Title: "TAP: Targeting and analysis pipeline for optimization and verification of TMS coil placement"

Article type: Techniques and Methods

Authors: Moritz Dannhauer [a], Ziping Huang [a,e], Lysianne Beynel [a], Eleanor Wood [a], Noreen Bukhari-Parlakturk [b], Angel V. Peterchev [a, c, d, e, *]

[a] Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC 27710, USA

[b] Department of Neurology, Duke University, Durham, NC 27705, USA

[c] Department of Electrical and Computer Engineering, Duke University, Durham, NC 27708, USA

[d] Department of Neurosurgery, Duke University, Durham, NC 27710, USA

[e] Department of Biomedical Engineering, Duke University, Durham, NC 27708, USA

[*] Corresponding author

Mail address:

40 Duke Medicine Circle

Box 3620 DUMC

Durham, NC 27710

USA

e-mail: angel.peterchev@duke.edu

Abstract:

Transcranial magnetic stimulation (TMS) offers possibilities to modulate function in regions of interest (ROI) in the brain via an induced electric field (E-field). The ROI E-field can be maximized using individualized computational head modeling to find an optimal scalp coil placement. We present a TMS targeting and analysis pipeline (TAP) software that uses an MRI/fMRI-derived brain target to optimize a coil placement considering experimental requirements such as subject's hair thickness and coil placement restriction. The coil placement optimization is implemented in SimNIBS 3.2 for which an additional graphical user interface (TargetingNavigator) is provided to visualize and adjust procedural parameters. The optimized coil placement information is prepared for neuronavigation software (Brainsight) which supports the targeting during the TMS experiment. The neuronavigation system can record the coil placement during the experiment and these data can be processed in TAP to evaluate retrospectively and visualize the TMS targeting accuracy.

Keywords: TMS, MRI, coil, electric field, model, neuronavigation

Highlights (85 characters with spaces for each bullet point):

- Automated TMS coil targeting pipeline based on MRI/fMRI data and E-field model
- Convenient adjustment for experimental requirements and targeting parameters
- Accuracy assessment of experimental TMS coil placement based on neuronavigation

Introduction

Precise placement of non-invasive brain stimulation devices [1,2,3], such as transcranial magnetic stimulation (TMS), offers promising avenues to understand basic [4] and higher cognitive [5] brain functions. In neuroscience experiments, TMS coil placement is often landmark-referenced and supported by neuronavigation technology [6,7], targeting a particular brain region of interest (ROI). These ROIs can be determined by means of anatomy [6] or brain activity measurements such as EEG or fMRI [1, 5, 8] for each experimental participant. Prior to a TMS session, individualized computational modeling of head tissues and the electric field (E-field) induced in the ROI [9] allows for identification of an optimal TMS coil placement on the scalp [1, 2]. We previously developed the fast auxiliary dipole method (ADM) for software-assisted TMS targeting to maximize E-field delivery to an ROI [2], and ADM is now part of the SimNIBS E-field simulation software package [10]. However, it remains challenging to combine ADM with individual functional or anatomical targeting data, subsequent experimental application using neuronavigation, and visualization and evaluation of the experimental accuracy.

We present a TMS targeting and analysis pipeline (TAP) software that helps bridge the gaps between individual imaging data, SimNIBS, and neuronavigation. SimNIBS can robustly generate head tissue models [10] from MRI data. The ADM method in SimNIBS finds the optimal TMS coil position and orientation on each participant's scalp to maximize the magnitude or a directional component of the ROI E-field [2]. To add to SimNIBS' basic functionality for adjustment and visualization of ROIs, the coil, and desired E-field parameters, TAP offers a graphical user interface (GUI), called ‘TargetingNavigator’.

