval between pulses, etc.) [17–19]. Research on these factors has proven challenging because, except for motor and sensory regions of the neocortex, little direct feedback of neuronal activation is provided, especially in cognitive areas that are frequent clinical targets of TMS.

It has been proposed that a significant factor in TMS-induced brain activation is the orientation of the cortical columns in relation to the direction of the applied magnetic field [20–23]. Cortical pyramidal neurons are organized into minicolumns that lie perpendicular to the outer surface of the gray matter. These structures form a critical functional role in the cortex; neurons within a column tend to fire together and display higher selectivity in influencing one another [21,24]. Furthermore, evidence supports that neurons are preferentially excited by externally applied E-fields when the field is oriented along (i.e., parallel to) the major axis of the neurons [25–27]. Therefore, despite the gyral crowns being exposed to a higher field magnitude during a typical TMS application, cortical activation is believed to occur closer to the sulcal bank [20]. It has been proposed that this is a result of the induced electric field (E-field) vector aligning with the cortical columns in the sulcal banks when the coil is oriented perpendicular to the sulcus [20]. When aligned in this manner, the cortical minicolumns on the crown of the gyrus will always be orthogonal to the E-field alignment. This sulcal orientation sensitivity would account for some of the variability in electromyographic (EMG) responses observed when rotating the TMS coil while maintaining the coil's position and intensity [5,28,29]. For more information on the basic biophysics of TMS activation, the reader is referred to Refs. [30–32].

At present, coil placement methods for most applications of TMS (e.g., depression treatment [3,4]) are relatively unsophisticated [33,34] mostly due to the extreme complexity of the brain. More precise targeting procedures could lead to improvements in patient outcome or clinical research results. Furthermore, investigation of the exact regions of TMS activation would lead to a better understanding of the factors that result in cortical depolarization. This could then be implemented for more precise protocols to be used during TMS applications.

In the current study, several PET scans were performed on human subjects during a voluntary finger-tapping task and during suprathreshold TMS application to the primary motor cortex (M1) of the first dorsal interosseous (FDI) muscle. These two datasets were used to investigate the correlation of cortical column orientation with either cortical activation modality; namely, evoked via task-based or TMS-induced activation. The

underlying hypothesis of this study was that the orientation of cortical columns relative to the scalp played a significant factor in determining the sites of cortical activation in response to TMS.

Methods

Subjects

Twenty-one healthy right-handed individuals (average age $\pm$ standard error (SE): 33.19 $\pm$ 8.69 years, 11 males) were enrolled in the study after approval by the University of Texas Health Science Center at San Antonio's Institutional Review Board. An informed consent was obtained from all subjects in accordance with the declaration of Helsinki. One subject had movement artifacts in their anatomical magnetic resonance image (MRI); hence data from this subject were not included in the final analysis. Furthermore, two subjects did not show significant blood flow response in the motor cortex in response to TMS. These subjects were considered 'nonresponders' [20] and were not considered in the analysis (for additional information, see 'Non-responders' heading under Discussion section).

Magnetic resonance imaging

We acquired high-resolution anatomical and functional MRIs using a 3T Siemens TIM scanner (Erlangen, Germany). Anatomical images were acquired at 1 mm³ resolution using a 3-D Turbo-FLASH sequence with an adiabatic inversion contrast pulse (TE/TR/TI=3.04/2100/785 ms, and flip angle=13°). Gradient-echo planar images (TE/TR = 45/2000 ms, a flip angle of 90°, and slice thickness = 6 mm, 20 slices, resolution of 3 $\times$ 3 mm²) were acquired during the abduction and adduction of the left index finger in a block design (30 s—finger abduction—adduction alternating with 30 s of rest). This task has been shown to maximally activate the FDI muscle [35].

Image preprocessing was done to remove non-brain tissues, correct for image intensity fluctuations and RF inhomogeneities, and register the brain to the anatomical MRI using image processing tools from the FMRIB's software library (FSL) [36]. A general linear model was employed to determine voxel-wise differences in activation patterns during the task and baseline conditions and statistical parametric images of t scores (SPI{ t }) were generated and thresholded for a $Z > 2.3$ and a cluster significance threshold of $P = 0.05$ (corrected for false discovery rate).

