Improving quality of life post-tumor craniotomy using personalized, parcel-guided TMS: safety and proof of concept

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Abstract

Purpose Deficits in neuro-cognitive function are not uncommon for patients who have undergone surgical removal of brain tumors. Our goal is to evaluate the safety and efficacy of repetitive Transcranial Magnetic Stimulation (rTMS) as a non-invasive tool for the treatment of neuro-cognitive dysfunctions following craniotomy.

Methods We present a retrospective review of individualized rTMS in twelve patients from Cingulum Health from December 2019 to July 2021 who presented with neuro-cognitive deficits following craniotomy. Multiple cortical targets were selected based on the patient’s neurological disorder, associated networks, and anomalies in the functional connectivity of the brain as determined by machine-learning. TMS treatment was performed for five consecutive days. EuroQol quality of life (EQ-5D), functional extremity scales, and neuropsychiatric questionnaires related to the patient’s deficit were assessed prior to, after, and during two-month follow-up of rTMS treatment.

Results Nine patients had unilateral functional deficits in either upper, lower, or both limbs. One patient reported post-operative depression, another experienced short term memory difficulties, and a third reported hypobulia. All twelve patients reported significantly improved EQ5D after rTMS treatment and during follow-up. More than half of the patients with lower and upper functional deficits had a 9-point improvement during follow-up. In the patient who developed depression, an 88% reduction in depressive symptoms based on the Beck’s Depression Inventory (BDI) was observed during follow-up. No adverse events, such as seizures, occurred.

Conclusion The personalized functional connectivity approach to rTMS treatment may be effective and safe for patients with post-craniotomy neuro-cognitive dysfunction.

Keywords Individualized · Functional MRI · Connectomics · rTMS · Craniotomy
**Introduction**

Intra-axial cerebral surgeries are associated with neurocognitive and motor deficits. The prevalence of these deficits is variable across studies, but the cumulative conclusion is that these deficits are problematic for a patient’s quality of life (QoL). The Glioma Outcomes Project (GOP), a database of 800 patients who had undergone glioma surgery across 60 surgical sites in the United States, found that of patients who underwent their first craniotomy, 32% of patients reported motor deficits, 35% endorsed memory loss, and 16% had altered levels of consciousness [1]. Ninety-three percent of patients reported new onset of depression-like symptoms following surgery [2]. Another study found that 36.2% patients developed treatment-related symptoms that prevented them from returning to work, citing neurological deficits and neuropsychological impairments as the second and third major causes [3].

Interventions for QoL are designed to be a one-size-fits-all therapy, but deficits and symptoms are specific. No existing versatile mechanism exists to deliver targeted specific treatment for individual symptoms. Only two interventions have been shown to be successful in improving clinical outcomes following surgery: a 6-week cognitive rehabilitation program for cognition impairment and fatigue and Donepezil to improve memory [4–6]. The numerous symptoms experienced by post-surgical patients and a one-size-fits-all approach to therapy for such diverse symptoms warrants a more personalized approach to post-craniotomy treatment to improve QoL.

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive tool that employs magnetic currents to reorganize cortical circuitry [7]. By modulating brain plasticity in target regions, it has been shown to improve motor function in stroke patients and to have anti-depressive effects in patients with depression [7, 8]. It has been approved by the FDA for the treatment of neuropsychological impairments, including major depressive disorder (MDD), MDD with anxiety, obsessive compulsive disorder (OCD), and migraines, and smoking cessation [9]. rTMS has been previously shown to improve motor function and language in patients following post-tumor craniotomy [10]. However, much less information has been studied on the improvement of psycho-cognitive deficits following craniotomy, and most importantly, QoL.

Using a personal, parcel-guided approach to rTMS, which we have coined the Agile Method, we could target multiple symptoms at multiple anatomical locations. We hypothesized that personalized rTMS could be used to address various neurocognitive and motor deficits and would be associated with improvements in QoL as assessed by the EuroQol (EQ-5D).

