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Brain Stimulation

The dependency of TMS-evoked potentials on electric-field orientation in the cortex

A R T I C L E I N F O

Dear editor,

Optimal targeting of transcranial magnetic stimulation (TMS) is often challenging due to the many stimulation parameters, such as the location and orientation of the induced electric field, the stimulation intensity, and the timing of the TMS pulse. All these parameters significantly affect the stimulation outcomes [1], yet their roles in shaping the TMS-evoked transcranial responses are not well known. Such knowledge would help target specific cortical circuits and increase the utility of TMS as a functional and structural neuroanatomical tool for mapping cortical regions [2].

The orientation of the induced electric field, a stimulation parameter that influences the efficacy of TMS [3,4], possibly also affects which neuronal populations are primarily stimulated by the TMS pulse [5–7]. The aim of this work is to determine how the amplitudes and effective connectivity patterns of TMS-evoked potentials (TEPs) depend on stimulus orientation.

We analysed a dataset [8] containing EEG responses to TMS delivered to the pre-supplementary motor region in 36 evenly spaced orientations in six subjects (2 male, ages 22–42), with 48 trials per orientation. Orientation 0° was defined as the posterior–anterior direction.

To explore the effects of the stimulus orientation on the TEP amplitudes in the spatiotemporal domain, we applied cluster-based statistics [9]. To increase the power of the initial statistics test, neighbouring orientations were paired into single distributions to increase within-group sample size, with 75–96 observations per grouped orientation. We merged the data from the different subjects by applying Stouffer's Z method [10]; Supplementary material] within the cluster-based permutation framework, after applying single-factor ANOVA as the initial test statistic. The threshold for clustering and the cluster-level alpha was set at 0.05, and 0–500 ms post-stimulus was examined with 1000 randomizations.

Source estimation was performed for each subject to further investigate changes in the propagation of TMS-evoked activity after giving pulses with different electric-field orientations. Each depth-weighted minimum-norm-estimated (MNE) source point was thresholded by first permuting the baseline across conditions 1000 times by drawing random trials to form random surrogate trial set for each orientation.

Then, the maximum over the whole spatiotemporal domain of the MNE estimate of each permutation was stored. The threshold was set at the 95th percentile of the stored maximum statistics distribution.

To investigate changes in the source estimates when stimulating in different orientations, we evaluated the Activation Concurrence (AC) at each spatiotemporal point, i.e., the number of orientation conditions that produced suprathreshold activations, as well as the Activation Variability (AV), i.e., the variance over the conditions, normalized by the maximum variance per subject.

The cluster-based statistical test showed a significant effect of orientation ($p = 0.001$) on the evoked responses, indicating largest differences across orientations at early time points (<50 ms) close to the stimulation site. After 50 ms, the centre of the cluster shifted laterally and posteriorly, extending to 114 ms post-stimulus.

Visually inspecting the TEPs in the electrodes with the largest test statistic in 25 ms blocks indicate that, at latencies shorter than 15 ms, a stimulus orientation of approximately 100° produced a larger negative deflection at the stimulated site, after which stimulus orientations around −90 and 90° produced the strongest responses (Fig. 1).

The source estimates suggested orientation-dependent differences in signal propagation from the stimulated site. The results were highly consistent across the subjects at 35–45 ms after the TMS pulse, showing both high AC and AV, indicating that the response is stable, yet the amplitude varies with orientation. After 45 ms, the heterogeneity in signal propagation increased: S2, S3, S4 and S6 showed central suprathreshold responses in specific orientations. S5 showed suprathreshold responses over M1 at approximately 55–65 ms.