Robotically positioned image-guided TMS

A Cadwell High Speed magnetic stimulator was used with a B-shaped TMS coil (Cadwell, Inc., Kennewick, WA, USA) for both single pulse and repetitive TMS (rTMS) procedure. The TMS coil's site of maximal electric field induction (i.e., "hot spot") was determined using methods developed by Salinas et al. [37,38]. These articles describe techniques which use an E-field probe to measure the E-field vectors induced by each TMS pulse in the volume below the coil. The location of the maximum induced E-field was used to stereotactically position the TMS coil over each subject's scalp location closest to the center-of-mass of region of maximal activation in right M1_{hand} area—determined by each subject's fMRI map of the M1_{hand} region. Once positioned, the TMS coil—i.e., induced E-field vector

—was oriented perpendicular to the subject's central sulcus (with the E-field directed anteromedially, toward the subject's nose); this approach was proposed by Fox and colleagues in their cortical column cosine principle [20]. Each of these steps was incorporated in the TMS planning tool of the irTMS system [33]. We applied single pulses of TMS to each subject's right M1_{hand} to establish each subject's resting motor threshold (RMT) at the FDI muscle of the contralateral (left) hand; the RMT was determined using a relative frequency method [39] in which we determined the minimum intensity of stimulation capable of producing a motor evoked potential with an amplitude of at least 100 μ V in at least 5 out of 10 trials.

Each subject underwent rTMS at a 3 Hz stimulation frequency to the right M1_{hand} at intensities of 100%, 108%, 117% and 125% RMT during concurrent H₂¹⁵O positron emission tomography (PET) scans; a sham TMS condition was employed by delivering 3 Hz rTMS at a distance of 10 cm off the vertex of the subject; the TMS intensity of each sham condition was adjusted so that the volume of each rTMS pulse matched the sound intensity levels encountered during 112% RMT stimulation (the average of 4 TMS intensities). Each subject also performed a finger-tapping task during each PET session for right M1_{hand} localization. Each rTMS frequency was delivered at least 60 s prior to the injection of ¹⁵O-water and continued until 60 s after the injection. The order of finger-tapping, rTMS stimulation intensities and rTMS sham conditions were randomized for each PET session. The combinations of rTMS frequency, stimulus duration, and TMS intensity fall within published rTMS safety guidelines [40,41].

Positron emission tomography

PET data were acquired with a CTI EXACT HR+ scanner (Knoxville, TN). Sixty-three contiguous slices (2.5 mm thick) in a transaxial field of view of 15.5 cm were acquired. Water labeled with oxygen-15 (H₂¹⁵O, half-life of 122 s) was administered intravenously—555 MBq H₂¹⁵O dose/scan—and cerebral blood flow (CBF) was measured using a bolus technique [20]. Each condition was repeated twice during the PET session. Images were corrected by measured attenuation using 68Ge/68Ga transmission scans and reconstructed at an in-plane resolution of 7 mm full width at half maximum (FWHM) and an axial resolution of 6.5 mm FWHM.

Data analysis

We performed image preprocessing using previously validated methods and in-house software [20]. PET images were reconstructed into 60 slices (2 mm thick) with an image matrix size of 128 × 128 × 60, using a 5 mm Hann filter resulting in images with a spatial resolution of approximately 7 mm FWHM. PET images were corrected for head motion using the MCFLIRT tool [42] in the FMRIB's Software Library (FSL; [36]). The PET and MRI images were spatially transformed to Talairach space [43]. Regional tissue uptake of ¹⁵O-water was value normalized to a whole-brain (global) mean of 1000 counts.

All analyses were performed using the Research Imaging Institute's (RII, UTHSCSA) free image browser Multi-Image Analysis GUI (MANGO; available at rii.uthscsa.edu). Each subject's intensity scans were analyzed using voxelwise statistical parametric images (SPIs).

Group Z -score images ($SPI\{z\}$) were obtained by contrasting each subject's rTMS intensity and sham conditions using the pooled standard deviation. The objective of the analysis was to determine the locations of the M1 response induced by that rTMS intensity. Only Z -scores corresponding to $P = 0.05$ are reported here.

