



Single-Subject TMS Pulse Visualization on MRI-Based Brain Model: A precise method for mapping TMS pulses on cortical surface



Nikolay Syrov^{a,*}, Alfiia Mustafina^c, Artemiy Berkmush-Antipova^b, Lev Yakovlev^{a,b}, Andrey Demchinsky^d, Daria Petrova^a, Alexander Kaplan^{a,b,e}

^a Vladimir Zelman Center for Neurobiology and Brain Rehabilitation, Skolkovo Institute of Science and Technology, Moscow, Russia

^b Baltic Center Neurotechnology and Artificial Intelligence, Immanuel Kant Baltic Federal University, Kaliningrad, Russia

^c Department of Invertebrate Zoology, Faculty of Biology, Lomonosov Moscow State University, Moscow, Russia

^d ANO Laboratory Sensor-Tech, Moscow, Russia

^e Department of Human and Animal Physiology, Faculty of Biology, Lomonosov Moscow State University, Moscow, Russia

ARTICLE INFO

Method name:

TMS-affected Cortical points Visualization on MRI-based Brain Model. The software tool is implemented using the Python language and runs on the Blender software platform. It uses a subject-specific 3D model of the brain's cortical surface reconstructed from MRI data. The software marks the points of TMS application on the cortical surface

Keywords:

Navigated transcranial magnetic stimulation
TMS
Neuronavigation
Motor-evoked potentials
Phosphenes
Blender
Neurovisualization

ABSTRACT

Highly accurate visualization of the points of transcranial magnetic stimulation (TMS) application on the brain cortical surface could provide anatomy-specific analysis of TMS effects. TMS is widely used to activate cortical areas with high spatial resolution, and neuronavigation enables site-specific TMS of particular gyrus sites. Precise control of TMS application points is crucial in determining the stimulation effects. Here, we propose a method that gives an opportunity to visualize and analyze the stimulated cortical sites by processing multi-parameter data.

- This method uses MRI data to create a participant's brain model for visualization. The MRI data is segmented to obtain a raw 3D model, which is further optimized in 3D modeling software.
- A Python script running in Blender uses the TMS coil's orientation data and participant's brain 3D model to define and mark the cortical sites affected by the particular TMS pulse.
- The Python script can be easily customized to visualize TMS points task-specifically.

Specifications table

Subject area:	Neuroscience
More specific subject area:	Subject-specific visualization of the brain cortical sites affected by transcranial magnetic stimulation
Name of your method:	TMS-affected Cortical points Visualization on MRI-based Brain Model. The software tool is implemented using the Python language and runs on the Blender software platform. It uses a subject-specific 3D model of the brain's cortical surface reconstructed from MRI data. The software marks the points of TMS application on the cortical surface.
Name and reference of original method:	No
Resource availability:	Visor2, 3D slicer, Blender 3D, python3

* Corresponding author.

E-mail address: kolasco@gmail.com (N. Syrov).

<https://doi.org/10.1016/j.mex.2023.102213>

Received 30 March 2023; Accepted 9 May 2023

Available online 18 May 2023

2215-0161/© 2023 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Method details

Transcranial magnetic stimulation (TMS) is a non-invasive method for stimulating the brain using a magnetic field [1]. By applying magnetic pulses to specific areas of the cortex, TMS can activate cortical neurons and modulate brain activity. TMS has broad applicability and is widely used in research and clinical settings to investigate cortical and corticospinal excitability, perturbations in excitation and inhibition balance, as well as to estimate neural impulse propagation speed [2]. In addition, TMS is utilized as a treatment for various conditions, such as depression and Parkinson's disease, etc. [3].