In line with previous research [3,4], the most prominent TEP amplitudes were evoked when orienting the electric field perpendicularly to a gyrus. Visual inspection of the TEP amplitudes did not reflect prominent changes with a 180° shift in stimulus orientation (supplementary material). This might be attributed to EEG measuring post-synaptic currents, which are more generic to all cortical activations compared to, for instance, corticospinal activations. In other words, due to the spatial limitation of EEG, 180° shifts in the orientation might produce similar responses despite potentially activating different neuronal populations. Thus, different stimulus orientations either activate similar neuronal populations and only affect the stimulation
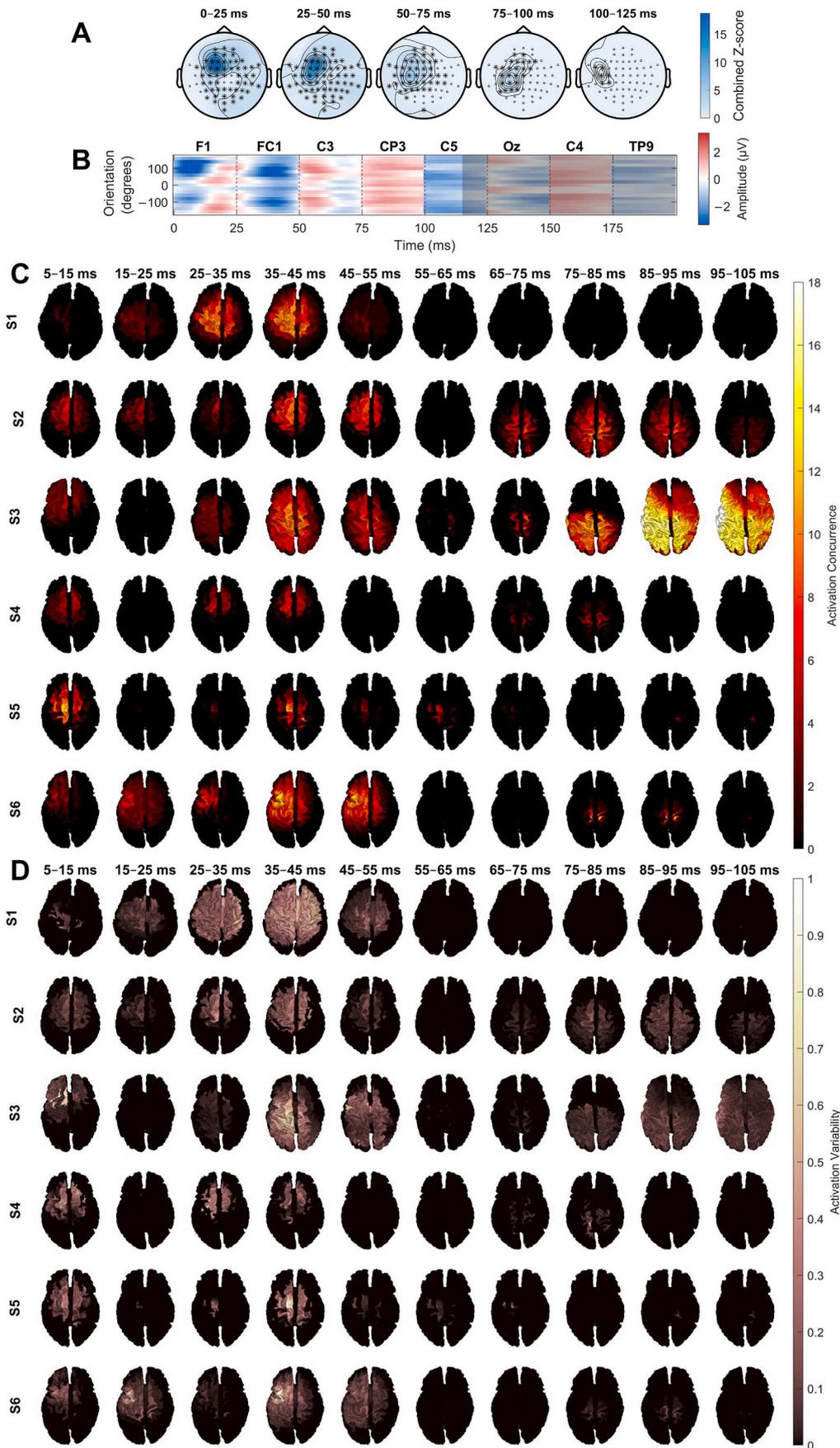
Fig. 1. A. The cluster-based statistical test showed a significant effect of orientation. The cluster is marked by asterisks, and the dark blue areas show the test statistic values within the cluster. **B.** Visually inspecting the data over the orientations in the channel with the largest test statistic in 25-ms time windows suggests that early responses (<50 ms) show largest peaks close to the stimulated site. Time windows outside of significant clusters are masked with a grey overlay. **C–D.** We quantified both the Activation Concurrence (AC; C), and the Activation Variability (AV; D). On the colormap, black indicates the absence of suprathreshold sources, relating to low AC. At 35–45 ms, both AC and AV are high in most subjects at the stimulated site, after which the heterogeneity in signal propagation from the stimulated site increases.

efficacy, and/or EEG cannot distinguish between the post-synaptic currents from different neighbouring neuronal populations.

