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**TMS Activation Site Estimation Using Multiscale Realistic
Head Models**

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Abstract

Objective: Transcranial magnetic stimulation (TMS) activates brain structures non-invasively. Computational models can be used to elucidate the activation site; however, the exact activation site is controversial. The aim is to present an imaging technique of the TMS activation cortical site estimation using individualized multi-scale realistic head models based on experimentally-derived TMS fields.

Approach: The induced electric field (EF) was computed using subject-specific head models and experimental-specific TMS coil configuration during suprathreshold stimulation for relaxed muscles. The experimentally-derived EFs were used to calculate the activation of pyramidal tract model embedded in the head models to derive the activation site on the cortical surface at the macroscopic level.

Main Result: The TMS activation site was located at the anterior wall of the central sulcus, which agreed with a concurrent TMS/fMRI study. In contrast, the EF strength was not entirely consistent with TMS/fMRI studies. Multiscale physical modelling is a feasible imaging technique to investigate the activation site for TMS.

Significance: By combining subject-specific multiscale modelling with experimental TMS measurements, we showed that this method could serve as a TMS imaging technique at suprathreshold condition.

Keywords:

Transcranial Magnetic Stimulation; Multiphysics Modelling; Electric Field; Nerve model; Personalized computation

1. Introduction

Transcranial magnetic stimulation (TMS) usually activates the cortical regions noninvasively by inducing a current in the brain with a magnetic coil placed over the scalp [1]. TMS is used for diagnosis and therapy for various neurological/psychiatric disorders. It is also used to understand the *in vivo* human brain function, in which the most common protocol is to measure the motor-evoked potential (MEP) when targeting the hand motor area [2,3], whereas the activation site on the cortical surface is used as metric for navigation systems and pre-surgical identification of brain functions [4–6]. Depending on the relative coil orientation and stimulus intensity, different circuitries within the motor cortex (M1) contribute to MEP generation [7,8]. However, evidence of how TMS interacts with the brain at the level of neurons is scarce due to difficulties in the *in vivo* direct measurements in the human brain [9].

Computational electromagnetics have recently been used as a complementary approach for experiments. The computed electric field (EF) in the brain is considered the main physical agent that activates neurons and thus, was used as a metric of the stimulation location in different studies [5,10–16]. Recently, computations of individualized electric fields (EFs) based on experimental measurements have been conducted [10,17,18]. These studies showed that the coil orientation, which induces posterior-anterior-directed currents in the hand motor area, results in the highest EF magnitude in the gyral crown [10,19]. Other studies suggested that TMS acts on the sulcal anterior wall where the effective stimulation corresponds to the EF component that is locally normal to the wall [20], or to the ventral and lateral parts of the hand knob [18]. The activation site, however, should be affected by the characters of activated neurons in addition to the EF distributions [21,22].

The multiscale approach (realistic biophysical modeling of the EF coupled to neuronal membranes) offers a more detailed description of TMS-induced effects [21,23–28]. Previous TMS multiscale approaches presented results that match the experimental observations using a single subject, and that mimics the general TMS experimental conditions. Individualized induced

EF computation based on TMS experiments with multi-scale modelling may allow a more detailed study of TMS. A difficulty in the multi-scale approach is the complexity of the neuronal models to investigate the TMS mechanism with its validation. As different neurons in the cortical circuits may be engaged depending on the induced current direction, coil current intensity, and measurement condition (e.g., relax or active muscle) [29,30], one alternative is to investigate a specific TMS condition that allows the application of simplified but plausible neuronal models [21,31].

This study aims to present an imaging technique of cortical activation site at a macroscopic level using subject-specific multiscale modelling based on physiological responses of suprathreshold TMS experiments targeting the hand motor cortex. The multiscale model computes the activation of pyramidal tract neurons embedded in the hand motor area from individualized induced EFs based on individual MR images during experimental suprathreshold TMS for relaxed muscles in eight subjects. Finally, the macroscopic activation site is verified with results of the previous concurrent suprathreshold TMS/fMRI studies.

2. Materials and methods

2.1 Subjects

Eight healthy right-handed volunteers (two females, mean age 21.8 ± 3.2 years old) participated in this study. None of the participants had any contraindications to TMS, took any medication on a regular basis, or had a history of psychiatric or neurological diseases [32]. A written informed consent was obtained from all the subjects before their participation. The study was approved by the local ethics committee of Fukushima Medical University and conformed to the latest version of the Declaration of Helsinki.

2.2 Magnetic Resonance Imaging

Structural T1- and T2-weighted MRI scans were acquired using a 3 Tesla MRI scanner (Siemens Biograph mMR). The acquisition parameters were as follows: T1 MPRAGE sequence with

TR/TE/TI/FA/FOV/voxel size/slice number = 1800 ms/1.99 ms/800 ms/9°/256 mm/0.976 mm x 0.976 mm x 1.0 mm/176, and T2 with TR/TE/FOV/voxel size/slice number = 3200ms/361 ms/256 mm/0.488 mm x 0.488 mm x 1.0 mm/176.

2.3 Electromyography (EMG) recording

The subjects sat on a comfortable reclining armchair during the MEP recording. MEPs were recorded from the right first dorsal interosseous (FDI) muscle by surface EMG. Pairs of Ag/AgCl electrodes were placed on the muscle belly and the metacarpophalangeal joint of the index finger. The EMG raw signal was amplified and band-pass filtered (100–3000 Hz; MultiAmplifier 1000; DIGITEX LAB Co. Ltd., Japan). The signals were digitized at 5 kHz, and data were stored on a computer for later offline analysis (MultiStim Tracer; Medical Try System, Japan).