This brain stimulation method involves placing a TMS coil near the scalp. The coil generates a brief, high-intensity magnetic field that freely passes through the skull and reaches the brain cortex, where it induces an electric current [4]. TMS offers high spatial resolution and can activate neural tissue in a small volume of roughly 2–3 cm³ [4,5]. The effects of TMS stimulation is largely dependent on the specific cortical area that is activated, as different brain regions are involved in different functions. The relative orientation of the magnetic field and cortical neurons also plays a crucial role in the effectiveness of TMS stimulation, as neurons from the gyral crown, gyral lip, and sulcus are influenced differently by TMS [6]. Therefore, precise coil placement is crucial to target the desired brain region, and the coordinates of the cortical points where TMS was applied should be analyzed afterwards in order to gain insight into the stimulation effects. To guide the placement of the TMS coil, TMS neuronavigation (NN) systems are used to control its location and orientation [7]. These systems reconstruct a 3D model of the brain using the patient's magnetic resonance imaging scans. The referencing procedure involves identifying several anatomical landmarks (fiducial), such as the nasion (the point between the eyebrows), the tragus (a small pointed eminence of the external ear, situated in front of the concha), and anatomical brain structures such as the anterior and posterior commissures (AC and PC), or they may use artificial markers, such as small beads attached to the head [8]. The same points on the subject's head are registered using an optically tracked pointer. The coordinates of both the brain's 3D model and the patient's head are aligned through the use of a transformation matrix generated during the referencing procedure. The positioning of the brain's 3D model relative to the patient's head is determined in real-time through the use of infrared lasers, cameras, or other sensors that can track the position and orientation of the TMS coil and the fiducials.

Despite the ability to track the stimulated cortical points in real-time during a TMS session, there are currently no tools available for offline analysis and visualization of the results of a TMS session. In practice, even a small shift of the TMS coil over the motor cortex by a few mm can result in significant variations in evoked potential amplitudes, indicating the crucial importance of precise knowledge of the coil position [7]. Since online monitoring of coil position is aimed at reproducing the hot spot or detecting a specific anatomical area, precise mapping of TMS effects to stimulated cortical point coordinates can only be performed offline after the experiment. Offline analysis of the cortical sites affected by TMS is therefore no less important than on-line monitoring during the stimulation session. While the NN software can provide large dataframes with the TMS coil position and orientation coordinates, it does not provide the coordinates of the brain cortical areas affected by TMS. Standard NN software solutions providing the visualization TMS session results are inconvenient and not customizable, thereby the resulting images cannot be tailored to specific needs (see Fig. 1, left). Customization tools, such as the ability to colorize TMS-affected cortical points, could be crucially useful. For example, cortical points could be colored based on motor-evoked potential amplitudes, which reflect the excitability of the primary motor area [3], or the color of a TMS point on the cortex could reflect the brightness and size of phosphenes elicited with stimulation of the visual cortex [9].

Currently, there are limited tools available for analyzing and visualizing the results of TMS mapping. While there are some tools available for processing magnetic resonance imaging (MRI) data and producing neuroimaging visualizations, such as Freesurfer [10], none of them are designed for TMS mapping results analysis and visualization after TMS session.

To address this issue, we present a method for matching the exported TMS coil coordinates with a 3D brain model reconstructed from the participant's MRI scans. This method allows the recreation of the cortical points that have been stimulated (not to be confused with the coil coordinates) and provides high-resolution visualization of TMS stimulation experiment results. Additionally, the coordinates data for stimulated cortical points can be used by other existing software packages for conducting further analysis.

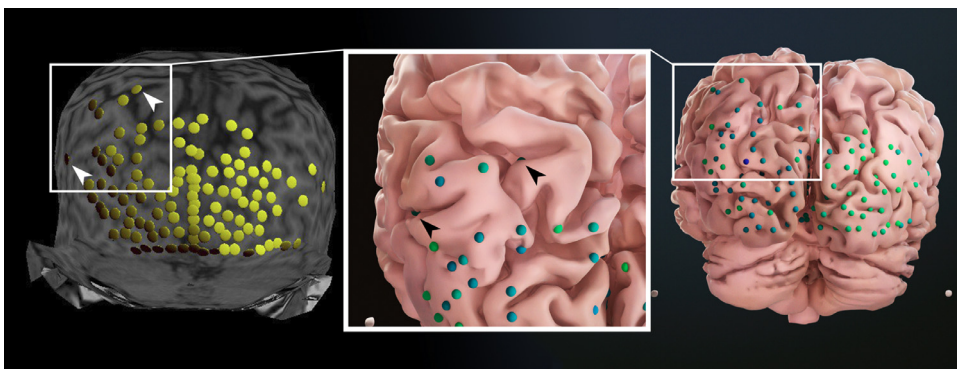


Fig. 1. Visualization of the results of TMS mapping of the occipital cortical area: Comparison of Experimental Results Provided by Neuronavigation Software (Left) and Generated by the Presented Method (Right and Middle (view from up above)). The area highlighted shows an example of TMS pulses falling into the sulcus (indicated by arrows).