TAP can be used for prospective targeting optimization before an experiment and/or retrospective targeting analysis after an experiment. The first step, in a prospective approach for TMS coil placement or E-field simulation, is to extract an ROI center from a volumetric target mask (i.e., a nifti file) for SimNIBS. In this approach, TAP generates specifically formatted ASCII text files readable by the TMS neuronavigation software [11]. The presented implementation is for the Brainsight neuronavigation system (Rogue Research, Canada), but TAP can be adapted to other systems as well. TAP can also control practical aspects of the coil placement such as the coil handle direction, which ideally should not block the TMS coil tracker or the participant’s sight and which may need adjustment to control the induced E-field direction in the cortex. Retrospective analysis uses TMS coil placement data from an existing experiment recorded by neuronavigation software. In retrospective analysis, TAP can detect problematic coil distances from the scalp, such as a coil placement being too far from or entering the scalp surface due to inaccurate coil–scalp co-registration; this analysis can incorporate measurements of the subjects’ hair thickness [5], if such are available.

In this paper, we describe TAP and illustrate its use in five TMS subjects who participated in a study of writer’s cramp dystonia.

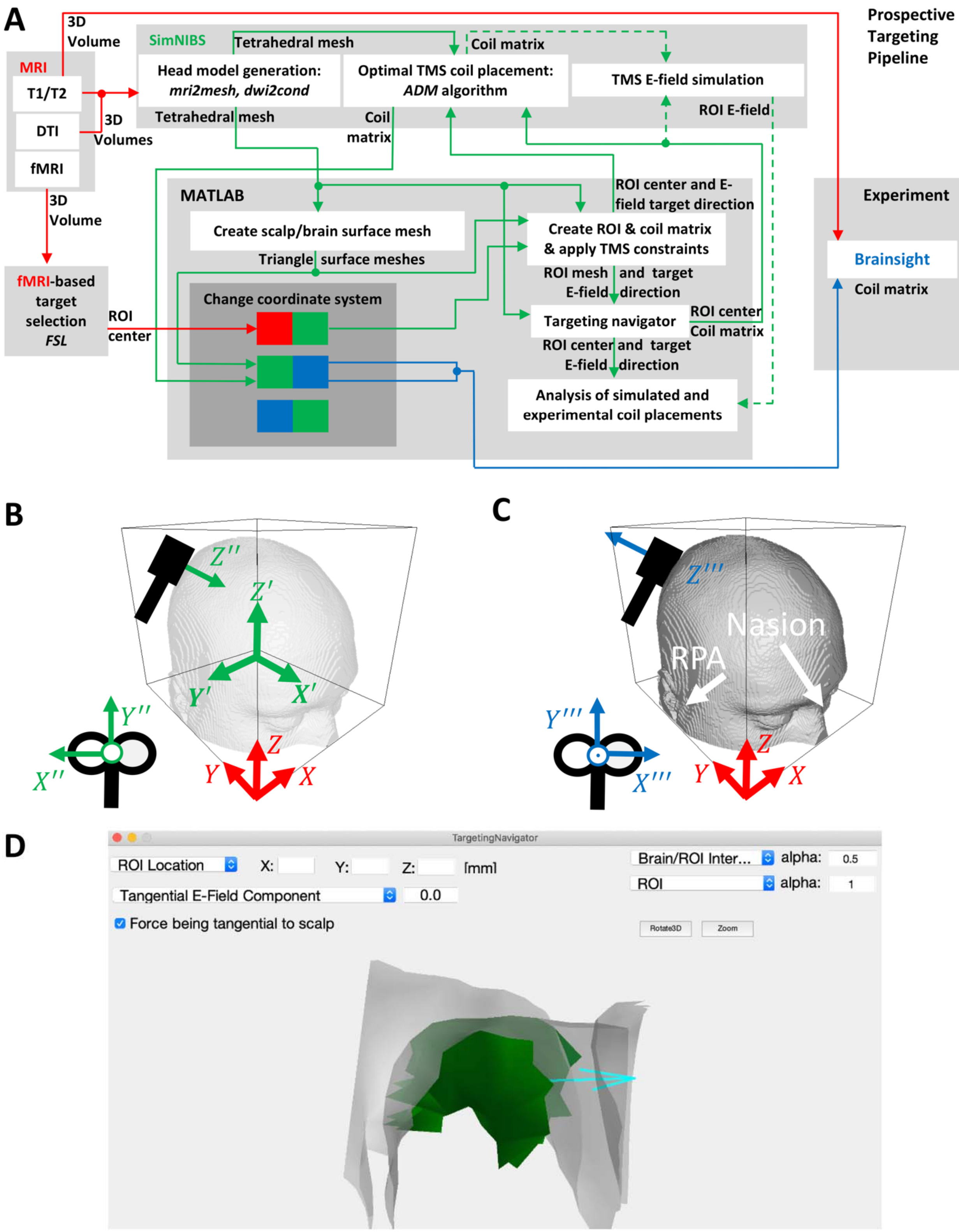

Figure 1. (A) Diagram of the TMS targeting and analysis pipeline (TAP) integrating different hardware and software components for prospective targeting. The dashed arrows indicate

optional steps that are not required for prospective targeting. (B) SimNIBS software coordinate convention (green) with origin at the volumetric center, X' and Y' axes flipped with respect to the MRI RAS convention (X, Y, Z, in red), and a TMS coil coordinate system (X''', Y''', Z'''). (C) Brainsight neuronavigation coordinate convention (blue) with pitch $X''' = -X''$ and yaw $Z''' = -Z''$ flipped compared to the SimNIBS convention. The nasion and right/left periauricular points (RPA/LPA) are typical registration points for neuronavigation. (D) A screenshot of the TargetingNavigator GUI: a MATLAB-based SimNIBS 3.2 add-on to adjust and visualize simulation parameters in prospective and retrospective TMS analysis.

Material and methods

