Normal component of TMS-induced electric field is correlated with depressive symptom relief in treatment-resistant depression

Letter to the editor

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that modulates brain activity by producing an electric field in the targeted brain region [1]. Theta burst stimulation (TBS), a patterned form of rTMS, is an FDA approved therapy for treatment resistant depression (TRD). However, reported effect sizes and response rates are heterogeneous [2]. Recent research suggests that the diversity of the induced electric fields (EF) in the brain due to individual differences in head morphology may partly explain the response variation to TMS [3]. Yet, predicting the clinical response based on EF calculations continues to be a challenge, as we still lack a clear understanding of the key EF component responsible for the observed treatment response. To inform this research gap, Fox et al. used positron emission tomography (PET) to examine TMS-induced cortical activation and found that "TMS active regions" had a higher EF normal component ($E_\perp$) in the inward direction (i.e., entering the cortex perpendicular to its surface) [4]. Conversely, recent computational simulation modeling research reported that the tangential component ($E_\parallel$) and the overall magnitude of the EF ($||E||$) were most relevant to TMS-induced effects [5].

The current study aimed to systematically investigate the relationship between TMS-induced EF characteristics and antidepressant effects in patients with TRD. We hypothesized that the reduction of depressive symptoms after three weeks of stimulation treatment would be proportional to the magnitude of one or more of the proposed EF components in the stimulated brain region.

The analysis was based on a subsample of patients from a longitudinal, clinical trial published previously [6]. Data of twelve TRD patients were included. Patients underwent 3 weeks of daily sequential bilateral TBS. Standard intermittent TBS (iTBS; 20 trains, 600 pulses) was utilized to stimulate the left dorsolateral prefrontal cortex (DLPFC) at Montreal Neurological Institute (MNI) coordinates x = −38, y = 44, z = 26, whereas continuous TBS (cTBS; 600 continuous pulses) was used to stimulate the right DLPFC at MNI coordinates x = 38, y = 44, z = 26 in individual subject space, and at an intensity of 120% resting motor threshold (RMT). Targets were based on a previous study that indicated largest antidepressant effects and strongest negative functional connectivity with the subgenual cingulate cortex compared with other DLPFC locations [7]. MRI scans and clinical assessments were performed at baseline and after the last TBS session (for details, see Ref. [6]). TBS induced EF were simulated in anatomically realistic, volume conductor head models by the finite element method (FEM) using SimNIBS v3.2 [8]. Individual T1-and T2-weighted structural MRI data were used for head model reconstruction. Segmentation was inspected to prevent tissue boundary establishment errors. A coil model of MagVenture MC-B70 was used for computations, which displays similar penetration depth and focality to the coil used for stimulation (MagVenture Cool-B70) [9]. The TMS coil was positioned over the patient's head according to the location extracted from the neuro-navigation system (LOCALITE® TMS Navigator Germany) with the handle pointing towards the vertex. The stimulation intensity was determined using the relative dI/dt (current rate-of-change) value obtained directly from the TMS stimulator (MagPro X100, Magventure, Tonica Elektronik A/S, Denmark). Left and right stimulation regions in the DLPFC at MNI coordinates (±38, 44, 26) were chosen as regions of interest (ROIs) and defined as spheres (r = 5mm) in head models (Fig. 1a). EF characteristics were analyzed on the ROI level. $||E||$, $E_\parallel$ and $E_\perp$ were calculated as the sum of the respective average values within the left and right ROI to simulate the real stimulation "dose" that patients received. The magnitude of $E_\perp$ component ($|E_\perp|$) was defined as the sum of the average absolute value of both left and right $E_\perp$ inside an ROI. In an exploratory post-hoc analysis, EF characteristics were also investigated separately for the left and right ROI. Generalized liner mixed model (GLMM, repeated measure: time; main effect: time, $||E||$, $E_\parallel$, $E_\perp$ and $|E_\perp|$; interaction effect: time by each characteristics of EF; dependent variable: IDS-C score) and post-hoc pairwise comparisons were used to analyze the relationship between EF characteristics and clinical improvement. Following the GLMM, we performed Pearson's correlations to confirm associations between antidepressant treatment effects and EF characteristics. Post-hoc analyses were corrected for multiple comparisons using the Bonferroni procedure. The level of statistical significance was set at $P < 0.05$.

