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Probing cortical reactivity before and after brain tumor resection: A TMS-EEG case

Dear Editor,

Brain tumors may result in network alterations beyond the site of structural damage, contributing to behavioral impairment and influencing functional recovery in patients. These functional alterations can often not be detected during functional magnetic resonance imaging or electroencephalography (EEG) recordings at rest or may be too subtle to be picked up through a transcranial magnetic stimulation (TMS) motor mapping procedure. Conversely, directly assessing cortical reactivity by probing the brain with TMS while recording the EEG response [1–4] can provide valuable insights into the extent of network disruptions. Moreover, the degree of preserved cortical reactivity can be used as a predictor for the postoperative recovery potential of a patient. In this study, we present the first case of TMS-EEG in a patient with glioblastoma pre- and postoperatively. Specifically, we hypothesized a reduction in cortical reactivity within peritumoral and tumoral areas, with a subsequent recovery following tumor resection.

The 66-year-old female presented with a parieto-occipital glioblastoma (WHO °4) in the right hemisphere and a large peritumoral edema. After an initial epileptic seizure, the patient was started on antiepileptic medication (Levetiracetam 500mg, twice-daily) and Dexamethasone (8mg three times daily) and consequently included in the study. She reported problems with concentration and memory, alongside a general lack of energy, which were also visible in her MoCA (25/30) and KPS (80 %) scores. Motor function was normal (BMRC for all muscles: 5; Finger Tapping right: 63, left: 55), but some difficulties while walking due to dizziness were reported. Consequently, a gross total resection was performed without any complications. Two days postoperatively, her overall status had slightly improved (KPS 90 %). The patient reported better concentration, energy and balance (MoCA: 27/30). Motor function remained comparable to the preoperative status (BMRC for all muscles: 5; Finger tapping right: 55, left: 52). 6 months postoperatively, her status was stable with a KPS of 90 % and BMRC of 5 for all muscles. Antiepileptic medication was continued throughout but reduced to 250mg twice-daily postoperatively. Dexamethasone was discontinued upon release from the hospital.

To assess cortical reactivity, we performed two TMS-EEG sessions, one week before surgery (t0) and 6 months postoperatively (t1). To guide the selection of TMS cortical targets, the patient's lesion was manually segmented from the T1-weighted MRI and tractography based on individual diffusion weighted imaging (DWI) was performed. The tumoral spot (BA19 right) was placed within the FLAIR hyperintensity surrounding the tumor and showed only local, short fiber connectivity, suggesting tumor-induced dysconnectivity. The peritumoral spot (BA4 right) was located outside the FLAIR hyperintensity and connected to fibers of the corticospinal tract (Fig. 1A and B), i.e. a tract displaced but not disconnected by the tumor. The contralateral target (BA4 left) was completely unaffected by tumor and edema and connected to fibers of the corticospinal tract (Supplementary Figs. 1 and 2). These targets were then optimized during the TMS session to reduce stimulation artifacts [5].

For each TMS target, TMS pulses were administered using a focal figure-of-eight coil (outer diameter 70mm) using a neuronavigated TMS (NBS5, Nexstim, Helsinki, Finland). A minimum of 200 pulses were delivered for each TMS target, with an inter-stimulus-interval randomly jittering between 2000 and 2300 ms and an intensity of 75V/m (estimated electric field at a peeling depth of 22.5mm). EEG responses to TMS were registered using a 64-channel, TMS-compatible BrainAmp DC amplifier (Brain Products GmbH, Germany) with a DC-to-1-kHz hardware filtering bandwidth, a 5-kHz sampling rate, and an acquisition reference electrode positioned on the forehead. Two additional channels were applied to record the electrooculogram. A noise masking sound [6,7] tailored to the specific TMS coil and customized on subject's perception was played through inserted earphones to abolish the auditory inputs associated with TMS coil discharge ([8]; see supplementary material for a detailed protocol and analysis description).

TMS-evoked potentials (TEPs) obtained from the contralesional point (left BA4) exhibited typical waveforms characterized by a 12μV peak-to-peak amplitude and site-specific oscillations within the first 50 ms after stimulation (Fig. 1C). By employing the same intensity of stimulation, TEPs recorded from the peritumoral and tumoral TMS spots in the right hemisphere (right BA4 and B19) exhibit a pathological response during the preoperative session (t0). These responses are marked by a 5μV peak-to-peak amplitude and no site-specific oscillations within the first 50 ms after stimulation, resembling the ones recorded after hemorrhagic stroke [6,7]. Yet, the observed residual reactivity and absence of a slow wave may suggest a preserved structural integrity in the areas affected by the tumor. Upon repetition after a 6-month period (t1) following surgery and radiochemotherapy, the same stimulation parameters elicited TEPs on the left BA4 analogous to TEPs recorded at t0. Notably, for both tumoral and peritumoral spots, TEPs characterized by a large increase in amplitude (up to 10μV peak-to-peak) were recorded.