**Method**

**Subjects**

A retrospective analysis was conducted of twelve patients who were treated at Cingulum Health from December 2019 to July 2021 for post-operative neurological and psycho-cognitive symptoms following craniotomy. Patients were included in the study if they had craniotomy for tumors and developed neurological or psycho-cognitive symptoms following surgery. These patients had to be over the age of 18 years. Patients were excluded if they were not able to undergo follow-up functional imaging with acceptable quality, patients who were not able to participate in rTMS, such as the inability to sit still, and those who could not participate in adjunctive therapy. This was a pilot study and therefore included all individuals fitting the inclusion and exclusion criteria and those who were physically available to engage in rTMS treatment discussions in person.

Patients presented to clinic when they developed symptoms of concern following craniotomy. For some patients, there was a gap between craniotomy and rTMS because the presented treatment strategy was not developed until later in 2019.

Patients provided informed consent on the off-label nature of the rTMS treatment and its potential risks. This study was approved by the Human Research Ethics Committee of the South Eastern Sydney Local Health District (2022/ETH00139).

**Evaluations**

Twelve patients submitted a EuroQol (EQ-5D) prior to rTMS treatment, directly after treatment, and during their follow-up from 1 to 4 months after treatment. One patient who had mild pre-operative depression (diagnosed by a psychiatrist) and reported an exacerbation of post-surgery depressive symptoms was administered the Beck’s Depression Inventory (BDI). For patients with functional deficits, lower extremity functional scales (LEFS) and upper extremity functional scales (UEFS) were administered either together or individually.

**Personalized target selection based on brain atlas**

A Phillips 3T Achieva was used to collect DTI, rsfRMI, and non-contrast T1-weighted images as described previously [10, 11]. DTI was performed based on the following acquisition parameters: 2 mm × 2 mm × 2 mm voxels, FOV = 25.6 cm, matrix = 128 mm × 128 mm, slice thickness = 2.0 mm, one non-zero b-value of b = 1000, 40 directions, gap = 0.0 mm. A T2-star EPI sequence with used for...
rsfMRI based on the following parameters: 3 × 3 × 3-mm voxels, 128 volumes/run, a TE = 27 ms, a TR = 2.8 s, a field of view – 256 mm, a flip angle = 90° and an 8-min total run time.

The machine learning-based parcellation software was based on DTI and rsfMRI as previously described [10]. Briefly, a hundred and eighty parcellations are delineated from an individual’s brain map and a machine-learning classifier determines atypical parcellations compared to 200 healthy subjects. Known as the Agile Method, anomaly detection matrices (Fig. 1) were produced for each patient to determine abnormal functional connectivity within these parcellations. No subjective, conscious guidance was provided in the creation of anomaly detection matrices. Connectivity anomalies greater than 3 sigmas from the normal range (as determined by the rsfMRI of 200 healthy individuals) were detected. From the anomaly detection matrices, a hypothesis-driven target selection approach was utilized to identify areas of target within connectivity networks that have been verified by literature to be implicated in the patient’s symptom of left sided weakness following the removal of a grade 1 brainstem ganglioglioma.

**rTMS treatment**

Accelerated Theta burst stimulation (aTBS) sessions were completed with a Magventure MagPro X100 TMS machine with a butterfly cool coil (Alfaretta, USA). Patients were administered aTBS for five sessions per day for five days in a maximum period of 2 weeks with an hour gap between sessions [10, 14]. cTBS was performed at one train of 600 stimuli applied at 3 pulses of 50 Hz bursts every 200 ms at a total of 1800 pulses. iTBS was performed at 3 pulses of 50 Hz bursts given every 200 ms for 40 trains with an inter-train interval of 6.3 s for a total of 1200 pulses.