2.4 Transcranial magnetic stimulation

Single-pulse TMS was applied with a Magstim 200² magnetic stimulator (Magstim Co., UK) connected to a figure-of-eight coil (external loop diameters, 70 mm). The current waveform was monophasic. The stimulating coil was held tangentially to the skull with the coil handle pointing backward and laterally at 45° from the anterior-posterior axis. The center of the coil junction was placed over the M1 hand area of the left hemisphere (motor hotspot). The “motor hotspot” was detected as the site where TMS consistently elicited the largest motor-evoked potentials (MEPs) from the right FDI muscle. The coil position was marked on the scalp with a felt pen alongside the front edge of the TMS coil to ensure constant coil placement throughout the experiment. At the hotspot, the stimulus intensity was adjusted to produce MEPs of, on average, 1 mV peak-to-peak amplitude in the relaxed FDI muscle. This measured threshold was expressed as the percentage of the maximum stimulation output (MSO). Fifteen MEPs were measured and averaged for a single stimulation point. The inter-trial interval varied between 6.0 s and 8.0 s to limit the anticipation of the next trial.

2.5 Anatomical Head Models

The brain and non-brain tissues of the head was segmented into a total of 14 tissues and body fluids (skin, fat, muscle, outer skull, inner skull, gray matter, white matter, cerebellar gray matter, cerebellar white matter, brainstem, nuclei, ventricles, cerebrospinal fluid, and eye tissues) using an in-house software [33] equipped with the FreeSurfer brain imaging software package [34], as shown in Fig. 1. In brief, the FreeSurfer image analysis software [34,35] was used to reconstruct the surfaces of the gray and white matter. Non-brain tissues were segmented from T1- and T2-weighted MRIs with a semi-automatic procedure of region-growing and thresholding techniques, as described previously [33]. Note that the cerebrospinal fluid is the volume inside the skull that is not classified as either nervous tissue or blood explicitly. The detailed parameters of the MRI acquisitions can be found in our previous study [18].

2.6 Coil Position

The coil position in the model was reconstructed offline based on the calculation of geodesic distances from several anatomical landmarks on a 3D surface model of the scalp surface as described in the previous work [18]. In brief, the coil was placed at the intersections of the constant distance contours from the nasion and left and right pre-auricular points. Only two distances were needed to define the location uniquely. The third distance was added for verification and removal of possible errors in the distance measurement. The point that minimized the root-mean-square error in the distances was selected as the coil location. The stimulating coil was fixed at 45° as explained in the TMS protocol but not recorded because we estimated that it had a marginal impact on the EF. The error caused by the coil placement was estimated to be at most a few millimeters, which would have a minor impact on the EFs [18].

2.7 Electromagnetic Computation

We used a volume conductor model to compute the induced EFs in the head models. We assumed that the electric displacement current is negligible when compared to the conduction

current (magneto-quasi-static approximation) and that the induced current does not perturb the external magnetic field [36]. A thin-wire approximation of the magnetic coil and the Biot–Savart law were used to model the magnetic vector potential. The coil consisted of two wings with nine concentric current loops spaced equally. The innermost and outermost loops had diameters of 7.2 and 9.7 cm, respectively. The time derivative of the magnetic vector potential $\frac{\partial A}{\partial t}$ was computed, and the electric scalar potential induced in the brain φ was determined from

$$\nabla \cdot \sigma \nabla \varphi = -\nabla \cdot \sigma \frac{\partial A}{\partial t}, \quad (1)$$

where σ is the electric conductivity, as a scalar piecewise constant conductivity, using the same values in [18]. The induced EF is calculated from

$$\mathbf{E} = -\nabla \varphi - \frac{\partial}{\partial t} \mathbf{A}. \quad (2)$$

Equation (1) was solved numerically by the finite-element method with first-order cubical elements (0.488-mm voxel of the volume conductor model), using an in-house software implemented with the geometric multigrid method with successive over-relaxation to solve the matrix equation resulting from the discretization of equation (1), as described in [36]. The basic principle of the geometric multigrid method was to use multiple numerical grid sizes to speed up the convergence of the numerical solution. The total induced EF in equation (2) was coupled with the pyramidal tract model in the next subsection.

The stimulation intensity of 100 % MSO corresponded to a 174 A/μs peak time derivative of the coil current [18,37,38]. The computed induced EF and scalar electric potential corresponded to temporal peak values. The waveform of the induced EF and scalar potential was assumed to be identical to the measured value using the same stimulator device [37], as shown in Fig. 2B-1.

The validation of the computed individualized induced EF was confirmed before by a good agreement between the computed hotspot based on TMS mapping and measured hotspot via direct

cortical stimulation during awake craniotomy [5]. Moreover, the measurements of induced EF distribution matched with the computed ones [38].

2.8 Microscale model of Pyramidal Tract

The effects of the computed extracellular electric scalar field were investigated on pyramidal axons originating from the motor area using the same coil orientation/position during suprathreshold TMS experiments. For each axon, the smallest stimulator output intensity to elicit a computational suprathreshold response was derived, as described by the following equation:

$$c_m \frac{dV_{m,n}}{dt} + \sum_x g_x (V_m - V_x) - \frac{\Delta^2 V_{m,n}}{R} = \frac{\Delta^2 \varphi}{R}, \quad (3)$$

where c_m is the membrane capacitance, $V_{m,n}$ is the membrane potential at position n along the axon, and the variable R denotes the intra-axonal resistance between the centers of two adjacent compartments. We have shown that pyramidal axon excitability could be described by the spatially extended nonlinear nodal representation of the axon [39,40] with nodes of Ranvier modeled by Chiu–Ritchie–Rogart–Stagg–Sweeney model (CRRSS [41]) for intraoperative stimulation. In brief, the spatial structure of the myelinated neuron consists of internodes (segments ensheathed by myelin) concatenated with nodes of Ranvier (ionic channels). At the nodes of Ranvier, the ionic membrane current depends on the dynamics of voltage-gated channels, which is formulated as a conductance-based voltage-gated model. At the myelinated internodes, the leak conductance g_x was modeled as a passive element.

The right-hand part of Eq. (3) corresponded to $\Delta^2 \varphi = \varphi(n-1) - 2\varphi(n) + \varphi(n+1)$, which described the driving term of activation. To incorporate the total induced electric field $\mathbf{E}$ of Eq. (2) in Eq. (3), the quasi-potential method was applied [42]. A local linear integral of the EF along the cable model's trajectory was used to obtain the extracellular driving potential φ :

$$\varphi = - \int \mathbf{E} \cdot d\mathbf{l}. \quad (4)$$

The terminal condition used for the proximal axon node at the seed point was clamped at 0 V. The length of the axon was of 3.5 cm on average.

