Prehabilitation and rehabilitation using data-driven, parcel-guided transcranial magnetic stimulation treatment for brain tumor surgery: proof of concept case report

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Abstract

Improved knowledge of the neuroplastic potential of the brain connectome has facilitated the advancement of neuromodulatory treatments for brain tumor patients especially in the perioperative period. More recently, the idea of inducing neuroplastic changes before surgery as "prehabilitation" has been suggested in low-grade gliomas with favorable data. However, it is uncertain the degree to which this treatment with transcranial magnetic stimulation (TMS) would benefit patients with high-grade gliomas, especially with additional rehabilitation after surgery and targets defined by personalized connectomic data. The current report details a case of a patient with recurrent glioblastoma in the right motor area 2 years after previous total resection. Given the desire for a more aggressive recurrent surgery in a highly functional area, the authors decided to proceed with "prehabilitation" by stimulating the surrounding motor cortices around the lesion to turn down the motor cortex connectivity before the recurrent surgery and then completing "rehabilitation" after the surgery. Structural-functional connectomic analyses were completed using Infinitome software based on an individualized patient brain atlas using machine-learning based parcellations. Repetitive TMS was employed, specifically using continuous and intermittent theta burst stimulation protocols. Prehabilitation consisted of using continuous theta burst stimulation at the estimated surgical entry point parcel and intermittent theta burst stimulation at adjacent parcellations for a total of 10 days with 5 sessions per day per target leading up until the surgery. A gross-total resection was obtained, but the patient woke up with left-sided hemiparesis. Resting-state functional magnetic resonance imaging derived connectivity demonstrated a case of a primarily pure cingulate-motor resection causing hemiplegia with an intact corticospinal tract and supplementary motor area. Functional connectivity outliers in cingulate-motor parcels were identified and compared with connectivity matrices from a healthy control atlas. Anomalies, parcels defined as functioning significantly outside a normal range, were chosen as rehabilitation TMS targets to be similarly treated for a total of 10 days with 5 sessions per day per target approximately two weeks after surgery. By using continuous theta burst stimulation on hyperconnected parcels and intermittent theta burst stimulation on hypoconnected parcels, the patient demonstrated significant motor improvement with only 4+/5 strength in the left arm 1 month after surgery. This report demonstrates for the first time the feasibility of using TMS treatment for glioblastoma surgery near "eloquent" cortices as a means of prehabilitation before surgery and rehabilitation after surgery. This parcel-guided approach for TMS treatment based on the cortical site of entry and individualized connectivity analyses allowed for maximal tumor resection and minimal long-term neurologic deficits.

Key words: brain connectome; brain tumor; case report; neuroimaging; neuromodulation; transcranial magnetic stimulation

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Introduction

The standard of care for high-grade gliomas (HGGs) consists of aggressive cytoreductive surgery, followed by adjuvant radiochemotherapy (Stupp et al., 2005). Given the mounting evidence for increased survival benefits with increasing rates of extension, a great deal of time and effort has been spent in the neurosurgical community to improve surgical techniques and adjuncts capable of maximizing resection rates (Dadario et al., 2021b, d). However, the benefits of aggressive surgery must be carefully weighed against the risk of inducing new neurologic deficits. Recent work demonstrates gliomas may preferentially localize to highly connected hub (or "eloquent") regions due to gliomagenesis mechanisms of activity-dependent migration (Venkatesh et al., 2019). Thus, gliomas which are commonly located near eloquent regions, such as Broca's area or the primary motor area, are often resected with careful preoperative and/or intraoperative mapping to identify and then preserve these neural substrates (Dadario et al., 2021c). However, given the neurosurgical community has traditionally encouraged resection only up until these boundaries to limit readily apparent motor or language deficits postoperatively, there has always been an inherent compromise in the extent of resection for gliomas which infiltrate eloquent cortices that may lead to increased recurrence in these eloquent regions and further postoperative deficits.