As diagrammed in Figure 1A, TAP combines existing software packages, including SimNIBS v3.2 [10] for TMS-induced E-field simulations and Brainsight v2.5b2 [11] for neuronavigation, with custom MATLAB code (R2018a, [12]). The following sections describe the different methodological aspects of TAP.

Experimental participants, MR imaging, and target selection

In this study-specific example, five participants in a study of writer's cramp dystonia underwent structural MR imaging acquisition (T1, T2, and DTI) for anatomical reference and generation of individualized head models for E-field simulations. fMRI was also acquired to identify voxels of peak brain activity while performing a writing task. The fMRI data were then used to select two

ROIs, one in premotor cortex (PMC) and one in primary sensory cortex (PSC), for repetitive TMS (rTMS). These ROIs were then used in TAP to create volumetric masks for computation of optimal TMS coil placements. This information was imported in Brainsight and used as targets during the rTMS sessions (active and sham for PMC and active only for PSC). Each session consisted of 4 blocks of 1000 pulses each. More details are available in the Supplementary Material.

Coordinate system transformations

Generally, coordinate transformations are needed to integrate all different software pieces (MRI, SimNIBS, and Brainsight) in the pipeline mediated by a custom MATLAB code. The coordinate transformations are defined as 4 × 4 matrices (denoted as $T_{i,j}$ with $i, j = 1, \ldots, 4$) which contain submatrices for rotation ($T_{i,j}$ with $i, j = 1, 2, 3$) defining axes rotations (with $\|T_{*,j}\| = 1$ for $j = 1, 2, 3$) and translation ($T_{i,j}$ with $i = 1, 2, 3; j = 4$ in units of mm; $T_{4,4} = 1$) adding a coordinate offset that moves the origin of a current coordinate system to the specified desired one. The matrix $T_{i,j}$ is used to map locations such as ROI and TMS coil center, coordinate space rotations (i.e., colored arrows or letters in Figure 1A–C), and coil coordinate transformations within a defined space denoted as 'Coil matrix' in Figure 1A.

Preparation and launch of SimNIBS

TMS coil placement optimization can be launched with TAP by executing the *run_simnibs(s)* command from the MATLAB prompt providing a MATLAB struct object *s* with different data fields, which should be initialized with the default struct *opt_struct('TMSoptimize')*.