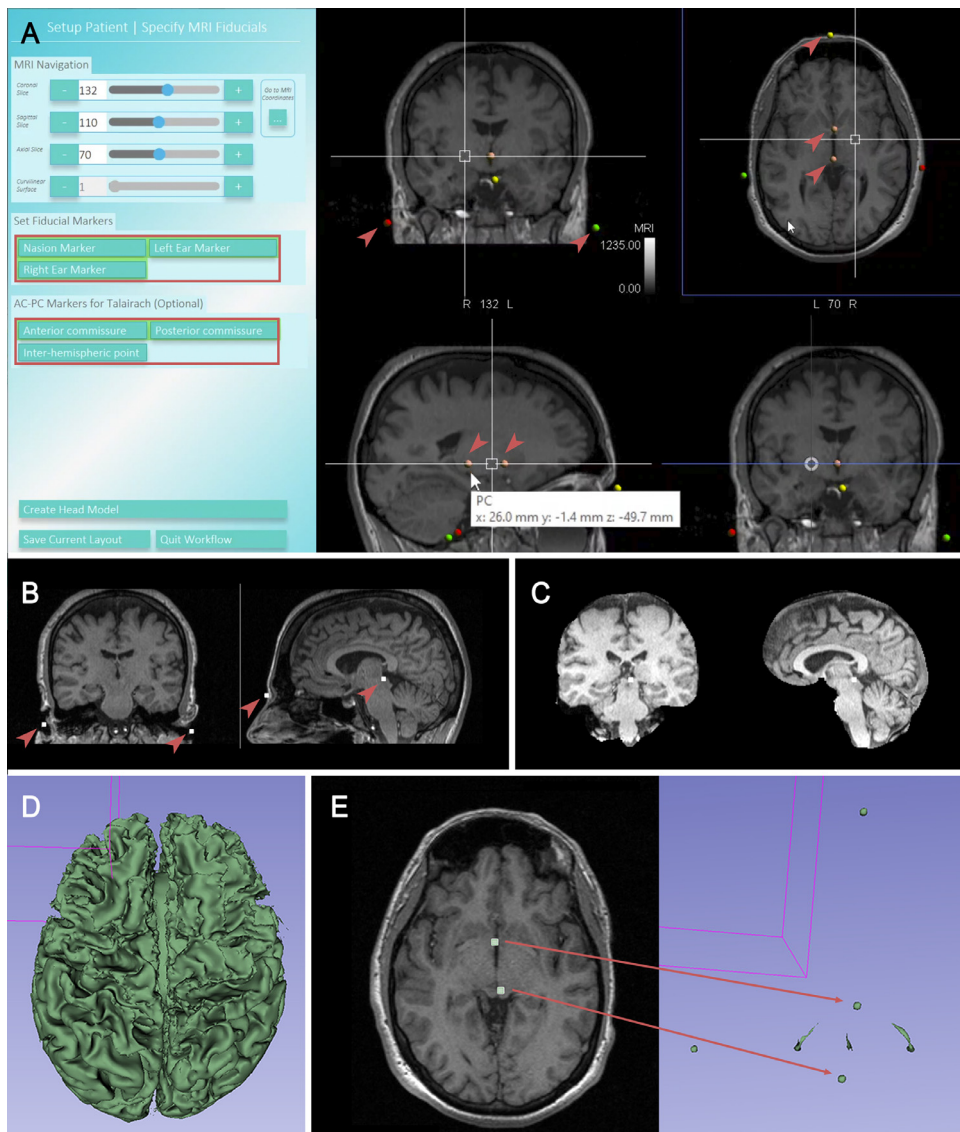


Fig. 2. Overview of the MRI data processing pipeline: A) MRI data presented in neuronavigation software showing selected fiducials marked on different MRI projections (arrows indicate their location). The sagittal projection (lower left) shows the fiducial marking the posterior commissure (PC) with corresponding coordinates. B) Exported MRI data from the neuronavigation software displayed in Slicer 3D with fiducial data (arrows indicate their location). C) Brain separated from the skull and other non-brain structures. D) 3D model of the segmented brain. E) 3D model of the segmented fiducials.

Method description

Since the proposed method is designed for visualization of data obtained in a neuronavigational TMS study, it requires the use of individual MRI data with all fiducials marked via NN software before the start of the TMS experiment (see Fig 2, A). In this article, we present a pipeline with example screenshots from the NN software Visor2 (ANT Neuro, Netherlands). This is a commonly used software with standard tools, so data obtained with other NN packages can also be processed using the presented pipeline.

Data preprocessing

1. Create fiducials before starting the TMS session. There are several ways to set them [8]. In the example shown in Fig. 2A, there are nasion, left and right tragus, AC and PC fiducials. Each of these has individual position coordinates that will be needed later as they create a common coordinate system for the brain model and the TMS coil. It is important to create at least 3 fiducials to align the coordinate systems correctly.

2. At the end of the TMS experiment export the MRI data and data containing the coil coordinates from NN software. Make sure to include the fiducials as part of the MRI data (see Fig 2, B).
3. Process the MRI data in Slicer 3D (<http://www.slicer.org>, Surgical Planning Laboratory, Harvard University, Boston, MA, USA, version 4.11.02) to obtain 3D models of the brain and the fiducials. Separate the brain from other tissues manually or by using special plugins e.g. Skull Stripper, which automatically creates masks for brain segmentation [11,12]. see Fig 2, C). To extract fiducials, move threshold to maximal value so to extract only white matters (as fiducials are). As we can see on Fig 2, D, the ventricular system can be extracted too.