Harnessing mechanisms of brain plasticity in the perioperative period provides one novel mechanism to safely resect gliomas in highly connected and functional regions while limiting severe neurologic deficits (Duffau, 2014a). Most of the available literature on neural plasticity in the neurosurgical community comes from neuroimaging studies of low-grade gliomas (LGG) which demonstrate their natural influence on robustly reshaping functional networks (Robles et al., 2008). Furthermore, in studies on resection of recurrent LGGs, it is clear that surgery itself also induces functional changes within a network, so that a motor network may be reshaped after initial partial resection and then the recurrent surgery can resect a previously near - "eloquent" glioma with no deficits (Duffau et al., 2002). Thus, understanding mechanisms of brain plasticity in the perioperative period is imperative moving forward as we expand our knowledge of highly functional cortices across the human brain (Dadario et al., 2021a; Tanglay et al., 2022). However, facilitating these processes in the setting of more aggressive, HGGs with shorter survival times than LGGs presents a potentially significant clinical opportunity moving forward to minimize the postoperative morbidity and mortality of intra-axial brain tumor surgery.

Delivering preoperative electrical pulses may allow for faster reshaping of a functional network near a tumor such that it may be safely resected with minimal deficits post-surgery. Cortical stimulations between staged surgeries of LGGs near the motor cortex or just following the natural progression of the disease after surgery have both allowed for safely increased extents of resection in second surgeries with limited long-term deficits largely due to neuroplastic changes (Rivera-Rivera et al., 2017). However, previous studies have generally required the use of invasive cortical electrodes for stimulation mapping to orient the extraoperative, non-invasive cortical stimulation mapping, which still can increase the risks of unnecessary complications like infection (Rivera-Rivera et al., 2017). Improved neuroimaging analyses combined with recent high-throughput approaches to map the brain connectome offer a novel non-invasive opportunity to potentially select more precise targets based on underlying network parcellations (Poologaindran et al., 2022).

Here, we report on a unique case with glioblastoma recurring in the sensorimotor area who underwent complete resection with minimal long-term deficits through the use of a novel surgical plan consisting of preoperative prehabilitation and postoperative rehabilitation transcranial magnetic stimulation (TMS) treatments in addition to a strong understanding of the surrounding brain connectivity. Unlike previous non-invasive electrostimulation paradigms which often relied on standard craniometric measurements to stimulate different underlying connectivity, we developed a connectome-based, parcel-guided neuroimaging approach based on previously established parcellation scheme for more accurate connectome targeting (Glasser et al., 2016). Our approach (1) targeted parcels in and surrounding the surgical entry point to turn down motor connectivity during prehabilitation, and then (2) attempted to improve patient functioning with rehabilitation in an unbiased, data-driven manner based on functional connectivity anomalies in the motor network. We believe that in cases where maximal surgical resection in or near highly functional regions is warranted according to patient goals, this approach may provide a useful surgical plan.

Case Report

A 32-year-old male patient presented to our clinic with a recurrent brain tumor after a previous gross-total resection of a grade III glioma 2 years ago that resulted in left-sided hemiparesis that gradually improved over the next few months to 4+/5. Additional workup demonstrated a likely high-grade recurrence in the motor and peri-motor cortices (**Figure 1**, column 1). Subsequent histopathological examination revealed that it was grade IV glioblastoma. The senior surgeon (author CT) and the patient agreed on the need for a more aggressive re-resection despite the emergence of significant motor involvement on neuroimaging suggesting a possible hemiparesis postoperatively. In an attempt to limit long-term deficits and facilitate an increased rate of resection, the decision was made to proceed with "prehabilitation" by stimulating the surrounding motor cortices around the lesion to turn down the connectivity of these motor cortices before the recurrent surgery, and then completing "rehabilitation" after the surgery to improve patient functional status.

The current study was completed with ethics approval by the Internal Review Board (IRB) at Prince of Wales Hospital (approval No. IRB #3099) and the participant gave informed consent after being informed of the functional magnetic resonance imaging based agile-targeting approach and its difference from standard approaches. This study is reported in accordance with the CAse REport (CARE) guidelines for case reports (**Additional file 1**).

Structural-functional connectivity analyses

The patient underwent diffusion-weighted imaging and resting-state functional magnetic resonance imaging (rs-fMRI) for detailed structural-functional connectivity analyses using the Omniscient Infinitome software (Sydney, Australia), which is a pipeline for machine learning-based brain image processing. These analyses allowed for the creation of an individualized brain connectome atlas using machine-learning based parcellations which aided in the selection of appropriate TMS targets and parameters. This pipeline has been detailed elsewhere.