The computed activated threshold is the lowest stimulus intensity necessary to propagate an action potential for each fast-conducting thickly myelinated pyramidal fibers (Betz cell's axon), 10 μm in diameter, that are embedded in the hand knob [43,44]. Consequently, the conduction velocity of the model was 58 m/s, which is close to pyramidal tract measurements (67 m/s) [43,45].

The 3D spline interpolation of the total induced EF components was obtained along the nerve axon path for Eq. (4). The difference between the resolutions of the nerve model (microscale) and induced EF (mesoscale) was not significant in our work, considering that the distance between node and internode was the same as the resolution of the volume conductor model (0.488 mm). Moreover, we investigated the effect of the resolution of the volume conductor model by using a volume conductor model with resolutions two times smaller (0.976 mm) and two times higher (0.244 mm). The thresholds of all axons in one subject varied on average by 2.8% between 0.976-mm and 0.244-mm and 1.5% between 0.488-mm and 0.244-mm model resolutions. Thus, higher resolutions of the volume conductor did not affect the interpolation of the EFs significantly. The elicitation of an action potential was indicated by the depolarization of the transmembrane potential by 80 mV, in at least three consecutive nodes using an in-house code [46] implemented in MATLAB using ode15s VSVO. The stimulation intensity was modified using a binary search algorithm to find the activation threshold until the preciseness of the intensity was lower than $1 \times 10^{-3} \text{ A}/\mu\text{s}$. The implemented model has been verified for the intraoperative stimulation of the corticospinal tract [46].

2.9 Pyramidal axons distribution and activation maps

Large pyramidal neurons originate from the gray matter (layer V), cross the gray–white matter interface almost perpendicularly, and descend to form the pyramidal tracts. In consequence, the pyramidal axons that start from the gyral wall bend when entering the white matter, and the pyramidal axons that start from the gyral crown descends in a straight line. As the activation effect of the EF increases in the axon bend [31], the bending of the pyramidal cell axon was included in

the model, and sensitivity analysis of bending level was investigated in Fig. 5. For the axon bending, we used prior anatomical information from stained pyramidal cell images [47,48] and previous computational implementations [23–25,49]. The axon pathways were embedded in the hand knob of the primary motor cortex [50] at an average of 2.5 mm below the cortical surface, as shown in Fig. 2C. A detailed explanation of the generation of the pyramidal axon models with different possible bending levels adjustment can be found in Appendix A. As the bend angle varies locally at different sites where the axon projects from the white-gray matter interface, we used a general term to describe a global bending level in M1. The map of the activation thresholds for all axons was projected in the motor cortex based on the initial position of each pyramidal axon, as shown in Fig. 2B-2.

2.10 Data Analysis

Individual activation maps were compared with previous concurrent suprathreshold TMS/fMRI targeting abductor pollicis brevis (APB) ($x = -32$, $y = -32$, $z = 68$, $n = 18$) by Shitara et. al. 2011 in [51,52]. In their work, the proprioceptive afferent sensory feedback caused by the muscle twitches were suppressed to obtain a pure TMS imaging. A summary of the imaging experiments is listed in Table 1.

An accuracy measurement (true positives divided by false positives) quantified the agreement between computed and reference hotspots (TMS/fMRI or PET-fMRI) in Table 2. True positives were considered for computed hotspots within a Euclidean distance of 5-10 mm from the reference hotspots. Otherwise, the hotspot was considered a false positive. Although it is difficult to define a specific range for a true positive, a prediction distance in the range of 5-10 mm was possible during preoperative mapping by TMS [5,53].

The computed hotspots were defined as 1) the position of minimum stimulus intensity in the activation map and 2) the center of gravity (CoG) of the activation maps. CoG is the mean location of the points located in the activation map region enclosed by the experimental stimulus suprathreshold intensity with coordinates r_i weighted by respective activation map intensity (SI)

as $(\sum SI(r_i) \cdot r_i) / \sum SI(r_i)$. The described computations were performed for each subject, and the mean and standard error of the mean were calculated for all subjects. In addition, the computed hotspot was obtained for the maximum EF or CoG calculated in the region $0.7 \times \max(EF)$. Furthermore, the hotspots of the activation map for each subject were registered on the standard brain template for comparison using a procedure similar to the one used in a previous study [33]. Similarly, the group-level analysis was conducted for the EF magnitude ($|EF|$), parallel (pEF), and normal (nEF) components to the cortical surface. Finally, hotspots obtained from navigation system [54–56] and EF-based metrics were presented. These metrics were based on measurements of motor threshold in voluntary contracted or relaxed muscle. The EF-based metrics included minimal relative standard deviation of weighted EFs [10], and the maximum correlation was obtained between normalized MT and inverse of the normalized $|EF|$ or nEF [18].

3. Results

3.1 Activation Distribution

Individualized activation maps are shown in Fig. 3A. They are obtained from direct activation of the pyramidal axon using TMS experimentally-derived EFs targeting FDI muscle. Enclosed areas showed the activation regions by the experimental stimulus intensity adjusted to produce MEPs of 1 mV peak-to-peak. The previous results on concurrent suprathreshold TMS/fMRI and threshold TMS/PET imaging are also included.

The experimental spot by suprathreshold TMS/fMRI is within the enclosed regions in most of the subjects, as shown in Fig. 3A. In contrast, the spot by threshold TMS/PET is outside the enclosed regions in most of the subjects. The computational locations of the minimum stimulus intensity and CoG spots are projected to the standard brain for comparison due to the inter-individual difference of the cortical anatomy, as shown in Figs 3B and 3C. Also, the computed locations are distributed consistently at the anterior wall of the central sulcus towards the gyral lip. The CoG location derived from the activation map is the most accurate metric with respect to TMS/fMRI,

as listed in Table 2. The relationship between computed thresholds of different hotspots and measured stimulation thresholds was analyzed by linear regression analysis across the subjects. For the two hotspots derived from the activation map, the correlations are $R^2 = 0.60$ ($p = 0.02$) and $R^2 = 0.40$ ($p = 0.09$) for minimum and CoG hotspots, respectively. For the two reference hotspots from imaging modalities, the correlations are $R^2 = 0.39$ ($p = 0.11$) and $R^2 = 0.23$ ($p = 0.20$) for TMS/fMRI and TMS/PET hotspots, respectively. The same measurement condition between our measurement protocol and TMS/fMRI study (i.e., high intensity and relaxed muscles) can explain the stronger correlation observed, in contrast to TMS/PET study (i.e., active motor threshold).