Surface-model creation

Using the T1 weighted MRIs mentioned previously, we constructed accurate geometric models for each subject's head. This was performed with a combination of freeware and custom in-house programming. First, Freesurfer (<http://surfer.nmr.mgh.harvard.edu>) was used to segment the cortical gray matter (GM) and white matter (WM) surfaces for each subject [44,45], creating detailed triangular surface meshes. Next, the Brain-Extraction Tool (BET) from FSL [36] was used to separate and create surfaces for the scalp, skull, and cerebro-spinal fluid (CSF). Once the five surface meshes were constructed, a re-meshing step was taken to optimize the quality of the surface triangles using MeshFix [46]; ReMesh was employed when manual editing was necessary [46]. This process ensured that there was no overlap between neighboring mesh surfaces.

Calculating the cortical surface orientation

To study the effects of cortical surface geometry on neuronal activation, we assigned numerical values that reflected each GM node's surface normal orientation with respect to the scalp's surface normal. This was done by calculating the cortical surface orientation (CSO) angle [θ ; see Fig. 1] as follows. Unit-normal direction vectors (facing outward) were calculated for each of the GM and scalp nodes (approx. 50,000 and 10,000, respectively). For each GM surface node, the nearest scalp node was found and the angle between the two vectors calculated. The resulting angle (θ) ranged from 0 to $\pi/2$ radians (i.e., 0–1.5708). Nodes located on the crown of the gyri or in the valley of the sulci have small angles ($\theta \sim 0$; Fig. 1A, nodes C1 and C3). However, if the GM node is on the sulcal bank, θ approaches $\pi/2$ (Fig. 1A, node C2). Thus, the θ value facilitates the identification of the cortical orientations through which activations are more likely to occur. An example of a representative subject's θ values throughout the entire cortical surface is displayed in Fig. 1B. It should be noted that the CSO angle is not an indirect measure of cortical surface distance. This is illustrated more completely in Fig. 1B inset where the gyral crowns and sulcal valleys have similar CSO angles but have very different cortical depths.

Finding the M1 region of interest—The PET images acquired during the finger-tapping task of the subject yielded a large region of activation in the M1 area of the cortex. This region lies in the general target area of the TMS site of activation but may not encompass all of the neurons being excited by TMS. In order to ensure that all of the stimulated regions were included in the analysis, a region of interest (ROI) was created around the site of activation of the finger-tapping contrasted with rest/sham image (i.e., task image). This was calculated by finding the maximum CBF response of the task activation site and considering only nodes that fell within a given radius of this location. Since the precise size of this region was unknown, radii of 10 mm, 20 mm, and 30 mm for each ROI were used and the results were compared. Results are shown for only the 20 mm radius however similar results were found for all three radii tested.

Calculation of CSO angle around ROI—The θ for all nodes that fell within the desired ROI were included. This information for all subjects was combined as the θ_{ALL} dataset and compared with the subsets mentioned as follows. Two subgroups of PET data were analyzed: 1) images that were taken during finger-tapping task and 2) those taken during suprathreshold TMS stimulation (100, 108, 117, and 125% RMT). Only the nodes that showed significant activation (Z -score > 1.96 , $P < 0.05$) for the given PET image and within the subject's ROI were used to create the 'task' and 'TMS' angle subgroups. This approach created θ_{TASK} and θ_{TMS} subgroups of the CSO angle, respectively.

To summarize, for a given ROI radius there were three subsets of CSO angles that were analyzed: θ_{ALL} contains the CSO angles for all nodes within the given ROI radius for all subjects considered, θ_{TASK} contains a subset of the θ_{ALL} nodes that showed significant CBF during voluntary finger-tapping task, and θ_{TMS} contains a subset of the θ_{ALL} nodes that showed significant CBF during TMS of the FDI.

Statistical analysis

ROI-angle vs. TMS- and task-angle—The CSO angle (θ) dataset is dependent on the surface geometry within the ROI of the subjects and does not follow a Gaussian (normal) distribution, thus requiring the use of non-parametric analysis. The Mann–Whitney rank sum test (for non-parametric analysis) was used to compare the overall θ_{ALL} , θ_{TASK} , and θ_{TMS} . Additionally, in order to compare specific θ_{TMS} datasets (e.g., TMS stimulation at 100% RMT) the median θ value of each subgroup was used and separate datasets were compared with the Median Test [47–49], a non-parametric form of Pearson's chi-square testing. Both Mann–Whitney rank sum and Median Tests resulted in similar outcomes and statistical levels of significance for all comparisons.