Notably, there was no clear effect of the orientation past 100 ms, indicating that the later responses may reflect other non-specific responses to the TMS pulse, or may have poorer signal-to-noise ratio than earlier components.

AC indicated that the 35–45 ms responses are robustly evoked, but vary in amplitude when the stimulus orientation changes, while later suprathreshold responses were only evoked with certain orientations. These results indicate that the orientation may also affect the efficacy of signal propagation from the stimulated site.

Our results indicate that the stimulus orientation plays a major role in overall cortical reactivity, which is reflected in the total response, including reactivity and effective connectivity. Moreover, our results imply that stimulating distant targets would require mapping to specify the exact orientation to reach the desired cortical structure.

CRediT authorship contribution statement

Ida Granö: Data curation, Formal analysis, Funding acquisition, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing, Conceptualization. **Tuomas P. Mutanen:** Conceptualization, Formal analysis, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Aino E. Nieminen:** Conceptualization, Formal analysis, Investigation, Methodology, Software, Writing – review & editing, Data curation. **Jaakko O. Nieminen:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing. **Victor H. Souza:** Funding acquisition, Investigation, Visualization, Writing – review & editing. **Risto J. Ilmoniemi:** Funding acquisition, Project administration, Resources, Writing – review & editing. **Pantelis Lioumis:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Declaration of competing interest

No authors have competing interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2025.04.021.

References

[1] Casarotto S, Romero Lauro LJ, Bellina V, Casali AG, Rosanova M, Pigorini A, et al. EEG responses to TMS are sensitive to changes in the perturbation parameters and repeatable over time. PLoS One 2010;5:e10281. https://doi.org/10.1371/journal.pone.0010281.

[2] Lioumis P, Roine T, Granö I, Aydogan DB, Ukharova E, Souza VH, et al. Optimization of TMS target engagement: current state and future perspectives. Front Neurosci 2025;19. https://doi.org/10.3389/fnins.2025.1517228.

[3] Gomez-Feria J, Fernandez-Corazza M, Martin-Rodriguez JF, Mir P. TMS intensity and focality correlation with coil orientation at three non-motor regions. Phys Med Biol 2022;67. https://doi.org/10.1088/1361-6560/ac4ef9.

[4] Thielscher A, Opitz A, Windhoff M. Impact of the gyral geometry on the electric field induced by transcranial magnetic stimulation. Neuroimage 2011;54:234–43. https://doi.org/10.1016/j.neuroimage.2010.07.061.

[5] Aberra AS, Wang B, Grill WM, Peterchev AV. Simulation of transcranial magnetic stimulation in head model with morphologically-realistic cortical neurons. Brain Stimulat 2020;13:175–89. https://doi.org/10.1016/j.brs.2019.10.002.

[6] Weise K, Worbs T, Kalloch B, Souza VH, Jaquier AT, Van Geit W, et al. Directional sensitivity of cortical neurons towards TMS-induced electric fields. Imaging Neurosci 2023;1:1–22. https://doi.org/10.1162/imag_a_00036.

[7] Pisoni A, Vergallito A, Mattavelli G, Varoli E, Fecchio M, Rosanova M, et al. TMS orientation and pulse waveform manipulation activates different neural populations: direct evidence from TMS-EEG. 2018, 308981. https://doi.org/10.1101/308981.

[8] Tervo AE, Nieminen JO, Lioumis P, Metsomaa J, Souza VH, Sinisalo H, et al. Closed-loop optimization of transcranial magnetic stimulation with electroencephalography feedback. Brain Stimulat 2022. https://doi.org/10.1016/j.brs.2022.01.016.

[9] Oostenveld R, Fries P, Maris E, Schoffelen J-M. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011;2011:1–9. https://doi.org/10.1155/2011/156869.

[10] Stouffer SA, Suchman EA, Devinney LC, Star SA, Williams Jr, Rm. The American soldier: adjustment during army life. (Studies in social psychology in World War II), vol. 1. Oxford, England: Princeton Univ. Press; 1949.

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