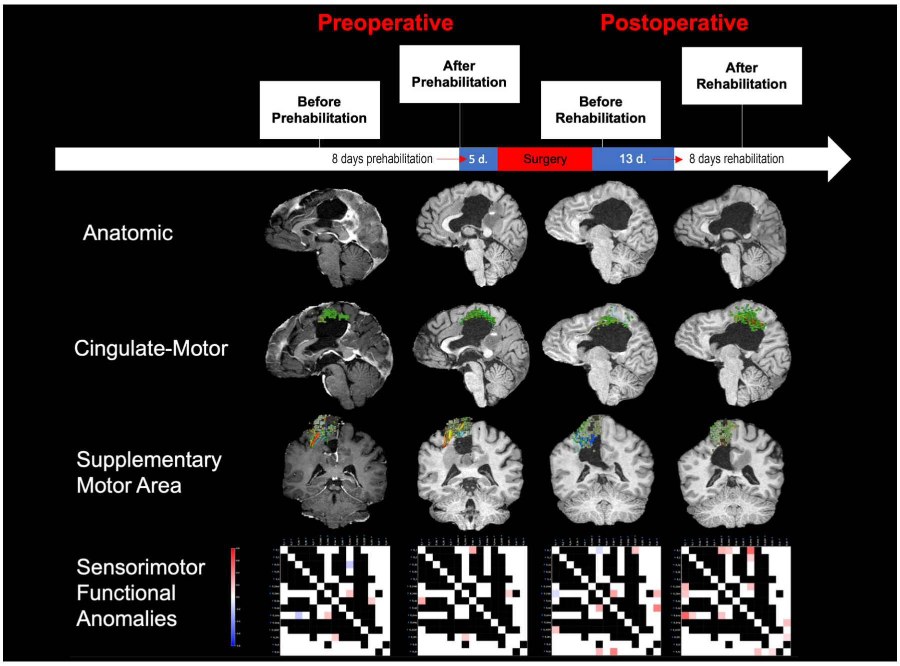

Figure 1: Timeline of events for prehabilitation, surgery, and rehabilitation.

Note: Columns 1 and 2 are in the preoperative period before and after prehabilitation transcranial magnetic stimulation (TMS) treatment, respectively. Columns 3 and 4 are in the postoperative period before and after rehabilitation TMS treatment. The amount of days off between prehabilitation, surgery, and rehabilitation are shown in blue boxes along the white timeline arrow. Rows present magnetic resonance imaging data without connectivity (row 1) and with connectivity in the cingulate-motor area (row 2) as well as the supplementary motor area (SMA) (row 3). From these data it is clear that postoperative hemiplegia occurred with a significant portion of the cingulate-motor connectivity lost despite an intact SMA. Row 4 presents functional connectivity adjacency matrices to highlight individual anomalies in the sensorimotor network. Abnormal connectivity specifically refers to a 3-sigma outlier for that correlation, after excluding the highest variance 1/3 of pairs (black), in order to further reduce the false discovery rate. Individual anomalies identified represent positive (red) and negative (blue) correlations between two blood-oxygen-level-dependent signals between two individual parcellations.

Structural-functional image acquisition

Magnetic resonance imaging was completed on a Phillips 3T Achieva (Amsterdam, The Netherlands). The diffusion-weighted imaging data was captured with the following acquisition parameters: 2 mm × 2 mm × 2 mm voxels, field of view = 25.6 cm, matrix = 128 mm × 128 mm, slice thickness = 2.0 mm, one non-zero b-value = 1000, 40 directions, gap = 0.0 mm. The rs-fMRI data was acquired as a T2-star echo-planar imaging sequence over an 8-minute total run time with the following parameters: with 3 mm × 3 mm × 3 mm voxels, 128 volumes/run, echo time = 27 ms, repetition time = 2.8 seconds, field of view = 256 mm, and flip angle = 90°.

Diffusion image pre-processing and individualized brain atlas creation

Diffusion-weighted imaging images are processed from the diffusion imaging in Python (DIPY) package (Garyfallidis et al., 2014) which includes correcting for motion, extraction of the brain, and correction for gradient distortion. Further details on the specific tractography preprocessing steps have been described previously (Ren et al., 2020; Doyen et al., 2022).