If *s* has the data field entry *s.target_direction*, ADM or the direct solver in SimNIBS will find the coil placement that maximizes the average E-field induced in the ROI along *s.target_direction*, or otherwise the overall magnitude, as specified. The ROI center location in SimNIBS space is assigned to data field *s.target*. The ROI size (*s.target_size*) considers all tetrahedral gray matter elements that fall within this radius (from the point specified in *s.target*). In our example, an ROI size value between 3–4 mm was chosen for all participants to ensure the ROI covers a significant part of the sulcal wall but not any part of a neighboring gyrus controlled for by visual inspection in TargetingNavigator. The ROI target direction is determined following these main steps:

(1) project the ROI center onto the brain surface;

(2) use Freesurfer's surface curvature information (files: lh.sulc, rh.sulc; value range: between –2 and 2) to find the closest brain surface mesh point that is numerically closest to zero;

(3) compute an outwards-pointing nodal normal by averaging the triangle normal vectors for the point of previous step; and

(4) project the ROI center point from (1) to the closest scalp surface mesh point, compute its nodal normal, as in (3), and use the corresponding plane it defines to project the normal direction from (3) onto it.

The resulting vector is a better approximation of the desired E-field direction parallel to the scalp-tangential plane of the coil.

For robust estimation of the scalp-tangential plane, we added a data field to the *s* structure (available in SimNIBS 3.2.5), namely *s.scalp_normals_smoothing_steps* (TAP default is 20), to adjust scalp-coil tangentiality and visualize it in TargetingNavigator.

SimNIBS allows constraining the scalp search space for possible coil center positions and orientations, which TAP sets to the default values of *s.search_radius* = 25 mm, *s.spatial_resolution* = 1 mm and *s.search_angle* = 1°. For a typical SimNIBS head model and those default values, the optimal coil placement search takes about 2 minutes on a regular laptop (Intel Core i5 1.6 GHz, 8 GB RAM) running ADM.

For prospective TMS dosing, the subject's hair thickness is often unknown before the TMS session but can be measured at the beginning of the session [5]. Therefore, multiple runs of SimNIBS's ADM are required for a range of hair thickness values. The default setting in TAP iterates through a reasonable range of hair thicknesses from 0 to 7.5 mm in steps of 0.5 mm.

Neuronavigation files

TAP generates different types of files that can then be visualized in Brainsight:

(1) scalp and brain surface of the SimNIBS head model converted to MRI/Brainsight space,

(2) SimNIBS/Freesurfer preprocessed T1-weighted MRI data set,

(3) ROI/scalp coil center converted to MRI/Brainsight space, and

(4) optimal coil placement (4 × 4 matrices) converted to Brainsight space and saved in a text file.

For retrospective analysis, the experimenter can save TMS coil placement recordings as text files (same format as in step (4)) that can be read into MATLAB and visualized in TargetingNavigator.

