Brain Stimulation 15 (2022) 942–945

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

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 headreco (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 (dI/dt = 75e6 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

https://doi.org/10.1016/j.brs.2022.06.008

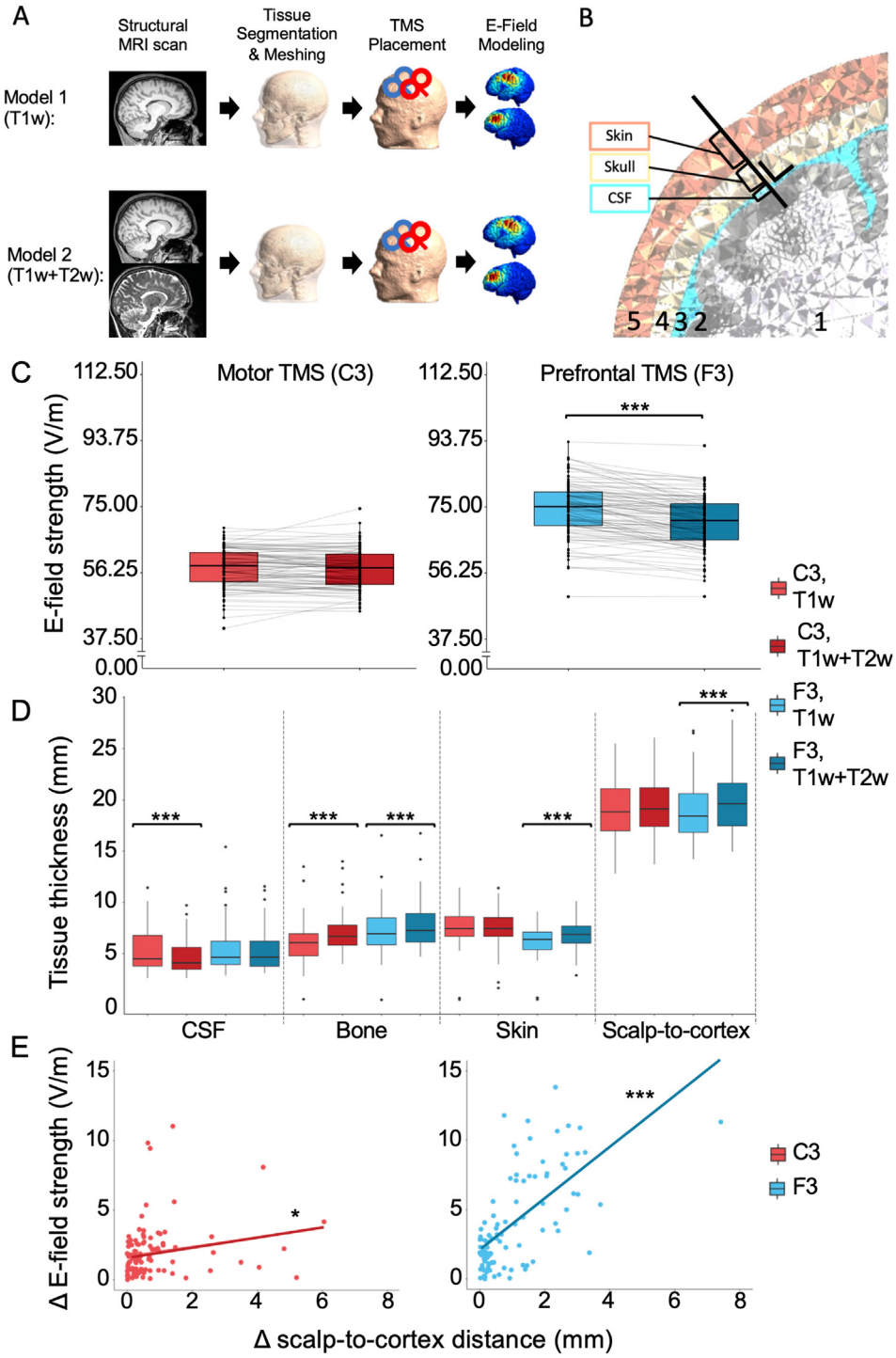

Fig. 1. Effect of T1w versus T1w + T2w magnetic resonance imaging (MRI) based meshes on electric fields (E-field) induced by transcranial magnetic stimulation (TMS). *$p < 0.05$, ***$p < 0.001$. **A.** Modeling steps. The upper and lower row demonstrate the pipeline using a T1w and a T1w + T2w scan, respectively. The red and blue coils designate motor and prefrontal TMS, respectively.
B. Extraction of cerebrospinal fluid (CSF), skull and skin thickness. White matter, grey matter, CSF, skull and skin (1–5) tissue layers are shown. A normal component going through the region of interest was created, orthogonal to the grey matter surface.
C. E-fields induced in central and prefrontal targets per meshing procedure.
D. Tissue thicknesses between the grey matter target and the coil, and scalp-to-cortex distance.
E. Scatterplots displaying the Spearman's correlation between the difference in E-field strength and difference in scalp-to-cortex distance per meshing procedure (T1w + T2w model - T1w model). (For interpretation of the references to colour in this figure, the reader is referred to the Web version of this article.)

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. To ensure that this procedure was not prone to graey matter morphometry at a single point, we repeated this process 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 CSF, bone and skin thickness. 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 between the tissue meshes and E-field strength were associated, we performed Spearman Correlations between the absolute E-fields strength difference in T1w versus T1w + T2w head meshes and the absolute SCD difference in the T1w versus T1w + T2w meshes. We performed these analyses for both ROIs and corrected for 2 multiple comparisons.