3.2 EF distributions

Figures 4A–C show the group-level EF distributions that correspond to $|EF|$, pEF, and nEF components at suprathreshold condition, respectively. Additionally, the positions of the maximum and CoG values of the EFs are plotted for each subject. Group-level of $|EF|$ and pEF presented the hotspots in the crown at almost the same locations, while nEF presented hotspots in the anterior bank of the central sulcus. Figure 4D shows activation sites estimated by navigation system-based and EF-based methods in low-intensity TMS studies, which likely correspond to the activation of interneurons. These activation sites are presented as a reference to contrast the activation sites involved in direct activation of the pyramidal axons using suprathreshold TMS (figure 3C). Maximum and CoG hotspots of nEF (suprathreshold condition) resemble in part the locations by the multiscale approach (Fig. 3B). They are also similar to the locations by navigation system-based and EF-based metrics in Fig. 4D. In general, EF-based metrics are closer to the TMS-PET hotspot (threshold condition) than TMS-FMRI (suprathreshold condition).

3.3 Bending Effect

The effect of the bending extent of the pyramidal axons is shown in Fig. 5. The activation thresholds of ten different bending cases were considered for each of the 40 pyramidal axons from

the hand–knob region (Figs. 5A–B). As a reference, the bend radius of axon number thirty varied from 1.5 mm (bending level 1) to 0.01 mm (bending level 10). A detailed explanation of the bending variation can be found in Appendix A.

In Fig. 5C, the first 15 axons corresponding to the crown and posterior lips were not activated for 100% MSO. The activation threshold was reduced for deeper sulcal position of the axons. We found a relative standard deviation of 20% of the activation thresholds between different bending levels. Moreover, we found no significant differences between the 3D activation maps with different bending levels. The larger variation of the hotspot at different bending was smaller than 0.7 mm and 3.5 mm for minimum intensity and CoG hotspots, respectively.

4. Discussion

This study computationally estimated the cortical activation site driven by experimentally-derived TMS targeting FDI muscle using individualized multi-scale realistic head models to determine direct activation of pyramidal tract neurons based on the accurate computation of the induced EF. The activated neurons depend on the current direction and the intensity of TMS. The low intensity, posterior-anterior or anterior-posterior directed TMS readily activates interneurons (I-waves), and high-intensity stimulation added D-wave activation [29]. In our experiment, we elicited 1 mV MEPs in the relaxed condition. In this recording setting, we used considerably higher-intensity stimulation, which should activate D-waves in most of the subjects. It is, therefore, plausible that the threshold for relaxed muscles may mostly reflect the threshold for D-wave activation. In addition to direct activation, interneurons are also activated during suprathreshold condition, which also contributes to MEP production. In the case of recording from active muscles and low-intensity TMS, the activation of interneurons mainly contributes to MEP production, which is not the target of this study. Thus, we used a pyramidal tract neurons model validated with experimental threshold–distance relationship during brain surgery [49]. Pyramidal axons were embedded in the motor area based on the anatomical location of Betz cells.

Suprathreshold and threshold concurrent fMRI or PET were used to compare the results of this study. The hotspots were located near the gyrus lip in the sulcus or deeper in the sulcus [20,57,58]. The difference in the depth of the fMRI hotspot can be explained by the activation of proprioceptive afferent sensory feedback caused by the muscle twitches between the threshold and suprathreshold conditions. To the best of our knowledge, there is only one concurrent TMS-fMRI study at suprathreshold condition in which the proprioceptive afferent sensory feedback caused by the muscle twitches was suppressed to have a purely TMS imaging [52]. Our results agreed with the computed activation site by the concurrent TMS/fMRI experiment [51] in the sulcal wall close to the lip of the gyrus instead of stimulation deeper in the sulci as proposed by the cortical column cosine model [20]. Also, linear regression analysis showed that the model thresholds at the putative threshold site correlate with the experimental motor thresholds. The minimum threshold position seemed to correlate most strongly with experiments and reach significance, while the CoG position explained less of the variability in the experimental motor thresholds and barely reaching significance. The correlations with the activation sites from the imaging modalities were not significant to explain the experimental motor thresholds. One limitation of imaging modalities is that measured metabolic changes can capture the summation of large neural populations' activities over several seconds and not the immediate electric effects of TMS [2].

EF distributions and different EF-based metrics are used as common physical quantities to investigate TMS hotspots [5,10,17,18,53] and are employed in neuro-navigation systems [59]. In particular, the normal component of the EF partially agreed with the multiscale modelling [10]. However, the normal component of the EF is also distributed in the ventral and lateral hand knob and similar to EF-based methods for motor threshold TMS studies, as shown in Fig. 4D [18]. As the EF does not assume specific neural circuitries, it is also possible that activation sites near the crown, as shown by EF, is related to activity from interneurons in particular for threshold conditions [10,18,28]. Other predictors may also be applied [60,61]. For instance, the activating

function did not show the same activation sites like the ones obtained by the neuron model [62], as shown in Appendix A2.

To investigate the consistency of the activation maps, we evaluated the effect of the bending degree used in the pyramidal axons models. No significant variation was found in terms of hotspots location and distribution of the activation map (Fig. 5). Another potential source of variability was the trajectory of the axon paths deep inside the gyri, but it was not expected to affect the results as the activation was initiated at the bending region. Some differences can be produced due to anisotropic effects of the white matter or small errors related to the estimation of the coil orientation in the experiments. The abrupt change of the conductivity in the interface of the gray and white matter generates high EF gradients may affect the activation site. However, the sharpness of the discontinuity did not have a significant influence in the pyramidal axon activation considering the length between the midpoints of the internode and the Ranvier node (a half millimeter). Also, we confirmed that the activation site still occurred at the bending part using a head model with homogeneous conductivity of the gray and white matter.