The Omniscient Infinitome software for creating an individualized brain atlas according to machine learning-based parcellations has also been detailed previously (Doyen et al., 2022). Ultimately, this software creates a subject-specific version of the Human Connectome Project (HCP) Multi-Modal Parcellation version 1.0 atlas based on diffusion tractography structural connectivity and machine learning based analyses (Glasser et al., 2016). By modeling the HCP atlas in NIFTI Montreal Neurological Institute space onto each individual's brain based on structural connectivity between each parcel, a subject-specific version of the HCP atlas is created with a total of 181 cortical parcels and 8 subcortical structures in each hemisphere as well as the brainstem (Doyen et al., 2022).

rs-fMRI pre-processing and functional connectivity anomaly detection

rs-fMRI pre-processing steps have also been well-described elsewhere (Ren et al., 2020) and include a variety of standard correction and alignment steps on the T1 and blood-oxygen-level-dependent images. Then, the subject-specific atlas described above is registered to the T1 image and localized to the grey matter regions. An average blood-oxygen-level-dependent time series from all 377 cortical regions is extracted (180 parcellations × 2 hemispheres, plus 17 subcortical structures) yielding 142,129 correlations. Then, to detect outlier parcellations according to functional connectivity differences compared to controls, outlier detection using a tangent space connectivity matrix was performed to create raw connectivity matrices. Ultimately, this raw matrix was analyzed to detect functional connectivity anomalies by comparing it against a healthy dataset of 200 subjects with rs-fMRI data which was processed similarly. Any 3-sigma outlier for that correlation is marked as abnormal, after excluding the highest variance 1/3 of pairs, in order to further reduce the false discovery rate. This pipeline was detailed in previous work (Ren et al., 2020).

The affiliation of individual parcels to brain networks was determined in agreement with an accepted network model in the literature (Yeo et al., 2011) and several previous coordinate-based meta-analyses and matching the HCP parcels to the coordinates of the activation likelihood estimation in Montreal Neurological Institute space, which has been previously published (or in review presently) by our group (Milton et al., 2021; Samuel et al., 2021). Notably, a significant amount of the data on HCP parcels illustrated by Akiki and Abdallah (2019) contributed to our parcel-network classification.

Agile target selection methodology and TMS treatment

Target selection was based on the premise that prehabilitation would be guided by the location of the surgical point of entry as well as surrounding parcels. In this setting, a stimulation paradigm would be utilized which would decrease the connectivity at the surgical entry point while increasing the connectivity of adjacent parcels. Differently, rehabilitation after surgery would be guided by the anomaly detection algorithm mentioned above to both (1) select specific abnormal targets for neuromodulation as well as (2) the type of stimulation required based on if the region was hyper- or hypo-connected to affected networks. Stimulation protocols consisted of intermittent theta burst stimulation (iTBS) and continuous theta burst stimulation (cTBS) protocols. Previous work suggests cTBS induces cortical depression while iTBS induces excitation (Huang et al., 2005). Thus, cTBS was used for functional areas that were hyperconnected or that we wanted to decrease in connectivity (i.e., surgical entry point). Differently, iTBS was used for functional areas that were hypoconnected or that we wanted to increase in connectivity (i.e., parcels surrounding the surgical entry point).

All TBS sessions were completed using a Magventure MagPro X100 TMS machine with a butterfly cool coil (Alfaretta, GA, USA).

Prehabilitation

Prehabilitation consisted of targeting parcels which included the estimated surgical entry point as well as immediately surrounding the surgical entry point (**Figure 2**). These targets ultimately included area right 4 and area right 3a, respectively. Area right 4 was stimulated using cTBS and area right 3a was stimulated using iTBS. Prehabilitation occurred for a total of 10 days over 2 weeks (Monday-Friday) leading up until the surgery at the beginning of week 3 (**Figure 1**, column 2). Each parcellation was treated with five sessions per day. Prehabilitation occurred at up to 120% resting motor threshold for the majority of sessions per the patient's ability each session. The minimum used was an 80% resting motor threshold.

Following the surgery, the patient woke up with left-sided hemiparesis (1/5). What was particularly interesting was this represents a case of a primarily pure cingulate-motor resection causing hemiplegia with an intact corticospinal tract (**Figure 3**). This is further evidenced by the intact connectivity seen in the supplementary area, thus likely ruling out a possible supplementary area syndrome (**Figure 1**). When investigating the mechanism of these motor deficits, it became clear according to functional connectivity analyses that the connectivity near the cingulate-motor area was abnormal. Thus, functional connectivity anomalies were investigated as potential TMS targets for rehabilitation in connections around this specific area.

