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Loss of stimulation intensity- and cortical activity-dependent TMS-evoked reactivity in poststroke primary motor cortex

Dear Editor:

Transcranial magnetic stimulation (TMS)-electroencephalography (EEG) can be utilized to record TMS-evoked potentials (TEPs), which have been proposed as direct readouts of brain responsiveness in terms of local neuronal activity and large-scale brain networks. TMS of the cerebral cortex elicits intensity-dependent early TEP components located at the stimulation site in healthy individuals [1], and demonstration of the intensity-response relationship could provide a causal explanation for the TMS-evoked brain network. In contrast, loss of the intensity-response relationship may imply pathological neuronal excitability or loss of neurons that are necessary for the generation of specific TEP components.

In stroke patients whose ipsilesional motor-evoked potential is unmeasurable, TEPs can be an optimal alternative. The strength of the induced electric field (EF) in the brain partially explains the cortical reactivity measured by TEPs in healthy individuals [2]. However, it remains unclear how primary motor cortex (M1)-originated TEPs are influenced by TMS-induced EF strength and how they relate to cortical activity at the TMS target in poststroke patients. To address this research gap, we recruited 15 chronic stroke patients (12 subcortical stroke, three cortical stroke) with mild motor impairment (Fugl-Meyer Assessment upper extremity: 59 ± 8.1) who attended our laboratory in two separate visits, one for TMS-EEG recording, and one for anatomical and resting-state functional magnetic resonance imaging (MRI, rs-fMRI, two patients' fMRI was not available). We hypothesized that contralesional TMS-EEG reactivity would be proportional to EF strength and resting-state cortical activity, whereas this relationship would disappear in the ipsilesional M1. This study was approved by the Institutional Review Board of the university (HSEARS20200621001).

TMS-EEG signal preprocessing has been published previously [3]. Because TEP components before 100 ms are less contaminated by sensory-evoked potentials [4], the global mean field power (GMFP) of the P30 peak amplitude was chosen to indicate the direct reactivity to a single suprathreshold TMS pulse. The TMS-induced network was analyzed by calculating the debiased weighted phase lag index between channels, and the whole-brain network was analyzed based on graph theory using the Brain Connectivity Toolbox. The areas under the curve (AUC) of weighted transitivity and global efficiency were calculated for subsequent statistical analyses [3]. All images were acquired using a 3-Telsa scanner (Siemens Prisma, Germany). T1-weighted images were obtained using an MPRAGE sequence: 320 axial slices, 0.8 mm slice thickness, and 208×300 matrix size. Functional images were obtained using an EPI sequence: 72 axial slices, 2 mm slice thickness, 104×104 matrix size, 600 volumes, and a scanning time of 8 min. Rs-fMRI data were preprocessed using RESTplus v1.3 according to a default pipeline. Finally, the fractional amplitude of low-frequency fluctuations was calculated and z-standardized (zfALFF) [5]. Two spheric ROIs in the ipsilesional and contralesional M1 were defined at MNI coordinates $x = \pm 37$, $y = -21$, $z = 58$, with a radius of 8 mm. The zfALFF values within the ROIs were extracted and averaged for subsequent analyses. TMS-induced EF was simulated through the finite element method using SimNIBS v4.1 [6]. A MagVenture Cool-B65 was utilized for EF simulation, which targeted the M1 at MNI coordinates $x = \pm 37$, $y = -21$, $z = 58$, pointing towards coordinates at $x = 0$, $y = 28$, $z = 85$, i.e., posterior-to-anterior 45°. The vector normal at the 99.9 % percentile of the simulated EF was used for subsequent analysis of EF strength. The level of statistical significance was set at $p < 0.05$.