The linear mixed model found that MESHING APPROACH ($F_{1,297} = 833.1626$, $p < 0.001$), ROI ($F_{1,297} = 15.3660$, $p < 0.001$) and MESHING APPROACH * ROI ($F_{1,297} = 9.2994$, $p = 0.003$) were significant fixed effects. Bonferroni-corrected post-hoc tests revealed that E-fields induced by motor TMS in the T1w mesh were not different compared to the T1w + T2w mesh ($t_{297} = 0.616$, $p = 1.000$) (Fig. 1C) [10]. In contrast, for prefrontal TMS, E-fields induced in the T1w mesh were significantly different from the T1w + T2w mesh ($t_{297} = 4.928$, $p < 0.001$). Moreover, the difference in E-field strength between T1w versus T1w + T2w meshes in the motor versus prefrontal region was also significant ($t_{297} = -3.049$, $p = 0.008$). Thus, the impact of T1w versus T1w + T2w scans in TMS E-field simulations is regionally specific and more consequential for prefrontal simulations.

For the motor ROI, CSF thickness ($t_{99} = 4.120$, $p = 0.001$) and bone thickness ($t_{99} = -7.778$, $p < 0.001$) significantly differed in the T1w versus T1w + T2w mesh (Fig. 1D). Additionally, a weak significant correlation between absolute E-field differences and SCD differences across T1w versus T1w + T2w meshes was present ($\rho = 0.280$, $p = 0.010$) (Fig. 1E). For the prefrontal ROI, bone ($t_{99} = -4.354$, $p = 0.001$), skin ($t_{99} = -5.489$, $p < 0.001$) and SCD ($t_{99} = -6.222$, $p < 0.001$) significantly differed in T1w versus T1w + T2w meshes. Here, a strong significant correlation was present ($\rho = 0.616$, $p < 0.001$). Taken together, these results indicate that SCD differences induced by segmentation differences of T1w versus T1w + T2w meshes partially underly the regionally-specific within-subject E-field differences between T1w versus T1w + T2w TMS simulations.

Compared to our prior finding that motor tES E-fields significantly differ due to T1w only meshes not accurately differentiating between bone and CSF tissues [2], TMS E-field modeling appears to be affected by the inclusion of T1w + T2w scans in a more intricate way. While motor E-fields do not appear to be as prone to T1w only head model inaccuracies, prefrontal E-fields significantly differ when utilizing T1w versus T1w + T2w head meshes.