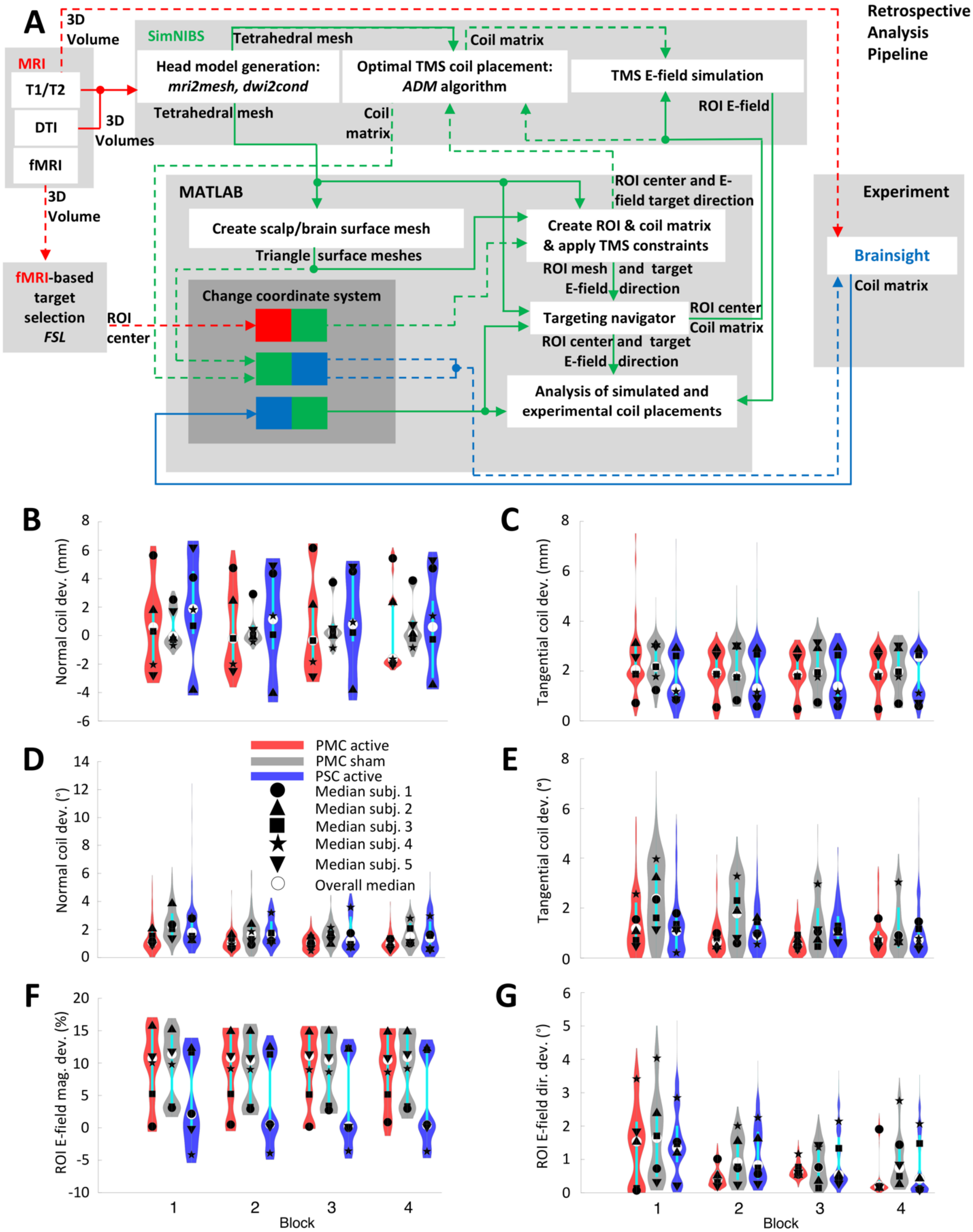

Figure 2. (A) Diagram of TAP as used for retrospective dosing analysis based on TMS coil

scalp placement data recorded via Brainsight. Dashed arrows indicate optional steps that are not required for retrospective TMS analysis. (B)–(G) Violin plots and medians of the differences in coil placement and induced E-field between prospectively-optimized and neuronavigation-recorded targeting in 5 subjects for 3 rTMS sessions of 4 blocks each. Deviation distance of (B) the coil center along the coil normal (yaw axis) direction (positive/negative values represent coil surface above/below the scalp surface) and (C) the coil center in the plane tangential to the scalp. Angular deviation of (D) the coil normal (yaw axis) and (E) the coil orientation about its yaw axis. (F) Magnitude and (G) angular deviation of the E-field vectors for each finite element in the ROI. Violin plots represent 99.3% of the raw data (± 2.7 standard deviations assuming normal distribution) with outliers excluded; the thin black and thicker cyan vertical lines represent the 95% confidence interval and the interquartile range, respectively [13].