4. Save the two 3D models (brain and fiducials) as STL files. It is important to mention that Slicer 3D creates a new coordinate system when exporting, this issue will be dealt with in the next steps.
5. Brain 3D model pre-processing. The model obtained during segmentation in 3D Slicer may contain artifacts. It is important to fix them before running the script, as they affect the projection of TMS pulses onto the cortex. It is possible to use any program that allows the manipulations of the model and its vertices. In this example, Blender version 3.0 or above is recommended (Blender documentation can be found here <https://docs.blender.org/>).
 1. **Deleting unnecessary mesh islands.** In case there are unnecessary parts representing scalp or brain meninges or lots of random unsensed points (vertexes) selecting and deleting mesh islands could be used. Senseful islands are to be selected by hovering above them in Edit mode and pressing L on a keyboard. This operation can be repeated to include all target mesh islands into one selection. To invert selection Ctrl + I could be used resulting in selection of all unnecessary mesh islands that could eventually be deleted by pressing X (or Mesh/Delete/Vertices).
 2. **Fixing normals.** The common segmentation artifact is flipped polygon normals: some polygon normals are directed inside of the model, others are directed outside of the model. To fix it the Recalculate Outside function can be used (Edit mode, Mesh/Normals/Recalculate outside or Shift+N in Edit mode). This function recalculates the normals of selected mesh so that they point outside the volume that the face belongs to ([docs.blender.org/manual/ 17 dec 2022](https://docs.blender.org/manual/3.0/2.1/Editing/Mesh/Normals/Recalculate%20Outside.html)). Save the fixed model in STL format for the next step.

