Accurate tissue segmentation from including both T1-weighted and T2-weighted MRI scans significantly affect electric field simulations of prefrontal but not motor TMS

Keywords:
- Electric field (E-field) modeling
- Transcranial magnetic stimulation (TMS)
- Finite element method (FEM)
- T1w structural MRI scan
- T2w structural MRI scan
- Computational modeling

Computational electric field (E-field) modeling is a valuable tool to simulate the cortical effects of noninvasive brain stimulation based on a person’s head anatomy. E-field modeling involves segmentation of a structural magnetic resonance imaging (MRI) scan into different tissue layers, and creation of an anatomically accurate head model. On this head model, the effects of noninvasive brain stimulation are then simulated. Given the interest in E-field modeling for understanding dose-response relationships and even prospective E-field dosing [1], it is important to maximize accuracy by critically evaluating E-field modeling methodology.

Recently, we showed that head meshes created from T1w + T2w MRI scans more accurately represent E-fields induced by high-definition transcranial electric current (tES) over the motor cortex than meshes created from T1w scans [2]. Further analyses indicated that the higher E-field variability of T1w only models was mostly attributable to poorer tissue layer segmentation, particularly of the cerebrospinal fluid (CSF) and skull. However, the use of E-field simulations is not exclusive to tES, but also relates to transcranial magnetic stimulation (TMS). Although tES and TMS both induce cortical E-fields to noninvasively alter neural activity, their differing mechanisms of actions (i.e., electric versus electromagnetic E-field generation) imply that the results of our previous work cannot be directly extrapolated to TMS. There is reason to believe that the more accurate tissue segmentation obtained from including an additional T2w scan might be less impactful for TMS modeling as TMS simulations were found to be less susceptible to head model and tissue accuracy decreases than tES simulations [3,4].

**Abbreviations:**
- tES, transcranial electric stimulation; TMS, transcranial magnetic stimulation; E-field, electric field; MRI, magnetic resonance imaging; ROI, region of interest; SCD, scalp-to-cortex distance; FEM, finite element method.

Here, we set out to extend our prior tES results to TMS. Furthermore, we aimed to test whether there is brain region specificity to simulation accuracy by simulating TMS over the motor and prefrontal cortices. We examined the influence of tissue thicknesses between the coil and cortex at both regions of interest (ROIs), as variations in scalp-to-cortex distance (SCD) could be a potential source of differences, given that distance is a determinant of magnetic field strength [5].

We computed E-field models in 100 healthy younger adults (57 females, 22–35 years old), randomly selected from the Human Connectome Project dataset [6]. T1w and T2w structural MRI-scans were acquired with the Siemens MAGNETOM 3T scanner (for detailed scanning parameters, see Ref. [6]). Two finite element method (FEM) tetrahedral head meshes were constructed per participant with headrec (Fig. 1A). The first mesh was based on a T1w MRI scan; the second mesh was based on a T1w + T2w MRI scan.

With SimNIBS (v3.2.3) [7], we simulated two TMS targets in each participant (one motor target, one prefrontal target), for a total of 400 E-field simulations (100 participants * 2 meshes * 2 TMS targets). All simulations were performed with a MagVenture 70mm figure-of-eight coil at 50% stimulator output on a MagPro R30 machine (dl/dt = 7566 A/s). For motor stimulation, the coil center was placed over C3 according to the electroencephalography 10–20 system, with a 45° angle to the sagittal plane. For prefrontal stimulation, the coil center was placed over F3 with a 45° angle. Standard conductivity values were used for the modeled tissues (white matter: 0.126 S/m, grey matter: 0.275 S/m, CSF: 1.654 S/m, bone: 0.01 S/m, skin: 0.465 S/m, and eyes: 0.5 S/m). For both meshes, the average E-field induced in the primary motor cortex (C3 TMS) and dorsolateral prefrontal cortex (F3 TMS) was extracted using a ROI analysis [2,7]. We centered the ROI at the subject space transformed peak MNI coordinate of the primary motor cortex (x = −37, y = −21, z = 58) or dorsolateral prefrontal cortex (x = −30, y = −43, z = 23) and extracted the average E-field in a 10 mm radius grey matter sphere in each model [8,9]. Linear mixed models were constructed with E-FIELD STRENGTH as the dependent variable, and MESHING APPROACH and ROI and their interaction as fixed effects. PARTICIPANT was included as random intercept. Results of the mixed model were investigated via Bonferroni-corrected post-hoc tests. The significance level was set to $\alpha = 0.05$.