Changes with stimulation intensity—To investigate how CSO angles change with increasing stimulation intensity (for example, if activation shifts towards the gyral crown or down into the sulcal bank), the subject data (θ_{TMS}) was divided further into subsets corresponding to each stimulation intensity (100, 108, 117, and 125% MT). The Mann–Whitney rank sum test and the Median Test were performed on each subset.

Correlation of distance and CSO angle to maximum activation—To investigate whether PET activation for the TMS and voluntary finger-tapping task datasets occur in the same general region, an analysis was performed using the nodes of highest activation within the ROI radius. For each subject, the cortical surface node closest to the point of highest activation for each stimulation intensity was found. The distance between this point and its nearest scalp node was measured. Similarly, the distance between the scalp and the point of maximum location for the task activation was found. Correlation of the TMS and task distances was tested within each subject for similarities/differences in the location of activation (a similar analysis was performed in Ref. [20]). This was found using Pearson's correlation coefficient in which significance was tested by comparing against the critical r -value. The correlation significance is presented as a P -value for these calculations. Likewise, an analysis was performed using the CSO angle of the nodes closest to the maximum location of activation. Correlations in CSO angles were tested between θ_{TMS} and θ_{TASK} .

Results

ROI-angle vs. TMS- and task-angle

For the 20 mm radius ROI, the median CSO values across all subjects were calculated to be 1.2133 for θ_{ALL} (18,100 nodes), 1.2849 for θ_{TMS} (6628 nodes), and 1.2585 for θ_{TASK} (5752 nodes). Statistical analysis using both the Mann–Whitney rank sum test and the Median Test showed that both the suprathreshold TMS (θ_{TMS}) and the finger-tapping task (θ_{TASK}) activations had significantly larger CSO angles than the θ_{ALL} ($P < 0.001$ for both) indicating that CBF was preferentially sulcal in origin. Figure 2 summarizes the results of the statistical analysis. Additionally, the ROI showed θ_{TMS} values to be significantly greater than the θ_{TASK} values. These results support the idea that both methods yielded highly selective activation profiles which were more sulcal than θ_{ALL} .

Increasing activation threshold of blood flow data

The cortical activations in the PET data were thresholded at a Z -score value of 1.96 ($P < 0.05$) in the prior analysis. After thresholding, large regions of activation remained in both the TMS and task PET datasets. To determine where the likely centralized location of activation would be during each PET session, we investigated the change of CSO angles with increasing Z -score thresholds; raising these thresholds reduces the probability of including extraneous CBF measurements in our analysis. The median θ_{TMS} and θ_{TASK} were calculated for all nodes at Z -score thresholds of 2.00, 2.50, 3.00, 3.50, and 4.00 to identify the orientation at location of maximum CBF responses.

Each subset of the θ_{TMS} and θ_{TASK} values were significantly different from θ_{ALL} at higher Z -score thresholds ($P < 0.001$ in all cases). The median value of θ_{TASK} increased with increasing Z -score thresholds (Fig. 3) suggesting that the location of the highest CBF response is located on the sulcal bank. θ_{TMS} , however, did not show this increasing trend with Z -score.

Changes with stimulation intensity

The effect of TMS intensity on median CSO angle was examined. Median θ_{TMS} showed significantly larger angles than θ_{ALL} with all stimulation intensity subsets (100, 108, 117, and 125% RMT), corresponding to more sulcal activation. The dependence between TMS intensity and CSO angle was tested but no significant correlation could be found supporting the idea that the site of activation in the neocortex with respect to its locations in the cortical infolding is not strongly dependent on stimulation strength.

Correlation of distance and CSO angle to maximum activation

The distance from the scalp to maximal CBF change measured during the finger-tapping task was compared to the distance calculated during TMS application at different intensity levels for each of the three ROI across individual subjects. The correlation of these two different activation modalities would assess whether or not the primary depth of neocortical activations were similar. Statistical analysis (see Methods section) indicated that correlations were highly significant (Fig. 4, $r = 0.429$, $P < 0.001$). This indicates that the depth of maximal CBF evoked by TMS was consistent with that observed during the voluntary task.

A similar analysis of the site of maximal CBF increase evoked by finger-tapping or different intensity TMS was compared by examining the correlation of CSO angles of the respective sites (Fig. 5). The CSO angles within the ROI were highly correlated ($r = 0.409$, $P < 0.001$).