Finally, our experiments explain the site of direct corticospinal axon activation (D-wave) to initiate MEP using high-intensity TMS. However, the contributions of direct and indirect descending activity on eliciting the MEP are unknown during high-intensity TMS, and the site of direct activation may differ from the intracortical site of activation responsible for the indirect descending activity. Thus, modelling of interneurons, as well as corticospinal tract neurons and their interconnections, are necessary for explaining the full evoked MEP for several TMS experimental conditions [28,64,65].

5. Conclusion

There is a difficulty in revealing the TMS mechanism by experimental or computational approaches alone. This study showed that multiscale modelling complemented with experimental measurements helps to characterize cortical activation site for suprathreshold TMS. The proposed

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4 imaging technique by multiscale modelling agreed with concurrent TMS/fMRI measurements at
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6 suprathreshold TMS for relaxed muscles.
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Reference

- [1] Barker A T, Jalinous R and Freeston I L 1985 Non-invasive magnetic stimulation of human motor cortex *Lancet (London, England)* **1** 1106–7
- [2] Rossini P M, Burke D, Chen R, Cohen L G, Daskalakis Z, Di Iorio R, Di Lazzaro V, Ferreri F, Fitzgerald P B, George M S, Hallett M, Lefaucheur J P, Langguth B, Matsumoto H, Miniussi C, Nitsche M A, Pascual-Leone A, Paulus W, Rossi S, Rothwell J C, Siebner H R, Ugawa Y, Walsh V and Ziemann U 2015 Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee *Clin. Neurophysiol.* **126** 1071–107
- [3] George M S and Aston-Jones G 2010 Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) *Neuropsychopharmacology* **35** 301–16
- [4] Takakura T, Muragaki Y, Tamura M, Maruyama T, Nitta M, Niki C and Kawamata T 2017 Navigated transcranial magnetic stimulation for glioma removal: prognostic value in motor function recovery from postsurgical neurological deficits *J. Neurosurg.* 1–15
- [5] Aonuma S, Gomez-Tames J, Laakso I, Hirata A, Takakura T, Tamura M and Muragaki Y 2018 A high-resolution computational localization method for transcranial magnetic stimulation mapping *Neuroimage* **172** 85–93
- [6] Picht T, Mularski S, Kuehn B, Vajkoczy P, Kombos T and Suess O 2009 Navigated Transcranial Magnetic Stimulation for Preoperative Functional Diagnostics in Brain Tumor Surgery *Oper. Neurosurg.* **65** ons93-ons99
- [7] Terao Y and Ugawa Y 2002 Basic mechanisms of TMS *J. Clin. Neurophysiol.* **19** 322–43
- [8] Di Lazzaro V, Profice P, Ranieri F, Capone F, Dileone M, Oliviero A and Pilato F 2012 I-wave origin and modulation *Brain Stimul.* **5** 512–25
- [9] Li B, Virtanen J P, Oeltermann A, Schwarz C, Giese M A, Ziemann U and Benali A 2017 Lifting the veil on the dynamics of neuronal activities evoked by transcranial magnetic stimulation *Elife* **6**
- [10] Bungert A, Antunes A, Espenhahn S and Thielscher A 2017 Where does TMS Stimulate the Motor Cortex? Combining Electrophysiological Measurements and Realistic Field Estimates to Reveal the Affected Cortex Position *Cereb. Cortex* **27** 5083–94
- [11] Gomez-Tames J, Hamasaka A, Laakso I, Hirata A and Ugawa Y 2018 Atlas of optimal coil orientation and position for TMS: A computational study *Brain Stimul.* **11** 839–48
- [12] Thielscher A, Opitz A and Windhoff M 2011 Impact of the gyral geometry on the electric field induced by transcranial magnetic stimulation *Neuroimage* **54** 234–43
- [13] Nummenmaa A, Stenroos M, Ilmoniemi R J, Okada Y C, Hämäläinen M S and Raji T 2013 Comparison of spherical and realistically shaped boundary element head models for transcranial magnetic stimulation navigation *Clin. Neurophysiol.* **124** 1995–2007
- [14] Laakso I, Hirata A and Ugawa Y 2014 Effects of coil orientation on the electric field induced by TMS over the hand motor area *Phys. Med. Biol.* **59** 203–18
- [15] Thielscher A and Kammer T 2004 Electric field properties of two commercial figure-8 coils in TMS: calculation of focality and efficiency *Clin. Neurophysiol.* **115** 1697–708
- [16] Iwahashi M, Gomez-Tames J, Laakso I and Hirata A 2017 Evaluation method for *in situ* electric field in standardized human brain for different transcranial magnetic stimulation coils *Phys. Med. Biol.* **62** 2224–38
- [17] Krieg T D, Salinas F S, Narayana S, Fox P T and Mogul D J 2015 Computational and experimental analysis of TMS-induced electric field vectors critical to neuronal activation *J. Neural Eng.* **12** 046014