**Safety and tolerability**

Scalp discomfort was mediated by allowing patients to adjust to intensity by gradually increasing from low levels to its full percentage. To minimize seizure risk, patients received the minimum effective dosage, referred to as the resting motor threshold (RMT), to provoke an observed response as a muscle twitch in their left or right hand. Prior to every treatment day, patients were assessed for changes in risk factors that could increase the likelihood of seizures, including the consumption of caffeine or alcohol, changes to medications, or inadequate sleep. If such risk factors were screened, the RMT was retaken.

**Statistical methods**

Wilcoxon matched pair signed rank tests and Mann–Whitney tests were performed as applicable using GraphPad Prism 9. A p-value of < 0.05 was considered significant.

**Results**

**Patient demographics**

Twelve patients met criteria for our study (Table 1). The average age of patients was 50.2 ± 11.1 years. The average follow-up time was 2.5 ± 1.1 months after rTMS treatment. Patient 8 was lost to follow up, and patient 9 passed away before follow-up could be conducted.

**Quality of life, motor, and psycho-cognitive assessments following rTMS**

EQ-5D scores were increased for patients after rTMS (p = 0.0024, Wilcoxon test, N = 12) and during follow-up (p = 0.0039, N = 10) compared to baseline (Fig. 2A). There was no difference in the magnitude of change in EQ-5D scores between males and females after treatment (p = 0.8409, N = 5–7) and during follow-up (p = 0.7143,
There was no difference in EQ-5D magnitude changes between younger (below age 48) and older (age 48 and above) patients after treatment (p > 0.9004, N = 6) and during follow-up (p > 0.3889, N = 5). Patients who underwent rTMS treatment within 1 year of surgery had greater magnitudes of change in EQ-5D scores between baseline and post-treatment rTMS (p = 0.0303, N = 2–10) and during follow-up (p = 0.0222, N = 2–8) compared to patients who underwent rTMS treatment after more than 1 year following surgery (Fig. 2B, C).

Motor function was assessed with LEFS and UEF. For both scales, a minimum of a 9-point change is required to detect a change with 90% confidence [15, 16]. Nine patients were administered the LEFS (Fig. 2D) after treatment (mean ± SD, 4.6 ± 4.7), and seven individuals were administered the LEFS during follow-up (9.9 ± 10.2). Three individuals improved between baseline and post-treatment, and four between baseline and follow-up. Out of those that improved, one individual showed improvements in both post-treatment and follow-up compared to baseline. Eight patients were administered the UEF (Fig. 2E) after treatment (7.4 ± 10.1), and six patients were administered the UEF during follow-up (10.7 ± 12.0). Four individuals improved between baseline and post-treatment, and four between baseline and follow-up. Out of those that improved, three individuals showed improvements in both post-treatment and follow-up compared to baseline. One patient worsened between follow-up and baseline due to the progression of his disease. In sum, six out of nine individuals improved following treatment in upper or lower motor function, and six out of seven individuals improved in upper or lower motor function during follow-up compared to baseline.

Patient 10 was treated for post-surgical depression and administered the BDI (Fig. 2F). She had a 47% and 88% reduction in depressive symptoms after rTMS and follow-up, respectively, compared to baseline.

### Area of resection and rTMS targets

Table 2 lists the target regions for rTMS in each patient. No patient has the same set of targets. The sensorimotor network was a common network shared by all nine patients with motor deficits. Six of the nine patients had additional rTMS targets within networks outside of the sensorimotor network. All twelve patients had at least one rTMS target outside of the immediate region of surgical resection. An example of this is seen in patient 12 who developed hypobulia after tumor resection of the right frontal lobe, removing significant regions of the salience network (Fig. 3A–C). His hypobulia resolved following rTMS. Patients 1 (Fig. 3D–F) and 3 had targets that were directly contralateral to the resection site. Patients 4, 6, and 10 had infratentorial resection sites which are difficult to target with rTMS. Patient 4 had a left thalamic resection with rTMS targets in the cortex (Fig. 3G–I). Patient 6 had a resection in the cerebellum with rTMS targets in the ventral premotor cortex (L6v) and the primary somatosensory cortex (L4). Patient 10 had a resection of the insular and had targets in the frontal lobe (L46), parietal lobe (LPFm), and posterior cingulate cortex (L7m).
Safety and tolerability