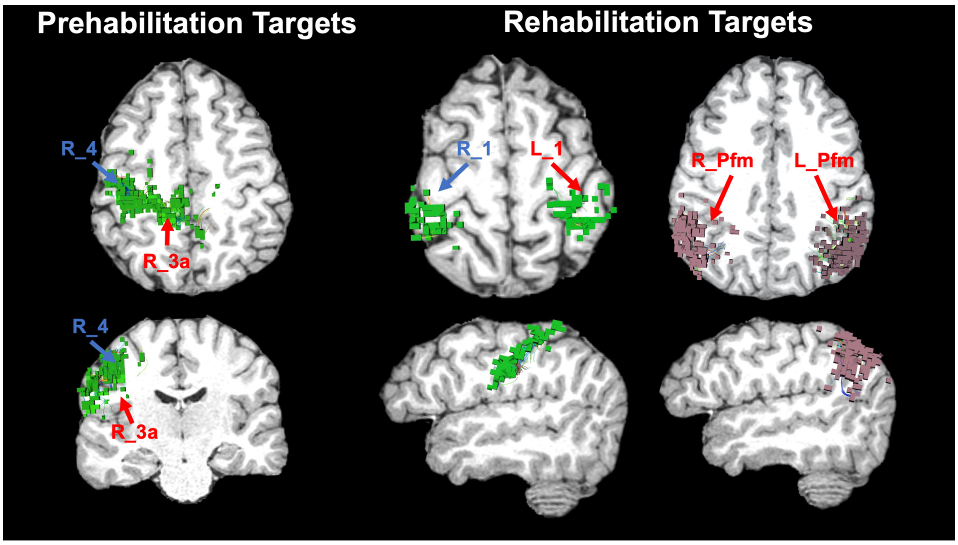

Figure 2: The targets of transcranial magnetic stimulation.
Note: The relative targets for prehabilitation before surgery (left column) and rehabilitation after surgery (right column) are shown. These areas consist of area 4 in the precentral gyrus, area 3a in the depth of the central sulcus, area 1 on the surface of the postcentral gyrus, and area Pfm (parietal area F, part m) on the anterior superior surface of the angular gyrus. Blue regions were targeted with cTBS to decrease connectivity and red regions were targeted with iTBS to increase connectivity.

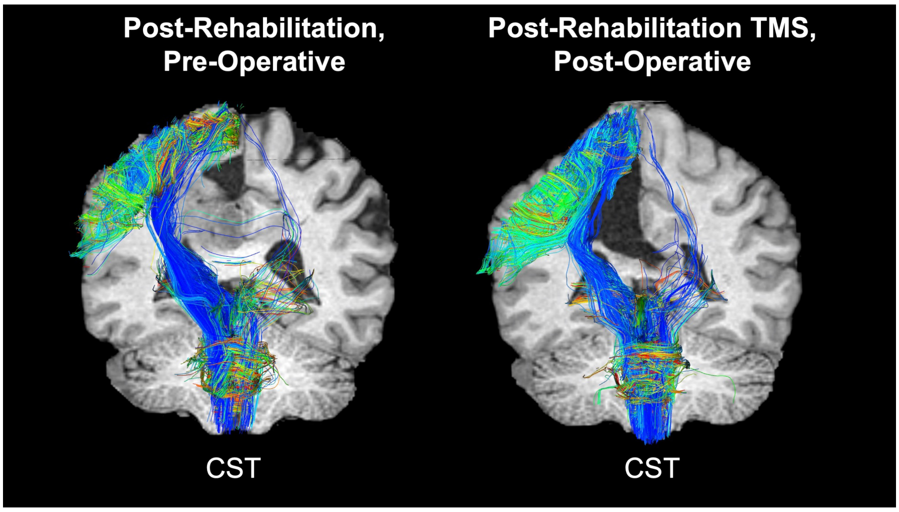

Figure 3: Preserved corticospinal tract after surgery.
Note: This figure highlights the occurrence of left-sided hemiparesis in this patient despite an intact corticospinal tract (CST) and supplementary motor area as shown in Figure 1, together suggesting a pure cingulate-motor injury after surgery.TMS: Transcranial magnetic stimulation