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- [18] Laakso I, Murakami T, Hirata A and Ugawa Y 2018 Where and what TMS activates: Experiments and modeling *Brain Stimul.* **11** 166–74
- [19] Opitz A, Legon W, Rowlands A, Bickel W K, Paulus W and Tyler W J 2013 Physiological observations validate finite element models for estimating subject-specific electric field distributions induced by transcranial magnetic stimulation of the human motor cortex *Neuroimage* **81** 253–64
- [20] Fox P T, Narayana S, Tandon N, Sandoval H, Fox S P, Kochunov P and Lancaster J L 2004 Column-based model of electric field excitation of cerebral cortex *Hum. Brain Mapp.* **22** 1–14
- [21] Salvador R, Silva S, Basser P J and Miranda P C 2011 Determining which mechanisms lead to activation in the motor cortex: A modeling study of transcranial magnetic stimulation using realistic stimulus waveforms and sulcal geometry *Clin. Neurophysiol.* **122** 748–58
- [22] Wongsarnpigoon A and Grill W M 2008 Computational modeling of epidural cortical stimulation *J. Neural Eng.* **5** 443–54
- [23] Goodwin B D and Butson C R 2015 Subject-Specific Multiscale Modeling to Investigate Effects of Transcranial Magnetic Stimulation *Neuromodulation Technol. Neural Interface* **18** 694–704
- [24] Seo H, Kim D and Jun S C 2016 Effect of Anatomically Realistic Full-Head Model on Activation of Cortical Neurons in Subdural Cortical Stimulation-A Computational Study *Sci. Rep.* **6** 27353
- [25] Nummenmaa A, McNab J A, Savadjiev P, Okada Y, Hämäläinen M S, Wang R, Wald L L, Pascual-Leone A, Wedeen V J and Rajj T 2014 Targeting of White Matter Tracts with Transcranial Magnetic Stimulation *Brain Stimul.* **7** 80–4
- [26] Soldati M, Mikkonen M, Laakso I, Murakami T, Ugawa Y and Hirata A 2018 A multi-scale computational approach based on TMS experiments for the assessment of electro-stimulation thresholds of the brain at intermediate frequencies *Phys. Med. Biol.* **63** 225006
- [27] De Geeter N, Lioumis P, Laakso A, Crevecoeur G and Dupré L 2016 How to include the variability of TMS responses in simulations: A speech mapping case study *Phys. Med. Biol.* **61** 7571–85
- [28] Aberra A S, Wang B, Grill W M and Peterchev A V. 2020 Simulation of transcranial magnetic stimulation in head model with morphologically-realistic cortical neurons *Brain Stimul.* **13** 175–89
- [29] Lazzaro V, Oliviero A, Mazzone P, Insola A, Pilato F, Saturno E, Accurso A, Tonali P and Rothwell J 2001 Comparison of descending volleys evoked by monophasic and biphasic magnetic stimulation of the motor cortex in conscious humans *Exp. Brain Res.* **141** 121–7
- [30] Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, Mazzone P, Tonali P and Rothwell J C 1998 Effects of voluntary contraction on descending volleys evoked by transcranial stimulation in conscious humans *J. Physiol.* **508** (Pt 2 625–33
- [31] Maccabee P J, Amassian V E, Eberle L P and Cracco R Q 1993 Magnetic coil stimulation of straight and bent amphibian and mammalian peripheral nerve in vitro: locus of excitation. *J. Physiol.* **460** 201–19
- [32] Rossi S, Hallett M, Rossini P M, Pascual-Leone A and Safety of TMS Consensus Group T S of T C 2009 Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research *Clin. Neurophysiol.* **120** 2008–39
- [33] Laakso I, Tanaka S, Koyama S, De Santis V and Hirata A 2015 Inter-subject variability in electric fields of motor cortical tDCS *Brain Stimul.* **8** 906–13
- [34] Dale A M, Fischl B and Sereno M I 1999 Cortical Surface-Based Analysis *Neuroimage* **9** 179–94
- [35] Fischl B 2012 FreeSurfer *Neuroimage* **62** 774–81
- [36] Laakso I and Hirata A 2012 Fast multigrid-based computation of the induced electric field for transcranial magnetic stimulation *Phys. Med. Biol.* **57** 7753

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- [37] Nieminen J O, Koponen L M and Ilmoniemi R J 2015 Experimental Characterization of the Electric Field Distribution Induced by TMS Devices *Brain Stimul.* **8** 582–9
- [38] Çan M K, Laakso I, Nieminen J O, Murakami T and Ugawa Y 2018 Coil model comparison for cerebellar transcranial magnetic stimulation *Biomed. Phys. Eng. Express* **5** 015020
- [39] McNeal D 1976 Analysis of a model for excitation of myelinated nerve *IEEE Trans. Biomed. Eng.* **4** 329–37
- [40] Reilly J P, Freeman V T and Larkin W D 1985 Sensory effects of transient electrical stimulation-evaluation with a neuroelectric model. *IEEE Trans. Biomed. Eng.* **32** 1001–11
- [41] Sweeney J D, Mortimer J T and Durand D 1987 Modeling of mammalian myelinated nerve for functional neuromuscular electrostimulation *IEEE 97th Annu. Conf. Eng. Med. Biol. Soc. Bost.* **9** 1577–8
- [42] Wang B, Grill W M and Peterchev A V. 2018 Coupling Magnetically Induced Electric Fields to Neurons: Longitudinal and Transverse Activation *Biophys. J.* **115** 95–107
- [43] Firmin L, Field P, Maier M A, Kraskov A, Kirkwood P A, Nakajima K, Lemon R N and Glickstein M 2014 Axon diameters and conduction velocities in the macaque pyramidal tract *J. Neurophysiol.* **112** 1229–40
- [44] Rivara C, Sherwood C, Bouras C and Hof P 2003 Stereologic characterization and spatial distribution patterns of Betz cells in the human primary motor cortex *Anat. Rec.* **270A** 137–51
- [45] Snooks S J and Swash M 1985 Motor conduction velocity in the human spinal cord: slowed conduction in multiple sclerosis and radiation myelopathy. *J. Neurol. Neurosurg. Psychiatry* **48** 1135–9
- [46] Gomez-Tames J, Kutsuna T, Tamura M, Muragaki Y and Hirata A 2018 Intraoperative direct subcortical stimulation: comparison of monopolar and bipolar stimulation *Phys. Med. Biol.* **63** 225013
- [47] Amunts K and Zilles K 2015 Architectonic Mapping of the Human Brain beyond Brodmann *Neuron* **88** 1086–107
- [48] Mai J K and Paxinos G 2012 *The human nervous system* (Elsevier Academic Press)
- [49] Gomez-Tames J, Hirata A, Tamura M and Muragaki Y 2019 Corticomotoneuronal Model for Intraoperative Neurophysiological Monitoring During Direct Brain Stimulation *Int. J. Neural Syst.* **29** 1850026
- [50] Yousry T A, Schmid U D, Alkadhi H, Schmidt D, Peraud A, Buettner A and Winkler P 1997 Localization of the motor hand area to a knob on the precentral gyrus. A new landmark *Brain* 141–57
- [51] Shitara H, Shinozaki T, Takagishi K, Honda M and Hanakawa T 2011 Time course and spatial distribution of fMRI signal changes during single-pulse transcranial magnetic stimulation to the primary motor cortex *Neuroimage* **56** 1469–79
- [52] Shitara H, Shinozaki T, Takagishi K, Honda M and Hanakawa T 2013 Movement and afferent representations in human motor areas: A simultaneous neuroimaging and transcranial magnetic/peripheral nerve-stimulation study *Front. Hum. Neurosci.* **7** 1–13
- [53] Opitz A, Zafar N, Bockermann V, Rohde V and Paulus W 2014 Validating computationally predicted TMS stimulation areas using direct electrical stimulation in patients with brain tumors near precentral regions *NeuroImage Clin.* **4** 500–7
- [54] Diekhoff S, Uludağ K, Sparing R, Tittgemeyer M, Cavaşoğlu M, von Cramon D Y and Grefkes C 2011 Functional localization in the human brain: Gradient-echo, spin-echo, and arterial spin-labeling fMRI compared with neuronavigated TMS *Hum. Brain Mapp.* **32** 341–57
- [55] Volz L J, Hamada M, Rothwell J C and Grefkes C 2015 What Makes the Muscle Twitch: Motor System Connectivity and TMS-Induced Activity *Cereb. Cortex* **25** 2346–53
- [56] Navarro de Lara L I, Tik M, Woletz M, Frass-Kriegel R, Moser E, Laistler E and Windischberger C 2017 High-sensitivity TMS/fMRI of the Human Motor Cortex Using a Dedicated Multichannel MR Coil *Neuroimage* **150** 262–9