Calculation of TMS pulse projections to the cortex in Blender software

1. Import the 3D models of preprocessed brain and fiducials into Blender. This can be done by using the “File” menu and selecting “Import” followed by the appropriate file type (e.g. STL).
2. Open the scripting mode and run the first part of the Python script that generates the fiducial meshes (use the fiducial coordinates taken from the NN software). Place 3D models of the brain and fiducials so as to match them with the generated fiducial meshes. Use Move and Rotation tools to put your fiducials model in the same position as the generated one. Make sure generated fiducials and MRI fiducials intersect closely. It is crucial to place the brain 3D model in the coordinate system of the TMS coil coordinates. Apply a new coordinate system of the brain model by pressing Object->Apply->Location or Ctrl-A.
3. Read the data containing the coil position and orientation coordinates (in the script specify a path to files containing the TMS coil coordinate and orientation data exported from the NN software) and run the second part of the script, which by using these data generates magnetic field gradient vectors as 3D meshes. These meshes are long rectangles which start from the position equal to the coil position, and direct along the coil orientation towards the cortical surface. The coil orientation is presented as a vector consisting of four components: w, x, y, and z. Such mathematical representation of 3D orientation corresponds to quaternions. The w component represents the angle of rotation, while the x, y, and z components represent the axis of rotation. One advantage of using quaternions to represent orientation is that they can avoid "gimbal lock" which is a phenomenon that can occur when using Euler angles (see [13]). To orient meshes of vectors correctly it is needed to change the rotation mode of a mesh from Euler to Quaternion (see Section 6 in Supplementary files). If the coil coordinates and orientations were read properly, the meshes of vectors should intersect the cortical surface of the brain model (see Fig. 3).
4. On the next step the algorithm finds the coordinates of all the intersected polygons and collects them into the list-type object.
5. The TMS-affected cortical points can only be determined by selecting the outer surface (i.e. cortical) polygons among all brain polygons intersected by the mesh of omitted vectors. In our algorithm, this is done by selecting the intersected polygons with the highest sum of all coordinates. The selected coordinates are used to create spheres representing the TMS pulse markers. The size and color of each sphere can be adjusted for different experimental purposes. (see Section 9 in Supplementary files).

Post-processing of the segmented 3D model

Artifacts of segmentation process in the model of the brain could affect visual appearance. For the best visualization results, artifacts could be fixed manually. This should be done after running the script, otherwise mesh changes may affect the accuracy of the proposed method.

The artifacts and issues that are most commonly encountered are listed below. We propose to solve them in that order.

Decreasing polygon count

A model may have an excess amount of polygons. The Decimate modifier decreases the polygon count without losing details ([docs.blender.org/manual/ 17 dec 2022](https://docs.blender.org/manual/3.0/2.1/Editing/Modifiers/Decimate.html)). It is necessary to apply the modifier to change the actual mesh.

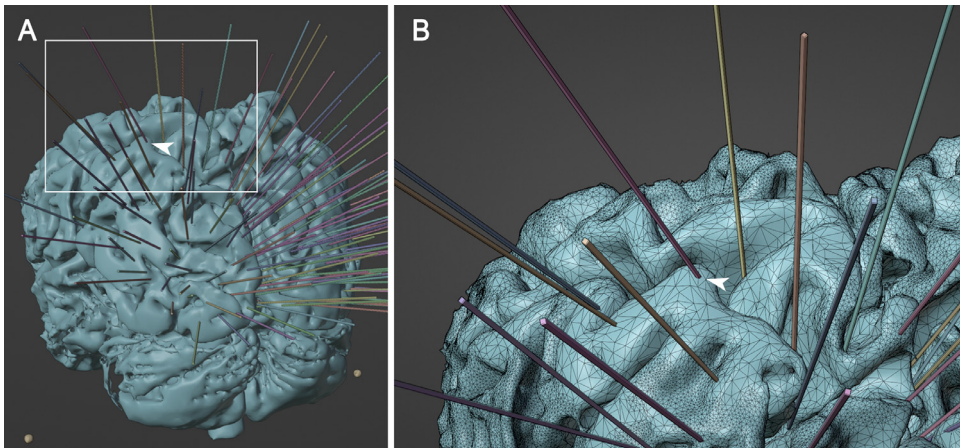


Fig. 3. A - Rectangular meshes aligned with the coil Position and Orientation data, intersecting the cortical surface of the Brain Model. B - Close view: cursor pointing intersected cortical polygons.