Paired-t tests showed no significant difference between the contralesional and ipsilesional M1 in the GMFP of P30 ($t = 0.67$, $p = 0.513$, Fig. 1), AUC of transitivity ($t = 2.13$, $p = 0.051$), AUC of efficiency ($t = 1.44$, $p = 0.172$), zfALFF ($t = 0.73$, $p = 0.477$), or EF strength ($t = 1.82$, $p = 0.094$). The GMFP of P30 was significantly correlated with zfALFF ($r = 0.61$, $p = 0.027$) and EF strength ($r = 0.54$, $p = 0.037$) in contralesional M1. Multiple linear regression analysis indicated that zfALFF ($B = 1.10$, $p = 0.017$) and EF strength ($B = 0.04$, $p = 0.025$) were independent predictors of GMFP of P30. Furthermore, EF strength within the contralesional M1 tended to be associated with the AUC of transitivity ($r = 0.50$, $p = 0.056$) and efficiency ($r = 0.46$, $p = 0.082$) of the TMS-evoked network. In contrast, the GMFP of P30 was not significantly correlated with zfALFF ($r = 0.24$, $p = 0.427$) or EF strength ($r = 0.40$, $p = 0.142$) in the ipsilesional M1. The EF strength within the ipsilesional M1 was not associated with the AUC of transitivity ($r = 0.22$, $p = 0.424$) or efficiency ($r = 0.10$, $p = 0.736$) of the TMS-evoked network.

This is the first study to analyze the relationships between brain reactivity to TMS, resting-state cortical activity, and EF strength in the contralesional vs. ipsilesional M1 in poststroke patients. Our findings indicate a loss of TMS intensity-dependent local and whole-brain reactivity in the ipsilesional M1 of predominantly subcortical stroke at the chronic stage. A healthy cerebral cortex is composed of numerous neurons connected by synapses and glial cells in an orderly manner, the activity of which is temporally and spatially associated with cerebral blood flow, as measured via BOLD signals. Neurotransmission via various excitatory and inhibitory synapses and ion channels is responsible for neuronal activity and can be assessed by TMS-EEG. The P30 is mediated by voltage-gated sodium channels and that its amplitude represents axonal excitability [7]. Therefore, the observed disassociation between EF strength and TMS-evoked local- and whole-brain reactivity may indicate secondary neuronal loss in perilesional and remote areas caused, *e.g.,* by microglial phagocytosis of stressed neurons [8]. In addition, abnormal regulation of voltage-gated sodium channel genes could also contribute to disassociation in the ipsilesional cortex [9]. BOLD signals are indirect indicators of cortical excitability in

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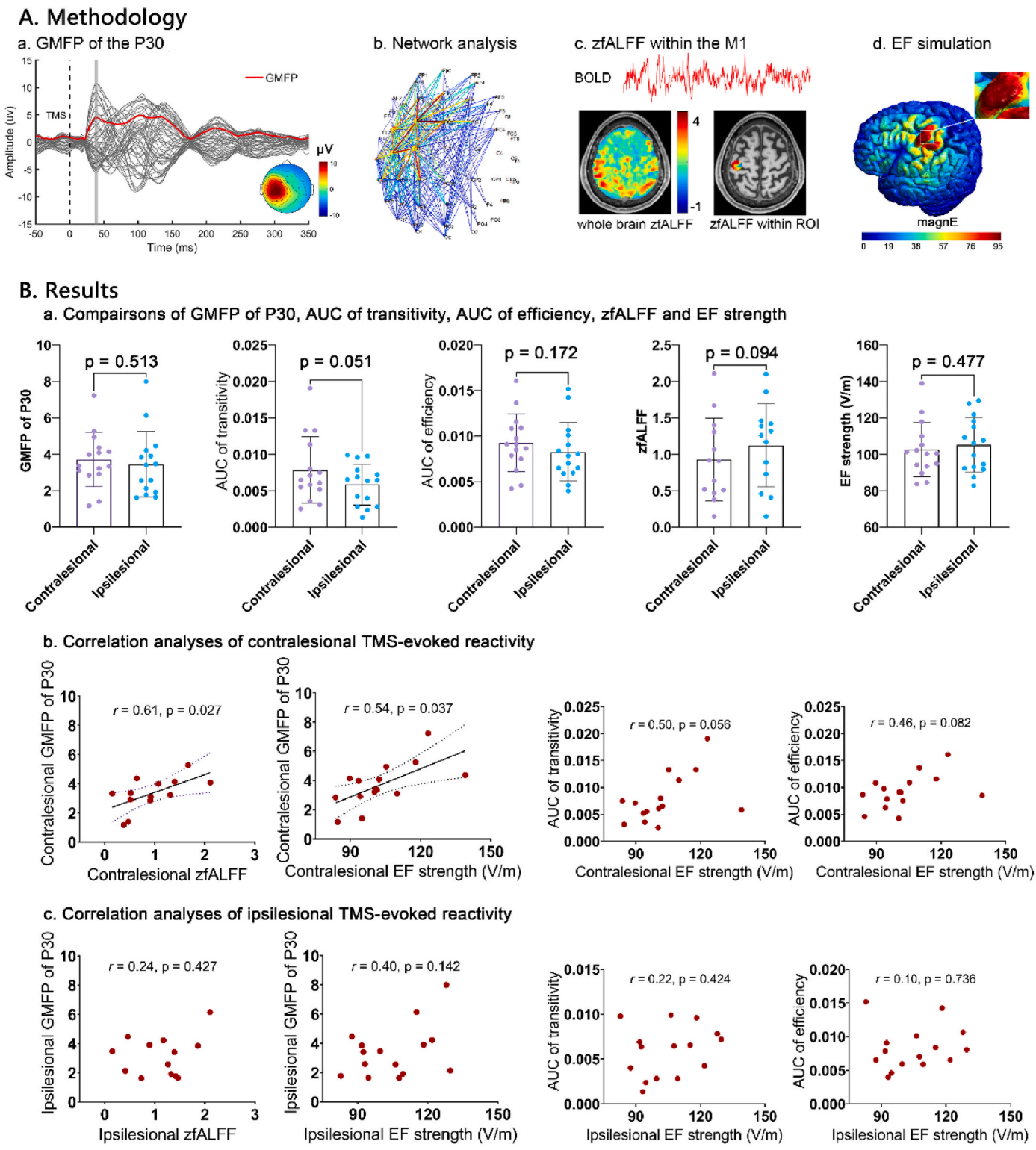