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- [57] Takano B, Drzezga A, Peller M, Sax I, Schwaiger M, Lee L and Siebner H R 2004 Short-term modulation of regional excitability and blood flow in human motor cortex following rapid-rate transcranial magnetic stimulation *Neuroimage* **23** 849–59
- [58] Siebner H R, Takano B, Peinemann A, Schwaiger M, Conrad B and Drzezga A 2001 Continuous Transcranial Magnetic Stimulation during Positron Emission Tomography: A Suitable Tool for Imaging Regional Excitability of the Human Cortex *Neuroimage* **14** 883–90
- [59] Picht T, Schmidt S, Brandt S, Frey D, Hannula H, Neuvonen T, Karhu J, Vajkoczy P and Süss O 2011 Preoperative Functional Mapping for Rolandic Brain Tumor Surgery: Comparison of Navigated Transcranial Magnetic Stimulation to Direct Cortical Stimulation *Neurosurgery* **69** 581–9
- [60] Rattay F 1986 Analysis of models for external stimulation of axons *Biomed. Eng. IEEE Trans. BME* **33**, 974–7
- [61] Warman E, Grill W and Durand D 1992 Modeling the effects of electric fields on nerve fibers: determination of excitation thresholds *IEEE Trans. Biomed. Eng.* **39** 1244–54
- [62] Silva S, Basser P J and Miranda P C 2008 Elucidating the mechanisms and loci of neuronal excitation by transcranial magnetic stimulation using a finite element model of a cortical sulcus *Clin. Neurophysiol.* **119** 2405–13
- [63] Jones S E, Buchbinder B R and Aharon I 2000 Three-dimensional mapping of cortical thickness using Laplace’s equation *Hum. Brain Mapp.* **11** 12–32
- [64] Tuch D S, Reese T G, Wiegell M R and Wedeen V J 2003 Diffusion MRI of complex neural architecture. *Neuron* **40** 885–95
- [65] Economo C Von 2009 *Cellular structure of the human cerebral cortex* ed T ed L C Triarhou (Basel: Karger)
- [66] Plonsey R and Barr R C 1995 Electric Field Stimulation of Excitable Tissue *IEEE Trans. Biomed. Eng.* **42** 329–36
- [67] Warman E N, Grill W M and Durand D 1992 Modeling the Effects of Electric Fields on Nerve Fibers: Determination of Excitation Thresholds *IEEE Trans. Biomed. Eng.* **39** 1244–54
- [68] Lacadie C M, Fulbright R K, Rajeevan N, Constable R T and Papademetris X 2008 More accurate Talairach coordinates for neuroimaging using non-linear registration *Neuroimage* **42** 717–25

Appendix A: Nerve axon bending model

The region of interest (hand knob) is divided by transversal planes orthogonal to the midline in the gyral crown, as shown in Fig. A1a. For each plane, we assumed that the axon pathways are perpendicular to the cortical laminae [63,64]. To achieve this, we computed the EF in the cortical laminae by setting the region outside the gray matter and the region inside the white matter, to two different potentials (e.g., 1 V and -1 V), and solved the Laplace equation. The resulting perpendicular EF lines are used as the partial axon segment in the cortical laminae starting from the middle (i.e., 0 V) as approximation of Layer V location [65], as shown in Fig. A1c. The full axon pathway is completed by a basis-spline function of fourth order constructed with the partial axon in the cortical laminae and two control seed groups placed inside the white matter (Fig. A1c). One seed group lies on the shrunk boundary of the white-gray matter and the other in the “exit” part of the pathways (manually). The final pathways are shown in Fig A1d. The model included 40 planes, each with an average of 100 neuron axons per plane (an average of 4,000 axons in each subject). The final 3D-view of the neurons trajectories in the primary motor cortex is shown in Fig. 2C. To create models with different bending levels (Fig. A1e), control seeds placed at different shrunk boundaries of the white-gray matter were considered. Control seeds at a shrunk boundary proximal to the white-gray matter interface produced more bending (i.e., a smaller bend radius) than control seeds placed at a distal shrunk boundary. In Fig. 5, the bending levels from 1 to 10 had control seed placed at shrunk boundaries at a distance of 2.5, 2, 1.5, 1.12, 0.08, 0.5, 0.28, 0.1250, 0.03, and 0.01 mm from the white-gray matter interface. As a result, a different bending radius is feasible for the same projecting pyramidal axon from the gray-matter.

Appendix B: Activating function

The activating function (AF) is proportional to the spatial derivative of the electric field along the nerve and describes the capacity of TMS to depolarize neurons. [60]. This predictor is used to determine the depolarization and hyperpolarization regions in particular for short pulses in comparison to the time constant. Also, it is used to estimate the initial polarization of the membrane response at the highest AF intensity. In fig. B1-a, the estimation of the initiation site for each individual axon was in good agreement between AF and nerve model despite the limitation of AF near axon terminals. In contrast, fig.B1-b showed that the spatial distribution of the AF did not agree with Fig. 3A. One reason is that the extent of the depolarization changes with long pulses, such as in TMS, and critically affects the estimated peak values of the activating function [66]. To obtain a better estimation with low computation power, the membrane potential based on the passive cable equation can be considered [67].