No patients reported any seizures following rTMS treatment. Four patients reported no noticeable side effects from treatment (33.3%), seven reported noticeable fatigue (58.3%), three reported headache (25%), four reported scalp discomfort at the stimulation site (33.3%), and one reported facial twitching due to stimulation (8.3%).

Discussion

QoL encompasses functional outcomes as well as psycho-cognitive wellbeing. In this retrospective pilot series, we present personalized rTMS treatment for persistent neurological and psycho-cognitive symptoms following surgical resections of brain tumors in twelve patients. QoL as assessed by the EQ-5D was significantly improved after treatment and during follow-up.
## Table 2 Patient clinical details

| Patient | Tumor type | Surgical site | Time from surgery to TMS | Symptoms | Targets |
|---------|------------|---------------|--------------------------|----------|---------|
| 1       | GBM        | R temporal lobe | 3 years | Paralysis and weakness of L side of body due to craniotomy (*U) (#U) | 1. L1 cTBS\(^a\)  
2. R6 iTBS\(^a\) |
| 2       | Astrocytoma grade 2 | Frontal craniotomy w excision of the portion in the superior frontal gyrus | 2 years | L arm deficit (*U) (#U) | 1. L6Mp cTBS\(^a\) (80–100%)  
2. R3a iTBS\(^a\) (80–100%)  
3. LPFm iTBS\(^b\) (80–100%) |
| 3       | GBM        | Debulking of right frontal parasagittal lesion | 1 week | L side paralysis (#U) (#L) | 1. R55b iTBS\(^d\) (100%)  
2. L8Av cTBS\(^b\) (100%)  
3. R6Mp iTBS\(^b\) (100%)  
4. L6Mp iTBS\(^b\) (100%) |
| 4       | High grade glioma | Left posterior thalamic contrast enhancing lesion w evidence of necrosis | 1 week | R side paralysis (*U) (#U) (#L) | 1. L4 iTBS\(^a\) (120%)  
2. L6v cTBS\(^a\)  
3. R6v cTBS\(^a\) |
| 5       | Right temporal tumor | Right pterional craniotomy | 2.5 months | L sided weakness and vertigo (#L) | 1. RA5 cTBS\(^a\)  
2. LTE1m cTBS\(^b\)  
3. R1 iTBS\(^a\) (100%)  
4. L6a cTBS\(^a\) |
| 6       | Ganglioglioma Grade 1 | Suboccipital craniectomy and surgical changes within L posterionferior cerebellum | 5 months | L sided mobility problems (*L) (#L) | 1. L6v cTBS\(^a\)  
2. R4 iTBS\(^a\) (100%) |
| 7       | GBM        | Debulking of multifocal enhancing lesions in the L frontal supraventricular white matter extending down to pericallosal white matter | 1 month | R sided weakness and language deficits (*L)(&U) | 1. L55b iTBS\(^d\)  
2. R6Ma cTBS\(^b\)  
3. LSCEF iTBS 26 Sessions |
| 8       | Oligodendroglioma grade 2 | Brain tumor in right temporal lobe (dx 2011) operated on 10 years later followed by immediate post- op stroke leading to ischemic changes in the right striatocapsular region | 1.5 months | Lack of movement in L arm following stroke–all L side affected (*U) (#L) | 1. L3A cTBS\(^a\)  
2. R4 iTBS\(^a\) 100%  
3. L8Av cTBS\(^b\) |
| 9       | GBM        | Left frontal | 3 days | R side hemiparesis and limited R side facial movement | 1. R6Mp cTBS (100%)  
2. L6v iTBS\(^a\) (120%)  
3. L6a iTBS\(^a\) (120%)  
4. LPHT cTBS\(^b\) (100%) |
| 10      | Astrocytoma grade 3 | L craniotomy of insula glioma | 5 weeks | Mild word finding difficulty (not deemed troublesome for patient and was not treated), extreme mood swings, suicidal thoughts and aggression | 1. L46 iTBS\(^a\)  
2. LPFm iTBS\(^b\)  
3. L7m iTBS |
| 11      | Oligodendroglioma grade 3 | R frontal | 2.5 months | Confusion and short-term memory deficits | 1. R6Ma iTBS\(^a\)  
2. RTE1p iTBS  
3. LTE1m cTBS\(^b\) |
| 12      | Oligodendroglioma grade 3 | R frontal | 2 days | Severe hypobulia | 1. R6Ma cTBS\(^a\)  
2. RPGi iTBS  
3. RTGd iTBS |