Ultimately, rehabilitation was based on the premise that resynchronizing the abnormal areas of the motor network which occurred due to resection in the cingulate-motor area would help regain some of the lost functions (**Figure 4**). Rehabilitation after surgery was similarly planned for 10 days of treatment over 2 weeks, with five sessions per target each day starting. Treatment started 13 days after surgery and ultimately only 3 days of treatment occurred in the first week as the patient was ill, while the second week consisted of 5 days of treatment to complete the full rehabilitation TMS treatment plan. The targets included area left 1 treated with iTBS and area right 1 treated with cTBS. Furthermore, it was believed that damage to the default mode network may have also occurred in the recurrent surgery given the patient also demonstrated mild cognitive dysfunction the week after surgery. Therefore, nodes of the default mode network were also targeted for rehabilitation, including area left PFm (parietal area F, part m) treated with iTBS and area right PFm treated with iTBS. Rehabilitation occurred at the standard 80% resting motor threshold each session.

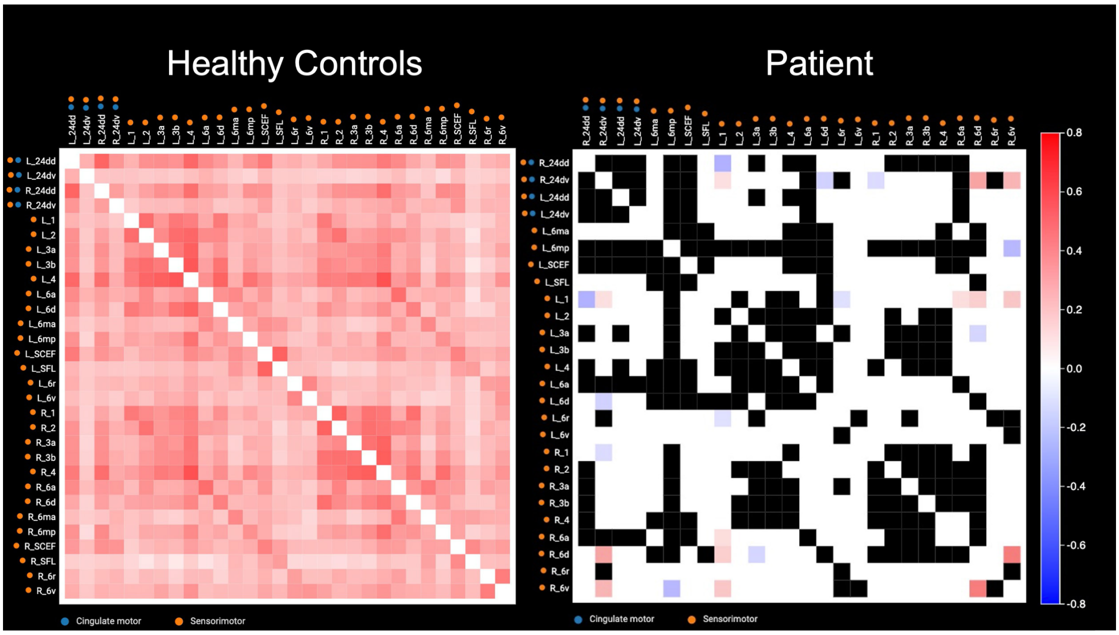

Figure 4: Functional connectivity anomalies for rehabilitation targets.
Note: Functional connectivity adjacency matrices are created to highlight individual anomalies in the sensorimotor network in the current patient as compared to a normative atlas of 200 healthy individuals. Abnormal connectivity specifically referred to a 3-sigma outlier for that correlation, after excluding the highest variance 1/3 of pairs (black), in order to further reduce the false discovery rate. Individual anomalies identified represent positive (red) and negative (blue) correlations between two blood-oxygen-level-dependent signals between two individual parcellations.

Ultimately 1 month after surgery, the muscle strength of the patient's left arm was improved to 4+/5 while that of all the other extremities was 5/5. Furthermore, the patient's cognitive status improved to baseline. The patient went on to live for an additional 2 years before passing away presumably due to disease progression.

Discussion

This report detailed the first case of a parcel-guided TMS prehabilitation and rehabilitation treatment to facilitate glioblastoma resection in or near highly functional ("eloquent") cortices. In this case, preoperative TMS before the surgery ("prehabilitation") was completed to turn down the functional connectivity of the motor cortices in and around the surgical entry point to facilitate a more aggressive, safe resection. While the patient still woke up with hemiparesis, postoperative rehabilitation with specific TMS targets based on functional connectivity anomalies identified with the cingulate-motor network resulted in dramatic long-term motor improvements for the patient. Thus, the current report demonstrates the feasibility of utilizing knowledge of the surrounding brain connectivity and a data-driven approach for TMS prehabilitation and rehabilitation based on personalized connectomic data to facilitate aggressive cytoreductive brain tumor surgery near highly functional regions with minimal long-term neurologic sequelae.