Retrospective Analysis

The Brainsight neuronavigation system can digitize the coil position and orientation for each TMS pulse. However, for fast rTMS trains the data saving may not work properly, so a reduced sampling rate may be needed—in our setup we recorded every fifth pulse during the 10 Hz trains. TAP reads in (*read_brain_sight_file*) the Brainsight-space exported text files and converts each line, corresponding to one digitized coil placement defined by a 4 × 4 transfer matrix, to SimNIBS modeling space (*convert_coord_brainsight_2_simnibs*). To avoid possible errors in the coil–scalp co-registration resulting in the coil center being inside the scalp, it is recommended to use Brainsight's "Snap to Scalp" option when exporting [12]. TAP then extrudes these snapped coil centers outwards along the scalp normal to account for the measured hair thickness. If hair thickness measurement is unavailable, TAP defaults to a value of 2 mm [5]. The distance between the hair-thickness-extruded coil center and the original experimentally recorded coil center without snapping and hair-thickness extrusion is determined along the recorded coil normal direction ('normal coil deviation' in mm). The hair-thickness-extruded coil center is then compared against the computationally optimal coil center on the scalp's tangential plane ('tangential coil deviation' in mm). TAP uses the computationally optimal coil placement to also check if the rotational part of the experimental coil placement matrices aligns, and sign-flips the components for minimal angular discrepancy. The scalp normal direction is used to assess the deviation of the coil plane from the scalp-tangential plane ('normal coil deviation' in ° equal to the arccosine of the dot product of the scalp and coil normals). Finally, the experimental coil placement is projected onto the scalp-tangential plane and the difference between the experimental and optimal coil orientation is computed ('tangential coil deviation' in °). When a targeted optimal coil placement is not available, TAP can still analyze the experimental TMS coil placements recorded with Brainsight.

As a second step, TAP evaluates the difference in induced E-field between the optimal (if one is provided) and all experimentally recorded coil setups. Since one E-field simulation requires several minutes of computation time, TAP chooses a median representative of the coil placements within an experimental block to simulate the E-field in the entire head model and then extracts the ROI E-field (using SimNIBS 'target.msh'). The median coil representation is chosen by evaluating the medians for the X''', Y''' and Z''' coordinates separately and picking the recorded coil placement with the smallest Euclidean distance from these median coordinates.

TAP then computes the deviation in magnitude and angle of the E-field vector in each tetrahedral ROI element between the simulations for the median experimental coil placement and the optimal coil placement.

Results and Discussion

Figure 2B–G quantifies of the deviation between the computationally optimized coil placement that was set as a target during the rTMS sessions and the actual placements recorded by the neuronavigation system. The plots exclude clear outliers that likely occurred due to brief disruptions in the coil tracking (see Supplementary Material). Across all subjects and sessions, the median position and orientation deviations were 0.29 mm and 1.60° relative to the scalp normal (Figure 2B, D) and 2.26 mm and 1.20° in the scalp tangential plane (Figure 2C, E), respectively. The corresponding median E-field magnitude and direction deviations (Figure 2F,G) were 9.66% and 1.25°, respectively, even though some of the individual medians were significantly larger. Furthermore, the positional deviation of up to ~ 6 mm along the scalp normal (Figure 2B) was larger compared to the tangential deviation (Figure 2C). This is likely due to the fact that the normal deviation is relative to the estimated absolute location of the individual's hair surface, and thus incorporates registration errors, whereas the tangential deviation is only relative to the registered coil target location. These values are comparable to neuronavigation error and deviation estimates in the literature. For example, cumulative inaccuracies from the head tracker registration to scalp landmarks and subsequent slight movements of the tracker relative to the head might reach 5–10 mm [14]. Excluding errors from the registration and shifts of the head tracker relative to the head, median tangential deviation of the coil position and orientation of 1.34 mm and 3.48°, respectively, was reported for a neuronavigated robotic coil holder [7]. Moreover, inter-session position error of about 2.5 mm was reported for neuronavigated manual coil placement [15].

Conclusions

TAP enables prospective and retrospective TMS targeting analysis based on E-field simulations coupled with individual imaging and neuronavigation data.

Declaration of Interest

A. V. Peterchev has received research funding, travel support, patent royalties, consulting fees, equipment loans, hardware donations, and/or patent application support from Rogue Research, Tal Medical/Neurex, Magstim, MagVenture, Neuronetics, BTL Industries, and Advise Connect Inspire. The other co-authors report no relevant disclosures.

Funding

This work was supported by grants from the National Institutes of Health (RF1MH114268, RF1MH114253, U01AG050618, KL2TR002554), Dystonia Medical Research Foundation, Doris Duke Charitable Foundation, and Dystonia Coalition. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

Availability

The software described herein (TAP, TargetingNavigator) is available on https://github.com/moritzdannhauer/fMRI-based_TMS_Targeting_Pipeline.git .