Inflation of gyrus

Another common segmentation artifact is deflated gyrus. gray matter of gyrus has insufficient contrast which leads to potential loss of data about gyrus gray matter volume. This issue can be solved by using the Shrink\Fatten tool (Alt + S or Mesh/Transform/Shrink/Fatten). This tool moves selected vertices/edges/faces along their own normal resulting in inflation of gyrus y (docs.blender.org/manual/ 17 dec 2022).

Inflation of gyrus in sculpt mode

Sometimes gyrus still does not have enough volume due to segmentation issues and lack of polygons in particular areas of cortex. In that case it is also possible to add polygon counts and apply inflation on desirable parts of a mesh in sculpt mode. To do so the Blender interface needs to be switched to sculpting mode by selecting the corresponding option above the viewport (the model should be in Object mode and selected). Ticking the Dyntopo option on the right upper corner of the interface allows adding polygons while sculpting. This option is dependent on viewport zoom level by default and can be switched off (docs.blender.org/manual/ 17 dec 2022). The less input px count is put - the higher polygon count can be achieved. It is necessary to be aware of adding too many polygons: it will be impossible to get rid of excess polygon count by Decimate Modifier. To inflate areas of cortex Inflate brush needs to be used.

Smoothering

If smoothering by shading smooth (right click on the object/shade smooth) is not enough Smooth Modifier can be used (docs.blender.org/manual/ 17 dec 2022). The Smooth modifier smoother a mesh by flattening the angles between adjacent faces in it. It is needed to apply the modifier to make sure it affects the actual mesh.

Additional edits

In case the model still has visible artifacts manual edits are needed, e.g. closing holes, filling gaps in gyrus, removing meningitis parts. Basic skills in 3D modeling are required.

Limitations

There are some limitations of the presented method that can impact its accuracy. The quality of the MRI images can be negatively affected by factors such as movement artifacts and low signal-to-noise ratio, as well as low spatial resolution. The example presented here is based on a brain model reconstructed from MRI data obtained using 1.5 Tesla tomography, which has a spatial resolution of approximately 1–2 mm in the plane and 3–5 mm through the plane. On the other hand, 7 Tesla MRI can achieve a spatial resolution of around 0.4–1 mm in the slice plane and 1–2 mm in the through-plane direction [14].

The accuracy of the method may also be influenced by errors in the referencing procedure, as the anatomical fiducials marked on the participant's head may differ from those determined from the MRI data. Additionally, the pre-processing of the brain model may impact the precision of the method. The decrease in the number of polygonal elements in the model (model decimation) can affect the coordinates of the polygonal elements and thus the reconstructed position of the stimulated cortical sites. Therefore, it is