Previously, we used dice calculations to demonstrate that T1w + T2w MRI scans produce more accurate head meshes primarily by improving skull and CSF tissue segmentation accuracy [2]. However, dice measures only provide information on whole head...
differences between meshing procedures and do not directly examine SCD, which is an important determinant of magnetic field strength. Therefore, in this study we sought to examine whether differing tissue thicknesses between T1w and T1w + T2w head
meshes at each ROI are related to potential differences in E-fields (Fig. 1B). We extracted the thickness of each tissue between the TMS coil and cortex from the T1w and T1w + T2w head meshes via custom MATLAB scripts. Specifically, per head mesh, we extracted the 5000 grey matter points closest to the ROI and used principal component analysis to find the normal of this grey matter plane-like data cloud. This normal, orthogonal to the cortex, was used to extract the intersection between the ROI and the most outer grey matter point. Subsequently, the Euclidean distance between the most outer grey matter point and the intersection of the normal with the outer surface of each tissue layer (i.e., CSF, bone, and skin) was calculated. That is, the thickness used to determine the intersection was: 

\[ \text{Normal} = \text{Plane orthogonal to ROI} \]

\[ \text{Distance} = \text{Distance of normal to ROI} \]

This normal was used to measure the thickness of each tissue layer. The thickness of each tissue was obtained by normalizing the distance to the average thickness of all tissues. We ensured that all normal components faced outwards. Summating the thickness of all three tissue layers values, we calculated the SCD.

Tissue thicknesses and SCD were compared between the T1w and T1w + T2w meshes via paired t-tests per ROI and were Bonferroni corrected for 8 multiple comparisons. To investigate if differences in SCD were additive, we also calculated the sum of the thickness differences across both meshing procedures for all grey matter points on the cortical surface within 10 mm of the ROI (n = 250–500 points per ROI). The obtained thicknesses per tissue layer for all points in the ROI were then averaged to obtain the SCD, and the analysis was repeated using each of the meshing procedures per head mesh, respectively.

Moreover, given the growing interest in utilizing E-field modeling for prospective TMS dosing, it is critical to produce the most anatomically accurate head meshes in order for participants to receive the intended doses.

Several weaknesses impact our work. First, we only investigated the relationship between SCD differences across both meshing procedures and E-field differences. Other factors, such as tissue morphology differences across both meshing procedures, likely also contribute to the observed E-field differences. Second, we simulated TMS at a set stimulator output across participants, whereas it is typically based on individual motor threshold values. Nevertheless, since we aimed to compare the impact of head meshes within-subject, other intensities such as the motor threshold would yield the same within-subject differences in E-field strength, as the intensities would remain identical across both meshing procedures per participant. Third, the simulations were conducted with SimNIBS (headrec) which is based on the finite element method. Although SimNIBS is predominantly used in the field, other approaches exist (e.g., boundary element fast multipole method) [12]. It remains unclear how T1w versus T1w + T2w meshes impact the accuracy of these approaches.

In summary, our findings demonstrate the importance of including T1w + T2w scans for accurate tissue segmentation and SCD, and for high fidelity prefrontal TMS modeling. For the most accurate (prefrontal) results, E-field modeling studies should include T1w + T2w structural MRI scans.

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Declaration of competing interest

We confirm that all authors have no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we partially call the validity of prior modeling studies using solely T1w MRI scans, including our own work, into question. For instance, we previously used T1w only meshes for TMS E-field modeling, finding that prefrontal TMS-induced E-fields were significantly lower than motor E-fields and prefrontal TMS should therefore be performed at 133.5% of the motor stimulation intensity to produce equivalent E-fields [11]. Given our current finding that prefrontal mesh accuracy and E-fields are differentially affected by T1w only scans, these prior results warrant further investigation.
confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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Sybren Van Hoornweder* REVAL - Rehabilitation Research Center, Faculty of Rehabilitation Sciences, University of Hasselt, Diepenbeek, Belgium

Raf L.J. Meesen REVAL - Rehabilitation Research Center, Faculty of Rehabilitation Sciences, University of Hasselt, Diepenbeek, Belgium

Kevin A. Caulfield** Movement Control and Neuroplasticity Research Group, Department of Movement Sciences, Group Biomedical Sciences, KU Leuven, Leuven, Belgium

* Corresponding author. Hasselt University, Faculty of Rehabilitation Sciences Agoralaan, Building A, 3590, Diepenbeek, Belgium.

** Corresponding author. Department of Psychiatry, Medical University of South Carolina 67 President Street, 504N, Charleston, SC, USA.

E-mail address: Sybren.vanhoornweder@uhasselt.be (S. Van Hoornweder).

E-mail address: caulfield@musc.edu (K.A. Caulfield).

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