These data show that MRI scanning choices can impact TMS E-field modeling results in a region-specific manner. As such, they 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. 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 current simulations were conducted with SimNIBS (headreco) 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.

Financial Support

This work was supported by the Special Research Fund (BOF) of Hasselt University (BOF20KP18), Research Foundation Flanders (G039821 N principal investigator Raf L.J. Meesen) and an NIH NINDS F31 NRSA grant (Principal Investigator: Kevin A. Caulfield; 1F31NS126019-01). Data were provided by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University.

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

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.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author.

References

[1] Caulfield KA, Li X, George MS. Four electric field modeling methods of dosing prefrontal transcranial magnetic stimulation (TMS): introducing APEX MT dosimetry. Brain Stimul: Basic, Transl Clin Res Neuromod 2021;14(4):1032–4.

[2] Van Hoornweder S, Meesen R, Caulfield KA. On the importance of using both T1-weighted and T2-weighted structural magnetic resonance imaging scans to model electric fields induced by non-invasive brain stimulation in SimNIBS. Brain Stimul 2022;15(3):641–4. https://doi.org/10.1016/j.brs.2022.04.010. In press.

[3] Saturnino GB, Thielscher A, Madsen KH, Knösche TR, Weise K. A principled approach to conductivity uncertainty analysis in electric field calculations. Neuroimage 2019;188:821–34.

[4] Saturnino GB, Madsen KH, Thielscher A. Electric field simulations for transcranial brain stimulation using FEM: an efficient implementation and error analysis. J Neural Eng 2019;16(6):066032.

[5] Stokes MG, Chambers CD, Gould IC, Henderson TR, Janko NE, Allen NB, et al. Simple metric for scaling motor threshold based on scalp-cortex distance: application to studies using transcranial magnetic stimulation. J Neurophysiol 2005;94(6):4520–7.

[6] Van Essen DC, Ugurbil K, Auerbach E, Barch D, Behrens TE, Bucholz R, et al. The Human Connectome Project: a data acquisition perspective. Neuroimage 2012;62(4):2222–31.

[7] Thielscher A, Antunes A, Saturnino GB. Field modeling for transcranial magnetic stimulation: a useful tool to understand the physiological effects of TMS? 2015 37th Ann Int Conf IEEE Eng Med Biol Soc (EMBC) 2015:222–5.

[8] Mayka MA, Corcos DM, Leurgans SE, Vaillancourt DE. Three-dimensional locations and boundaries of motor and premotor cortices as defined by functional brain imaging: a meta-analysis. Neuroimage 2006;31(4):1453–74.

[9] Cieslik EC, Zilles K, Caspers S, Roski C, Kellermann TS, Jakobs O, et al. Is there "one" DLPFC in cognitive action control? Evidence for heterogeneity from Co-Activation-Based parcellation. Cerebr Cortex 2013;23(11):2677–89.

[10] RStudio Team, RStrudio. Integrated development for R. PBC. Boston, MA: Rstudio; 2020.

[11] Caulfield KA, Li X, George MS. A reexamination of motor and prefrontal TMS in tobacco use disorder: time for personalized dosing based on electric field modeling? Clin Neurophysiol 2021;132(9):2199–207.

[12] Makarov SN, Wartman WA, Daneshzand M, Fujimoto K, Raij T, Nummenmaa A. A software toolkit for TMS electric-field modeling with boundary element fast multipole method: an efficient MATLAB implementation. J Neural Eng 2020;17(4):046023.

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

Movement Control and Neuroplasticity Research Group, Department of Movement Sciences, Group Biomedical Sciences, KU Leuven, Leuven, Belgium

Kevin A. Caulfield**
Brain Stimulation Laboratory, Department of Psychiatry, Medical University of South Carolina, Charleston, SC, USA

* 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: caulfiel@musc.edu (K.A. Caulfield).

25 May 2022
Available online 30 June 2022