Fig. 1. Methodology and results. (A) Global mean field power of P30 derived from single-pulse TMS-EEG targeting the primary motor cortex was extracted; network analysis based on graph theory; z-standardized low-frequency fluctuations within regions of interest at x = ±37, y = −21, z = 58 was measured; vector normal at 99.9 % percentile of electrical field strength was found. (B) Paired-t tests were used to investigate any significant difference on global mean field power of P30, AUC of transitivity, AUC of efficiency, z-standardized low-frequency fluctuations, and electrical field strength between the contralesional and ipsilesional M1. Pearson correlation analysis was conducted to investigate the relationship between the abovementioned variables. GMFP: global mean field power; AUC: area under curve; zfALFF: z-standardized low-frequency fluctuations; EF: electrical field.

healthy brains because they adequately reflect synaptic activity. However, we found that P30 was not significantly associated with BOLD signals in the ipsilesional M1, demonstrating dysfunctional neurovascular coupling in patients with chronic stroke, which has been previously reported [10]. In contrast, TEPs reveal direct neuronal reactivity to TMS-targeted and connected brain areas, showing advantages over fMRI in the readout of cortical excitability.

In conclusion, our study suggested that EF strength and zfALFF independently contribute to the P30 amplitude in the contralesional M1. However, the loss of TMS intensity- and cortical activity-dependent TMS-evoked reactivity suggests a pathological state of brain activity in the ipsilesional hemisphere. This finding underscores the importance of employing multimodal neuroimaging and electrophysiological indicators in poststroke mechanistic research.

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Zhongfei Bai: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jack Jiaqi Zhang:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Eden Chun Hang Ti:** Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Minxia Jin:** Investigation, Methodology, Writing – review & editing. **Feifei Zhu:** Investigation, Methodology, Writing – review & editing. **Shan Liang:** Investigation, Methodology, Writing – review & editing. **Jing Zhang:** Investigation, Methodology, Writing – review & editing. **Yefang Yang:** Investigation, Methodology, Writing – review & editing. **Ronghua Hong:** Investigation, Methodology, Writing – review & editing. **Danmei Lan:** Investigation, Methodology, Writing – review & editing. **Raymond Kai Yu Tong:** Investigation, Methodology, Supervision, Writing – review & editing. **Ulf Ziemann:** Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Lingjing Jin:** Conceptualization, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing.

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Declaration of competing interest

We wish to confirm that thereare 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 the work covered in this manuscript that has involved 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 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 accessibleby the Corresponding Author, and which has been configured to accept email from (lingjingjin@163.com).

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