The concept of prehabilitation for brain tumor surgery was first demonstrated in a case report by Barcia et al. (2012) and then in a subsequent larger study of five patients (Rivera-Rivera et al., 2017). In Rivera-Rivera et al.'s study (2017), they reported five patients with LGGs near the motor and language areas in which the authors sought to induce functional reorganization in-between staged surgeries to facilitate increased, safe resection rates in the second surgery. However, unlike our report which utilized structural-functional resting-state neuroimaging data to obtain connectivity derived TMS targets non-invasively, the above authors required implantation of a grid of electrodes over residual tumor with functional tissue within it. After implantation, the subdural grid was then sutured to the dura and the wound closed so that in between the 2–3 weeks before the second surgery, continuous cortical stimulation could be provided through these electrodes. While the authors report this prehabilitation methodology increased safe resection rates by displacing eloquent areas within the tumor, it also resulted in notable infection rates. The foundational work underlying these neuromodulatory concepts could likely be best traced back to the body of work provided with LGGs undergoing staged surgeries especially as described by Duffau (Duffau, 2014a). Namely, it became well-understood that, even without electrostimulation, there is significant cerebral plasticity after surgical resection of LGGs such that a second-staged surgery may facilitate safe resection of tumors near or in motor and language cortices due to significant topographical functional reshaping (Duffau et al., 2002; Robles et al., 2008). While these mechanisms partially support a novel idea of regularly resecting previously considered "inoperable" LGGs through a multi-stage approach after functional reshaping, this approach may take years which is not often provided for patients with HGGs as in the current case. Given our patient's previous tumor was completely resected, previous surgical insult may have further facilitated our subsequent perioperative modulatory treatments for functional reorganization (Robles et al., 2008).

The brain maintains a high capability for plastic remodeling from the level of large-scale networks down to individual cells (Cirillo et al., 2017; Stephens et al., 2021). In particular, the short- and long-term effects of TMS on neuroplasticity are well-established in both animals and humans (Hallett, 2000), and now TMS is a Food and Drug Administration approved neuromodulatory treatment (Brunoni et al., 2017). Of all the repetitive TMS protocols, theta-burst stimulation may represent the best option for brain tumor patients due to the ability of theta-burst stimulation to induce longer-lasting effects with shorter application times as well as the high safety profile (Stephens et al., 2021; Poologaindran et al., 2022). The capability for specific neuroplastic changes vary further according to the specific theta-burst stimulation intensities and patterns utilized: continuous uninterrupted bursts (cTBS) produce long-term depression like inhibition of cortical excitability and repeated intermittent bursts (iTBS) cause long-term potentiation like effects of cortical excitability (Huang et al., 2005; Chung et al., 2018). The neurochemical and neurophysiological mechanisms which underlie these long-term structural-functional changes represents a complex area of current study, but they may include some form of altered levels of glutamate transmission and calcium influx which causes an increase or decrease in additional α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid/N-methyl-D-aspartate receptors and brain-derived neurotrophic factor levels (Gersner et al., 2011) as well as accompanying structural gains/losses of dendritic spines (Segal et al., 2003; Nägerl et al., 2004). These changes can be further influenced by the number of stimulation sessions (Tang et al., 2021) as well as any concomitant behavioral training (Kozyrev et al., 2018).

The technique of using stimulation to induce cortical subcortical plasticity has been most studied in stroke patients, and less so in glioma patients who are believed to have drastically different mechanisms of pathophysiology and plasticity challenges (Desmurget et al., 2007). Differences in neuroplastic potential may also exist between LGGs and HGGs as well due to temporal factors which differentially cause cortical damage or affect functional reorganization (Kong et al., 2016). Importantly, most previous studies in stroke or glioma patients using neuromodulatory treatments seem to suggest the need for concomitant behavioral training to provide more robust changes in connectivity (Rivera-Rivera et al., 2017; Lang et al., 2020). However, such training or even task-based functional neuroimaging is often precluded in the case of progressed HGGs which present with severe cognitive deficits. Uniquely, the current study demonstrates the feasibility of using rs-fMRI data to choose appropriate targets in these patients. In the current case, targeting bilateral nodes in the default mode network seemed to result in improved cognitive function after rehabilitation treatment, but detailed neuropsychological testing was not performed.