Discussion

TMS/task vs. ROI

In this study, the cortical orientation profiles of M1 during transcranial magnetic stimulation and a voluntary finger-tapping task were characterized. Both the finger-tapping task and the TMS-induced brain activations in M1 as assessed by PET-based CBF profiles demonstrated consistent CSO angles indicating primarily sulcal activations. The depth of activation for both the task and TMS modes of activation was also highly correlated across all subjects. The research described here provides further evidence that the primary hand motor cortex (specifically the FDI muscle) lies primarily in the sulcal bank of the motor cortex and that this region is being selectively activated by TMS (even though the induced E-fields are larger at the gyral crowns).

By increasing the threshold significance of each PET scan, we found that the CSO angles maintained a more sulcal activation and tended to increase for both the TMS and task studies thus providing further evidence that these activations are occurring in the anterior bank of the central sulcus as opposed to the gyral crown. This finding provides quantitative support that the TMS-induced cortical activations are not primarily determined by the magnitude of the induce E-field but instead by the relative direction of the E-field in relation to the cortical surface normal (i.e., the cortical columns). These findings are consistent with the basic premise of the cortical column cosine (C3) model put forth by Fox et al. [20]. Hence, the results of this study support the notion that TMS as applied typically to activate FDI muscles primarily targets the neurons lying in the sulcal bank of M1 despite being subjected to a lower magnitude induced electric field as a result of their greater distance from the stimulating coil compared to cortical columns in the gyri.

Further dividing the θ_{TMS} values by stimulus intensity demonstrated that all intensity levels stimulated locations with significantly higher CSO angles compared to the θ_{ALL} values (i.e., more sulcal). Furthermore, the observation that TMS activation occurs at the sulcal bank is independent of the stimulation intensity suggests that E-field orientation is the more significant factor to neuronal activation, at least in the neocortex.

The correlation shown in Fig. 4 between task-scalp distance and TMS-scalp distance is much weaker than similar results in Fox et al. [20]. However, the method used to find the point of activations differed between the two studies. Fox et al.'s work used the centroid of the activation region, the current study used the gray matter surface node that is closest to the point of maximum activation. Furthermore, our results included all suprathreshold stimulation intensities (100, 108, 117, 125% MT) while the previous work only used a single high suprathreshold intensity (125% MT). When we reduced the ROI to 10 mm radius and only the 125% MT stimulation is used, the correlation greatly improves ($r = 0.857$), mirroring the results of the previous study. It appears that the larger ROI and inclusion of

lower stimulation intensities add some noise to the data. However, despite this, significant correlation can still be found with our datasets.

Comparison with electrical stimulation

The results found here for TMS activation are different from those believed to occur during electrical stimulation (e.g., transcranial electric stimulation (TES), transcranial direct current stimulation (tDCS), epidural cortical stimulation (ECS)). Through modeling, it has been shown that electrical stimulation methods generate E-fields directed normal to the scalp, below the anode [50]. This leads to preferential activation of neurons on the crowns and lips of the gyri [51], the location where the E-field is both the largest in magnitude and in alignment with cortical columns. It should be noted that tDCS, depending on the electrode configuration, typically stimulates everything between the anode/cathode in an unidirectional (less controlled) manner.

Non-responders

Currently, TMS-induced activation of a single muscle group is thought to occur at different local circuits (not necessarily all located in M1) depending on coil position, orientation, and stimulation intensity [52]. This is evident by varied action potential signals recorded via epidural electrodes. Different activation neocortical pathways are thought to be involved in direct axonal stimulation (i.e., D-wave) and indirect, trans-synaptic activation of pyramidal tract neurons (i.e., I-waves) [52], which can either be early (I1-wave) or later (I2, I3, etc.). Fox et al. [20] reported that 4 out of 11 subjects (36.4%) demonstrated no CBF response to TMS. Therefore, in these ‘non-responders’ it is believed that direct axonal stimulation alone was responsible for TMS-induced contractions of the contralateral hand muscles. Perhaps this high percentage of ‘non-responders’ could have been an artifact of their population sample, which may have been more susceptible to direct axonal stimulation than in previous TMS studies. In our study, we report 18 ‘responders’ and 2 ‘non-responders’ which is more consistent with the concept of D-wave and I-wave contributions to TMS-induced brain activity. Furthermore, most excitations are thought to originate at or near the axon (e.g., at either the axonal terminations or axon-tract bending) [53] which would mean that all subjects would have very small rCBF changes and would be considered ‘non-responders’. However, a local network of neurons being excited could lead to the depolarization of the corticospinal neuron that leads to the FDI muscle, leading to an I-wave action potential. This network of neuronal activation, despite it originating at axonal bending or terminations, would cause an rCBF change.