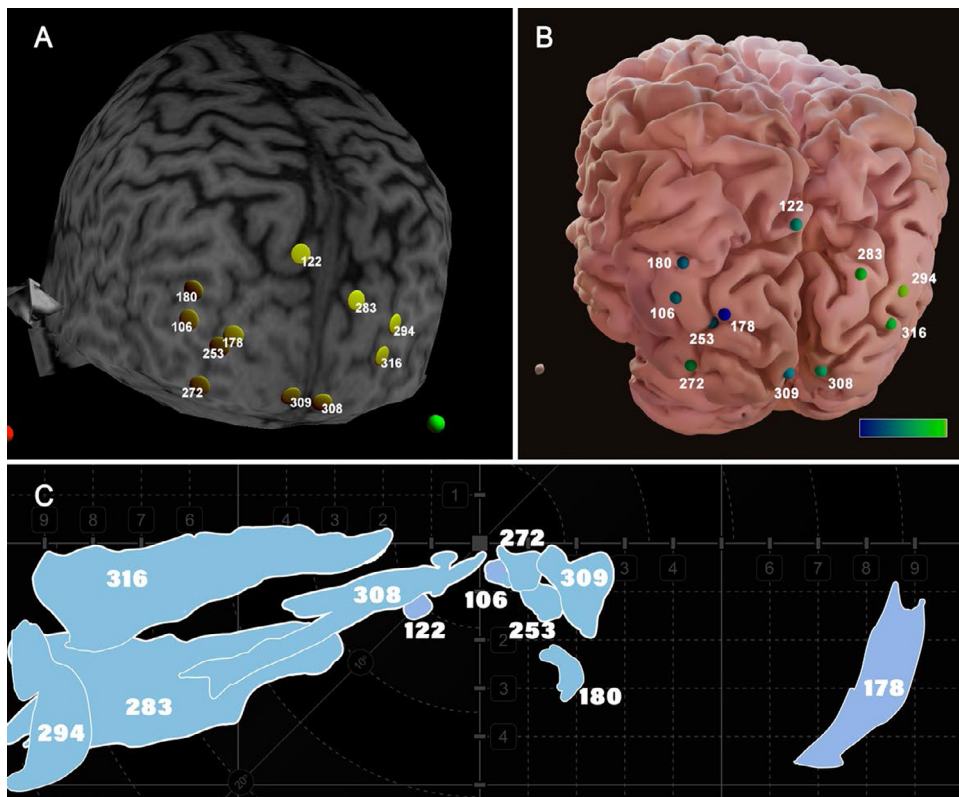


Fig. 4. A,B - Visualization of the results of visual cortex mapping obtained through TMS-induced phosphenes analysis. Special markers on the cortical surface indicate points where TMS stimulation led to phosphene occurrence. The color of markers on (B) represents the position of corresponding phosphene in the visual field. C - Example of several phosphenes elicited by TMS applied to specific areas of the visual cortex: the numbers of phosphenes correspond to the numbers near the coloured markers on the cortical surface; It can be seen that phosphenes were elicited in the visual field contralateral to the stimulated hemisphere.

recommended to optimize the model after reconstructing the TMS pulses. However, these fluctuations are considered to be negligible compared to the resolution of the TMS and can be ignored. The use of Blender for 3D data processing is highly recommended, as it is an open-source package that is actively integrated into neuroimaging data processing, such as the example at https://github.com/ezemikulan/blender_freesurfer.

Applications

The method discussed above is applicable to a range of TMS mapping studies, including investigations of primary motor cortex excitability and visual cortical neuron specificity. An example is provided below to demonstrate the use of this method in analyzing and presenting results from a TMS-induced phosphene study of primary and secondary visual cortices (for more information on TMS-induced phosphenes, see [15]).

Phosphenes' location in the visual field depends on the specific area of the visual cortex that was stimulated by TMS, which is determined by the position and orientation of the TMS coil. It is widely accepted that phosphenes follow the principle of contralateral specificity, meaning that stimulation of the left visual cortex would cause phosphenes to appear on the right side of the visual field. However, some visual areas do not conform to this pattern, and TMS-induced stimulation of these regions can result in ipsilateral phosphenes. In Fig. 4, the results of TMS mapping of the visual cortex are presented, demonstrating the specific cortical sites that were stimulated by TMS (spheres) and their shading, indicating the lateral direction (the color gradient corresponds to the direction from the right to the left periphery of the visual field) of the phosphenes in the visual field. The lateral direction of each phosphene was determined by analysis of pictures drawn by the participant (for example, see Fig. 4,C). The participant's brain model was created using MRI slices, and the locations of all TMS-affected cortical sites were reconstructed using coil coordinates. This brain model with stimulated points obtained by the presented method can be used to systematically analyze the contralateral specificity, excitability, and other properties of different parts of the visual cortex. Moreover, it provides information on whether the TMS pulse was applied to a gyrus or sulcus. This information can be obtained through visual inspection or automatically by examining the coordinates of the reconstructed stimulated cortical sites, which can then be exported for further analysis.

Ethics statements

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Nikolay Syrov: Conceptualization, Methodology, Writing – original draft, Software, Investigation, Data curation, Resources. **Alfiia Mustafina:** Conceptualization, Methodology, Writing – original draft, Visualization. **Artemiy Berk mush-Antipova:** Investigation, Data curation, Resources. **Lev Yakovlev:** Investigation, Data curation, Resources. **Andrey Demchinsky:** Investigation, Data curation, Resources. **Daria Petrova:** Investigation, Data curation, Resources. **Alexander Kaplan:** Supervision, Writing – review & editing.