One of the most important concepts demonstrated in the current case report is the feasibility and possible benefit of numerous parcel-guided TMS treatments in the perioperative period based on individualized connectomic data in a brain tumor patient. Surface-based multimodal parcellation schemes allow for better hypothesis comparison between studies as well as more precise neuromodulatory targeting (Moreno-Ortega et al., 2020), which is particularly important given millimeter differences between parcels can preferentially alter different network connections, which may or may not be warranted (Rosen et al., 2021). As we begin to move toward a more connectome-based neurosurgical era with an improved understanding of the structural-functional organization of the brain (Briggs et al., 2021; O'Neal et al., 2021; Dadario et al., 2022; Wu et al., 2022), it is imperative that we appropriately modulate these areas in an unbiased manner, such as through a data-driven approach based on individualized connectomic anomalies (Poologaindran et al., 2022).

Improvements in the efficacy of neuromodulatory treatments to promote plasticity in brain tumor patients have also been discussed in the context of "metaplasticity" as a means of persistent synaptic plasticity, or the plasticity of plasticity (Abraham and Bear, 1996). In this higher-order synaptic plasticity form, inducing metaplasticity may allow for an improved ability to facilitate subsequent synaptic plasticity in the perioperative period (Samuel et al., 2021). This would provide obvious improvements for patients with more severe brain damage that may have less neuroplastic potential, such as following severe subcortical injury (Duffau, 2014a). Biomathematical models which can calculate an individual "plasticity index" can offer novel opportunities moving forward which can demonstrate key connections to target and also the possible limitations of these neuromodulatory treatments on a patient-by-patient basis (Duffau, 2014b).

Despite the novel approach discussed above, it is important to interpret our report in the context of its limitations. Namely, we demonstrate significant motor recovery following an aggressive surgical resection in the motor cortices through what we believe was due to our use of preoperative and postoperative TMS treatments, but in a single patient. Thus, larger studies are necessary to confirm the benefit of our prehabilitation and rehabilitation TMS approach based on individualized connectomic information in a larger, prospective series. It is likely that certain patients would not benefit from these treatments given the extent or location of their injury, and thus decisions for similar neuromodulatory treatments would greatly benefit from additional patient-specific information about a patient's capacity for structural-functional remodeling, such as a plasticity index (Duffau, 2014b). Furthermore, the mechanisms of plasticity were not rigorously examined in the current patient and therefore cannot be discussed with great confidence. The neurobiological mechanisms of TMS-induced plasticity is an active area of clinical research that may expand our understanding and subsequent use of this treatment for brain tumor patients moving forward (Cirillo et al., 2017).

The current study for the first time demonstrates the feasibility of using TMS treatment in the perioperative period of glioblastoma surgery near "eloquent" cortices as a means of prehabilitation before surgery and rehabilitation after surgery. A novel parcel-guided approach of TMS treatment based on the cortical site of entry and personalized functional connectivity analyses allows for maximal tumor resection and minimal long-term neurologic deficits.

Author contributions

Study conceptualization, investigation and resources: MES, CT, SD; methodology and validation: MES; software analysis and manuscript review & editing: NBD, IMY, MES; formal analysis, data curation: NBD, MES, CT; visualization: NBD; supervision and project administration: XZ, MES, CT; original manuscript draft: NBD. All authors read and approved the final manuscript.

Conflicts of interest

MES is the Chief Medical Officer, co-founder, and stake-holder in Omniscient Neurotechnology. IMY and XZ are employees of Omniscient Neurotechnology. CT is a consultant for Aesculap and share-holder of Omniscient Neurotechnology. SD is the Chief Data Officer, co-founder and stake-holder in Omniscient Neurotechnology. No products directly related to these companies were discussed at all in the current work. No other authors report any conflicts of interest.

Editor note: MES is an Editorial Board member of *Brain Network and Modulation*. He was blinded from reviewing or making decisions on the manuscript. The article was subject to the journal's standard procedures, with peer review handled independently of this Editorial Board member and his research group.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Additional file

Additional file 1: CARE checklist.

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