This proof-of-concept study is the first to show the feasibility of performing TMS-EEG in glioma patients. We suggest a method to determine TMS stimulation spots a priori based on individual tractography (similar to Refs. [6,7]), thus taking into account the potential displacement of normal anatomy due to the tumor. Further, we provide evidence for abnormal cortical reactivity in areas outside the tumor border, suggesting that tumors may affect the brain beyond the pure infiltration zone. To understand the exact mechanisms underlying this effect, such as diaschisis [9], a mass-effect of the tumor, or inflammation, future studies (see supplementary material) should study stimulation targets more distant from the tumor. Finally, by showing a residual reactivity in tumoral stimulation preoperatively alongside the

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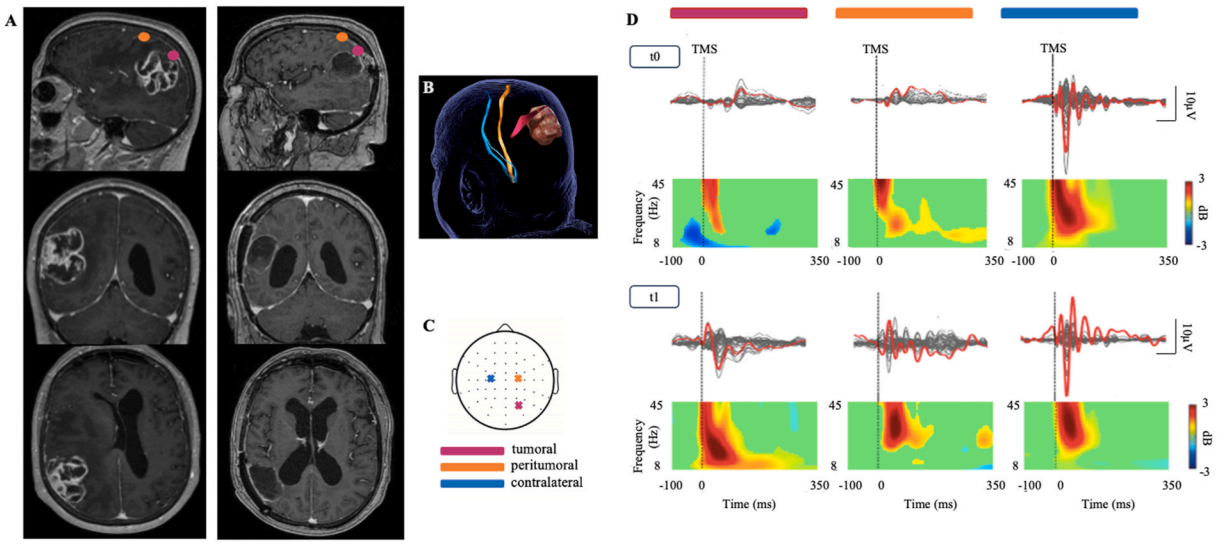

Fig. 1. Panel A. Subject's MRI in sagittal, coronal and axial view (top to bottom). Left panel: MRI at T0 (preoperative); Right panel: MRI at T1 (postoperative). The orange and red dots indicate the peritumoral and tumoral TMS target spots respectively. **Panel B.** 3D reconstruction of the tumor and visualization of the tracts originating from each of the three stimulation target points (blue: contralateral, orange: peritumoral, red: tumoral). **Panel C.** EEG channel layout highlighting the three TMS spots (orange-peritumoral BA4 right; red-tumoral B19 right; blue contralateral BA4 left). **Panel D.** EEG responses to TMS of the three cortical targets at t0 and t1. Butterfly plots of the TMS-evoked EEG potentials recorded at all 64 channels (gray traces) are depicted. A dashed vertical line marks the occurrence of the TMS pulse. Red traces represent the electrode closest to the TMS target.

postoperative tendency toward renormalization of cortical reactivity and recovery of the patient, our results identify a candidate marker for the recovery potential of the brain after tumor removal. Future studies should validate these findings further, while controlling for potential cofounding factors such as medication changes, tumor recurrencies or larger edema.

CRediT authorship contribution statement

Giulia Meneghini: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Melina Engelhardt:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Milena Burzlaff:** Writing – review & editing, Investigation. **Aleksandra Zaykova:** Writing – review & editing, Investigation. **Peter Vajkoczy:** Writing – review & editing, Resources. **Pantelis Lioumis:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Mario Rosanova:** Writing – review & editing, Software, Conceptualization. **Thomas Picht:** Writing – review & editing, Supervision, Resources, Conceptualization.

Ethics approval

Approval was obtained by the local ethics committee of the Charité-Universitätsmedizin Berlin (EA2/103/22). Written informed consent was obtained prior to the TMS-EEG acquisition.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Mario Rosanova is an advisor of Intrinsic Powers, a spin-off of the University of Milan. The other 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.12.004.

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