Tables

Table 1 Summary of Imaging studies during suprathreshold TMS

Study	Subjects	TMS	Coil Positioning	Imaging	MNI Coordinate /Target
Shitara et.al 2011, 2013 [51,52]	<ul style="list-style-type: none"> 18 health adults (15 females) Mean age of 29.3 y.o (range: 20-46 years) 	<ul style="list-style-type: none"> An MRI-compatible figure-of-eight TMS coil (outer wing diameter of 7 cm) The TMS stimulator produced biphasic electrical pulses of approximately 250 μs duration and a rise time of 50 μs. 120% of the resting motor threshold (Rossini <i>et al.</i>, 1994). 	<ul style="list-style-type: none"> Coil positioned tangentially to the scalp at the hotspot was approximately 45° from the medial-lateral axis The hotspot evoked a maximal motor response in the right abductor pollicis brevis (APB) The TMS coil was fixed immobile to the scanner bed with a custom-made holder. 	<ul style="list-style-type: none"> Concurrent TMS-fMRI Suppression of proprioceptive afferent sensory feedback caused by the muscle twitches. 	<ul style="list-style-type: none"> x = -32 y = -32 z = 68 (APB)
Siebner et.al 2001 [58]	<ul style="list-style-type: none"> 6 healthy adults (one female) Mean age: 39 y.o (range: NR) 	<ul style="list-style-type: none"> A PET-compatible figure-of-eight TMS coil (outerwing diameter of 10 cm) The stimulus had a biphasic waveform with a pulse width of 200 μs, a rise time of 50 μs 90% of the active motor threshold (Rossini <i>et al.</i>, 1994) 	<ul style="list-style-type: none"> The handle of the coil was oriented perpendicularly to the plane of the coil. The hotspot evoked a maximal motor response in the right abductor pollicis brevis (FDI) Coils were kept in a constant position by a coil holder during the entire experiment 	<ul style="list-style-type: none"> -Concurrent TMS-PET 	<ul style="list-style-type: none"> x = -29 y = -31 z = 71 (FDI)^a

a: Talairach coordinates were transformed to MNI coordinates using the method in [68].

Table 2 Accuracy of different hotspots metrics with respect to measured hotspots (TMS/fMRI or TMS/PET).

Hotspot Metric	Accuracy [%]	
	a	b
	(TMS/fMRI)	(TMS/PET)
Maximum EF	00.0-12.5	00.0-12.5
Maximum nEF	00.0-37.5	00.0-25.0
Minimum Act. Map.	00.0-62.5	37.5-75.5
CoG EF	00.0-12.5	00.0-12.5
CoG nEF	00.0-37.5	00.0-62.5
CoG Act. Map	87.5-100	50.0-87.5

Figure Legends

Figure 1. Subject-specific human head model of one subject constructed from MRI participating in the TMS experiments. (A1-A2) Views of the axial and coronal slices of the T1- and T2-weighted MRIs with the boundary of some tissues visible. (B) Electrical conductivity of final segmented tissues. (C) Outer and inner skull surfaces, gray matter, and white matter.

Figure 2. TMS computational set-up based on suprathreshold TMS measurements. (A) Suprathreshold TMS activates FDI muscle (Posterior-anterior coil direction, MEP of 1 mV, 15 trials averaging). MEP waveform sample obtained during the experiments. (B1) The magnitude of the temporal peak value of the computed induced electric field (EF) for experimental stimulus suprathreshold intensity (SI). The temporal variation of the EF waveform is measured in [37] and used as input into the nerve model. (B2) The activation map of the primary motor cortex is shown in the original and standard brain space. The activation is shown from 10% to 150% of maximum stimulation output (MSO) of the device and equivalent dI/dt of the coil current. The enclosed region by the white line corresponds to suprathreshold activation area in the activation map. (C) The activation map of thresholds is derived from the computation of the action potential of each pyramidal axon descending from the 'hand knob.' 3D and 2D visualizations of the pyramidal axons are shown for illustration. To facilitate visualization, only 10% of the total number of pyramidal axons are shown (4,000 axons are embedded in each subject).

Figure 3. Activation maps. (A) Individualized activation maps ($n = 8$) in the primary motor cortex template. (B) Activation map for each subject after registration to the standard brain template (MNI coordinates). The enclosed region by the white line corresponds to suprathreshold activation area. (C) Averaged activation map in the standard brain template. Previous concurrent suprathreshold TMS/fMRI (a) [51] and concurrent TMS/PET studies (b) [58] are marked.

Figure 4. Group Level EFs maps ($n = 8$) at suprathreshold TMS intensity. (A) EF magnitude ($|EF|$). (B) Parallel EF (pEF) to the cortical surface. (C) Normal EF (nEF) to the cortical surface at suprathreshold condition. (D) Hotspots of previous studies based on TMS navigation system at threshold condition (a [54], b [55], c [56]*, d₁ [10]), and EF-based projections (d₂-d₄ [10] and e₁-e₂ [18]*). Reference marked with * indicates voluntary contraction. Otherwise, resting conditions of the target muscle.

Figure 5. Pathway bending effect of the pyramidal axons. (A) Illustration of 10 different bending levels (a higher number indicates a higher bending) of two pyramidal axons. (B) Illustration of one bending level applied to all the pyramidal axons from the gyrus wall (2D plane). (C) Activation threshold variability considering 10 different bendings for each pyramidal axon in the 2D hand knob of (A). (D) 3D activation map for different pyramidal axon bending levels in subject number 3.

Figure A1. (a-d) Generation of pyramidal axon pathways from the primary motor cortex construction of the pyramidal axons planes (e) Illustration of different bend radius levels.

Figure B1. (a) Activation site in individual axons by activating function (AF) and nerve model. (b) Distribution of the normalized AF for the subject $n = 1$ in Fig. 3A.