Data availability

Data will be made available on request.

Acknowledgments

The work was supported by the [Russian Science Foundation](#), grant number No. 21-75-30024.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.mex.2023.102213](https://doi.org/10.1016/j.mex.2023.102213).

Supplementary material and/or additional information [OPTIONAL]

<https://github.com/kolascoco/TMS-Brain-Visualization.git>

References

- [1] Y. Terao, Y. Ugawa, Basic mechanisms of TMS, *J. Clin. Neurophysiol.* 19 (4) (2002) 322–343.
- [2] P.M. Rossini, S. Rossi, Transcranial magnetic stimulation: diagnostic, therapeutic, and research potential, *Neurology* 68 (7) (2007) 484–488.
- [3] M.J. Burke, P.J. Friede, A. Pascual-Leone, Transcranial magnetic stimulation: neurophysiological and clinical applications, *Handb. Clin. Neurol.* 163 (2019) 73–92.
- [4] H.R. Siebner, K. Funke, A.S. Aberra, A. Antal, S. Bestmann, R. Chen, ... Y. Ugawa, Transcranial magnetic stimulation of the brain: What is stimulated? - a consensus and critical position paper, *Clin. Neurophysiol.* 140 (2022) 59–97.
- [5] F. Maeda, A. Pascual-Leone, Transcranial magnetic stimulation: studying motor neurophysiology of psychiatric disorders, *Psychopharmacology (Berl.)* 168 (4) (2003) 359–376.
- [6] A. Opitz, M. Windhoff, R.M. Heidemann, R. Turner, A. Thielscher, How the brain tissue shapes the electric field induced by transcranial magnetic stimulation, *Neuroimage* 58 (3) (2011) 849–859.
- [7] U. Herwig, C. Schönfeldt-Lecuona, A.P. Wunderlich, C. von Tiesenhäusen, A. Thielscher, H. Walter, M. Spitzer, The navigation of transcranial magnetic stimulation, *Psychiatry Res.* 108 (2) (2001) 123–131.
- [8] P.M. Rusjan, M.S. Barr, F. Farzan, T. Arenovich, J.J. Maller, P.B. Fitzgerald, Z.J. Daskalakis, Optimal transcranial magnetic stimulation coil placement for targeting the dorsolateral prefrontal cortex using novel magnetic resonance image-guided neuronavigation, *Hum. Brain Mapp.*, 31, 2010, pp. 1643–1652.
- [9] E. Fernandez, A. Alfaro, J.M. Tormos, R. Climent, M. Martinez, H. Vilanova, ... A. Pascual-Leone, Mapping of the human visual cortex using image-guided transcranial magnetic stimulation, *Brain Res. Protoc.* 10 (2) (2002) 115–124.
- [10] B. Fischl, FreeSurfer, *Neuroimage* 62 (2) (2012) 774–781.
- [11] S. Bauer, T. Fejes, M. Reyes, A skull-stripping filter for ITK, *Insight J.* 2012 (2013) 70–78.
- [12] X. Zhang, K. Zhang, Q. Pan, J. Chang, Three-dimensional reconstruction of medical images based on 3D slicer, *J. Complex. Health Sci.* 2 (1) (2019) 1–12.
- [13] J. Kozak, D. Friedrich, Quaternion: An Alternate Approach to Medical Navigation, in: *World Congress on Medical Physics and Biomedical Engineering*, Munich, Germany, 2009, pp. 7–12.
- [14] D. Stucht, K.A. Danishad, P. Schulze, F. Godenschweger, M. Zaitsev, O. Speck, Highest resolution in vivo human brain MRI using prospective motion correction, *PLoS One* 10 (7) (2015) e0133921.
- [15] T. Kammer, K. Puls, M. Erb, W. Grodd, Transcranial magnetic stimulation in the visual system. II. Characterization of induced phosphenes and scotomas. Characterization of induced phosphenes and scotomas, *Exp. Brain Res.* 160 (2005) 129–140.