Limitations

It has been shown that the location of fMRI activation and the optimal location for TMS of the FDI muscle in M1 can vary by as much as 14 mm [40,54,55], leading to a possible over-stimulation of cortex if the coil location is determined from fMRI. Recently, Diekhoff et al. [56] studied this discrepancy with respect to fMRI acquisition sequence and found that Gradient-Echo (GRE-BOLD) fMRI was the best option to minimize this difference in location. However, while Diekhoff et al. used fMRI scans to position the coil, they did not vary the coil’s orientation. The research presented in this article used GRE-BOLD fMRI sequences to find the optimal coil position, but orientation was determined per subject based

on the cortical column cosine model. While the coil position may have been slightly spatially different from the optimal RMT location found by other means, the proper coil orientation would have minimized any over-stimulation of the cortex.

Similarly, a recent study by Thordstein et al. [57] showed that lower MEP thresholds could be used to produce a more sensitive RMT estimate (e.g., 50 μ V instead of the 100 μ V used here). When this data were acquired (~2007) the standard and accepted definition of RMT was followed. While this might have led to a small overestimation of RMT and subsequent over-stimulation, this is believed to have a minor effect on these findings.

Conclusions

The results presented in this research may provide a more coherent framework for predicting cortical responses to TMS treatment that would permit more precise targeting of cortical areas in the brain during clinical or research applications. Thus, by accounting for cortical (i.e., columnar) orientation, practitioners may more efficiently deliver TMS to the desired target regions. Furthermore, TMS application protocols that target different regions in the neocortex may need to pay particular attention to magnetic field profiles relative to the target regions in order to maximize the focality and efficacy of stimulation.

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Figure 1.

Calculation of cortical surface orientation (CSO) angles. (A) Schematic displaying unit-normal vectors for the scalp ($\hat{n}_s$) and cortical ($\hat{n}_c$) surfaces. Shown is an example of cortical normal and its closest scalp normal illustrating the relationship underlying the CSO angle (θ) [left inset]. Calculation of the CSO angle for nodes C1, C2, C3 where S1, S2, S3 are the closest corresponding scalp nodes, respectively [right inset]. (B) The CSO angle of one subject's entire cortical surface is displayed showing how the CSO angle is distributed. The color bar at the bottom indicates range of θ in panel. Inset shows a coronal slice of cortex and CSO values. Note that the top of gyral crowns and the bottom of the sulcal valleys have similar CSO angles (highlighted by arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Figure 2.

Using CSO angles to compare median θ_{ALL} , θ_{TMS} , and θ_{TASK} values. Statistical analysis shows significant differences between both the median θ_{TMS} and θ_{TASK} datasets when compared to the θ_{ALL} values (** $P < 0.001$). The inset demarcates the approximate location of median CSO angle, in which location shading corresponds to bar graph shading. While this figure only shows ROI of 20 mm radius, both 10 mm and 30 mm ROIs were tested and similar results were obtained.

Figure 3.

CSO angle changes with increasing Z -score threshold. The median CSO angles for task- and TMS-evoked activations exhibited variation as the Z -score threshold was increased. Data shown are for 20 mm ROI (10 and 30 mm results were similar). The median CSO angle for the task-based activation increases with an increasing Z -score threshold demonstrating that cortical activations are more likely occurring on the sulcal bank rather than the gyral crown

Figure 4.

Correlation of the distance from the scalp to point of maximal activation per subject evoked by TMS and the finger-tapping task. The distance between the scalp surface and the cortical surface point of maximum blood flow was highly correlated between the finger-tapping task and TMS at different stimulus intensities ($P < 0.001$). These results suggest that both cortical activation modalities produced maximal blood flow at very similar depths in the cortex.

Figure 5.

Correlation of the CSO angle at the point of maximal activation per subject evoked by TMS and the finger-tapping task. The angles between the scalp surface and the cortical surface point of maximum blood flow were highly correlated for the finger-tapping task and TMS ($P < 0.001$). These results suggest that both cortical activation modalities produced maximal blood flow at similar locations on the sulcal banks in the cortex.