References

[1] Balderston N.L., Roberts C., Beydler, E.M., Deng Z.D., Radman T., Luber B., Lisanby S.H., Ernst M., Grillon, C. (2020). A generalized workflow for conducting electric field-optimized, fMRI-guided, transcranial magnetic stimulation. *Nature Protocols*, 15(11):3595-3614. Doi: 10.1038/s41596-020-0387-4. Epub 2020 Sep 30. PMID: 33005039.

[2] Gomez, L.J., Dannhauer, M., Peterchev, A.V. (2021). Fast computational optimization of TMS coil placement for individualized electric field targeting. *NeuroImage*, 228 (2021), 117696

[3] Cash R.F.H., Weigand A., Zalesky A., Siddiqi S.H., Downar J., Fitzgerald P.B., Fox M.D. (2020). Using Brain Imaging to Improve Spatial Targeting of Transcranial Magnetic Stimulation for Depression. *Biological Psychiatry*, Jun 7:S0006-3223(20)31668-1. Doi: 10.1016/j.biopsych.2020.05.033. Epub ahead of print. PMID: 32800379.

[4] Jung J., Bungert A., Bowtell R., Jackson S.R. (2020). Modulating Brain Networks With Transcranial Magnetic Stimulation Over the Primary Motor Cortex: A Concurrent TMS/fMRI Study. *Frontiers in human neuroscience*, Feb 14;14:31. Doi: 10.3389/fnhum.2020.00031. PMID: 32116612; PMCID: PMC7033446.

[5] Beynel, L., Davis, S.W., Crowell, C.A., Dannhauer, M., Lim, W., Palmer, H., Hilbig, S.A., Brito, A., Hile, C., Luber, B. (2020). Site-specific effects of online rTMS during a working memory task in healthy older adults. *Brain Sciences*, 10, 255

[6] Rusjan P.M., Barr M.S., Farzan F., Arenovich T., Maller J.J., Fitzgerald P.B., Daskalakis Z.J. (2010). Optimal transcranial magnetic stimulation coil placement for targeting the dorsolateral prefrontal cortex using novel magnetic resonance image-guided neuronavigation. *Human Brain Mapping*, Nov;31(11):1643-52. Doi: 10.1002/hbm.20964. PMID: 20162598; PMCID: PMC6871247.

[7] Goetz, S.M., Kozyrkov, I.C., Luber, B., Lisanby, S.H., Murphy, D.L., Grill, W.M., Peterchev, A.V. (2019). Accuracy of robotic coil positioning during transcranial magnetic stimulation. *Journal of Neural Engineering*, 15, 054003. doi:10.1088/1741-2552/ab2953

[8] Ding, Z., Ouyang, G., Chen, H., & Li, X. (2020). Closed-loop transcranial magnetic stimulation of real-time EEG based on the AR mode method. *Biomedical Physics & Engineering Express*, *6*(3), 035010.

[9] Gomez, L.J., Dannhauer, M., Koponen, L.M., Peterchev, A.V. (2020). Conditions for numerically accurate TMS electric field stimulation. *Brain Stimulation*, 13, 157-66

[10] Thielscher, A., Antunes, A., Saturnino, G.B. (2015). Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS?. *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, Milan, 2015, pp. 222-225, doi: 10.1109/EMBC.2015.7318340.

[11] Rogue Research Inc., Brainsight v2.5b2, https://www.rogue-research.com/downloads/

[12] MATLAB (2018). version 9.4.0.813654(R2018a). Natick, Massachusetts: The MathWorks Inc.

[13] Bechtold, B., 2016. Violin Plots for Matlab, Github Project https://github.com/bastibe/Violinplot-Matlab, DOI: 10.5281/zenodo.4559847

[14] Goetz, S.M. and Kammer, T. (2021). Neuronavigation. In *The Oxford Handbook of Transcranial Stimulation.* ed. E.M. Wassermann, *et al.* Oxford University Press (in press).

[15] Schönfeldt-Lecuona, C., Thielscher, A., Freudenmann, R.W., Kron, M., Spitzer, M., Herwig, U. (2005). Accuracy of stereotaxic positioning of transcranial magnetic stimulation, *Brain Topography*, 17 (4): 253–9.