GLMM indicated a significant interaction effect between time and $|E_\perp|_{sum}$ on IDS-C scores ($F = 8.911$, $P = 0.01$), but not for other EF characteristics. Post-hoc pairwise comparison showed significantly lower estimated IDS-C scores after treatment compared to baseline scores (mean ± SD = −15.5 ± 2.327; $t_{14} = -6.662$, $P < 0.001$, corrected) (see supplementary file for further details). Pearson correlation analyses confirmed a negative correlation between change in IDS-C scores after treatment and the $|E_\perp|_{sum}$ component ($r = -0.752$, $P = 0.005$, corrected P = 0.0125, Fig. 1b). No other EF characteristics showed significant associations with IDS-C scores (Fig. 1c−e). When investigating each ROI separately, we observed a negative correlation between $|E_\perp|_{right}$ and change of IDS-C scores ($r = -0.781$, $P = 0.003$, Fig. S1a) but not for the left ROI ($r = -0.458$, $P = 0.135$ Fig. S1b).
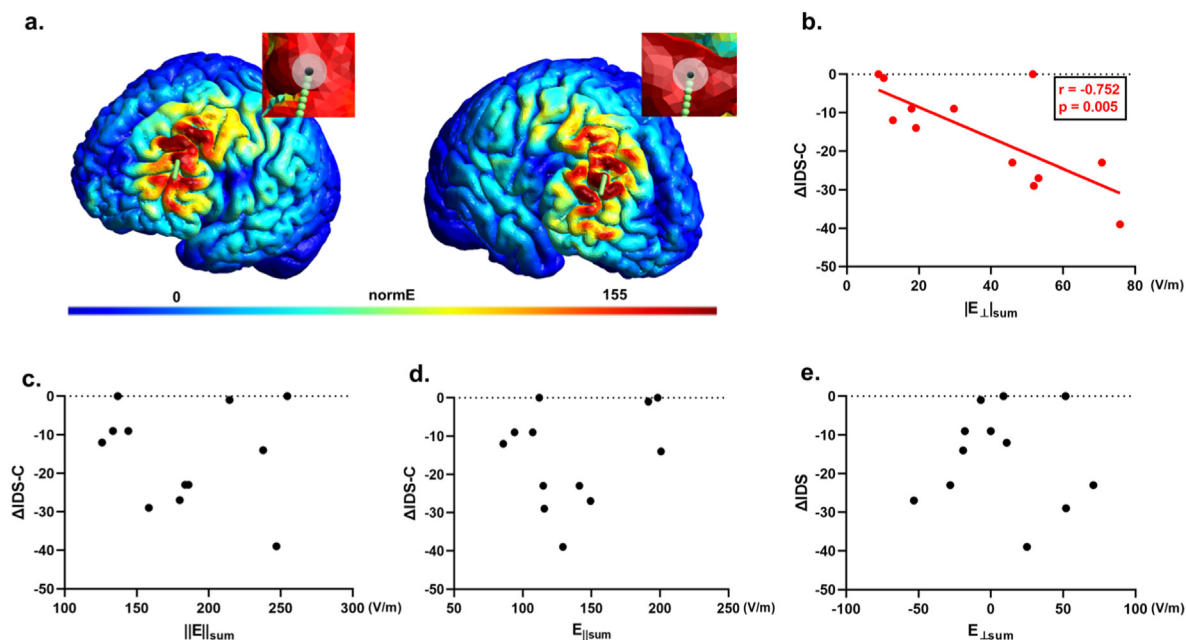
Fig. 1. (a) Simulation results of the electric field distribution in the left (left side of image) and right (right side) hemispheres demonstrated using data from one subject. Close-up shows the ROI in the left (left side) and right (right side) hemispheres. The gray circle indicates the ROI used for calculating EF characteristics. The black dot indicates both the stimulation target and the TMS coil's center. The green line indicates the current direction in the coil. (b) Correlation between change in IDS-C scores and $|E_\perp|$, with the latter calculated as the sum of both left and right ROI. (c) Correlation between change in IDS-C scores and $\|E\|$, with the latter calculated as the sum of both left and right ROI. (d) Correlation between change in IDS-C scores and $E_\|$, with the latter calculated as the sum of both left and right ROI. (e) Correlation between change in IDS-C scores and $E_\perp$, with the latter calculated as the sum of both left and right ROI.

To our knowledge, this is the first study using a computational simulation modeling approach to investigate the association between TMS-induced EF characteristics and clinical improvement in TRD patients. Our findings indicate that the $|E_\perp|$ component rather than $\|E\|$ or $E_\|$ in the DLPFC is related to symptom improvement. This is in line with a previous study indicating a correlation between the $E_\perp$ component and TMS induced effects [10]. However, the exact mechanism of how TMS stimulates the brain is still a matter of debate. On the one hand, research suggests that not only $E_\perp$ but also the $\|E\|$ and $E_\|$ substantially contribute to the neuronal depolarization [3,5] On the other hand, the cortical column cosine model claims that the stimulation effect is proportional to the cosine of the angle between the E_field and the normal of the cortical surface [4]. The latter explanation seems to be the most parsimonious explanation for our data, with recent findings bolstering the rationale for this theoretical model. Aberra et al. [3] reported that TMS initiates action potentials at the axon terminal, with layer 5 pyramidal cells (the main integration unit of the cortical column) demonstrating the lowest depolarization thresholds and preferentially activated by the $E_\perp$ component. More studies are needed to resolve these controversial results, and to clarify the clinical significance of EF characteristics for left and right DLPFC in bilateral stimulation protocols. Lastly, we observed a significant correlation only for the right but not for left DLPFC when examining each hemisphere separately, an observation that requires replication.

In conclusion, our results suggest that the magnitude of $E_\perp$ component of the TMS-induced EF is associated with the antidepressant response to bilateral sequential TBS in patients with TRD. Future studies using a tailored TMS treatment approach may consider maximizing the $|E_\perp|$ component in order to enhance clinical effects. However, our results are exploratory and must be interpreted with caution due to the limited sample size.

Author contributions

Bella B.B. Zhang: Methodology, Software, Data Curation, Formal analysis, Writing-Original Draft, Writing-Review & Editing, Visualization; **Peter Stöhrmann**: Methodology, Software, Data Curation, Formal analysis, Writing-Review & Editing; **Godber M Godbersen**: Data Curation, Stimulation Treatment, Writing-Review & Editing; **Jakob Unterholzner**: Data Curation, Stimulation Treatment, Writing-Review & Editing, **Siegfried Kasper**: Resources, Methodology, Writing-Review & Editing; **Rupert Lanzenberger**: Conceptualization, Methodology, Writing-Review & Editing, Supervision, Project administration; **Georg S. Kranz**: Conceptualization, Methodology, Writing-Original Draft, Writing-Review & Editing, Supervision, Project administration.

Declaration of competing interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2022.09.006.

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