**GBM** glioblastoma, **R** right, **L** left

Tumor types that are bolded indicate individuals (patient 3 and 7) who experienced rapid progression of disease with tumor recurrence confirmed by MRI. rTMS targets were stimulated at 80% of RMT unless otherwise specified in the column. rTMS treatment was 25 sessions for each target unless otherwise specified. Upper and lower motor improvements between baseline and post-treatment are indicated with \(*U\) and \(*L\), respectively, and between baseline and follow-up with a \#U and \#L, respectively. Upon follow-up, patient 7 was found to decreased UEFS function (\&U) due to the progression of disease. Targets indicated in\(^a\) are within the sensorimotor network. Targets indicated in\(^b\) are within the Central Executive Network. Targets with\(^c\) are within the Salience Network. Targets with\(^d\) are within the Language Network. Targets in bold are within the Default Mode Network. The target in italics is within the Multiple Demand Network. The target underlined is within the Limbic and Paralimbic Network.
Personalized, multi-network rTMS treatment

A transdiagnostic approach to clinical interventions for neurological dysfunction goes beyond diagnosis and categorization of diseases to better understand an individual’s affliction and its underlying cause [17]. For patients with brain tumors, a transdiagnostic approach allows physicians to treat the symptoms by addressing problematic brain 

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**Fig. 3** Patient MRI with rTMS targets. A–C Hypobulia and prefrontal cognitive initiation “axis.” Patient 12 developed severe hypobulia after right frontal tumor removal. The prefrontal cognitive initiation “axis,” responsible for goal initiation, comprises of the DMN, Salience network, and supplementary motor area (SMA) and is connected by the cingulum and frontal aslant tract [20]. Right sagittal (A) and left sagittal view (B) of the MRI scan showing the Salience, DMN, and SMA. C Right sagittal view of the three rTMS target. The R6ma, RPGi, and RTGd rTMS targets are labeled with green and blue tractography connecting parcellations. Two of the three rTMS targets for this patient were within the prefrontal cognitive initiation “axis”: RPGi and R6Ma. While R6Ma of the sensorimotor network is proximal to the tumor resection site, RPGi is within the DMN but outside of the immediate region of the resection site. D–F rTMS target contralateral to tumor site. An axial (D), coronal (E), and sagittal (F) view of rTMS targets superimposed on top of the MRI of Patient 1 who had a right temporal lobe craniotomy. rTMS targets include L1 of the left primary somatosensory cortex and R6d of right dorsal premotor cortex. G–I rTMS targets outside of tumor resection site. A coronal (G), sagittal (H), and axial (I) view of rTMS targets superimposed on top of the MRI of Patient 4. Patient 4 had a resection of the thalamus and had rTMS targets in the ventral premotor cortex (L6v and R6v) and the primary somatosensory cortex (L4).
circuitry following the growth and resection of a tumor. When tumor location and symptom manifestations are so variable, a personalized approach is the ideal strategy. The theory is that once the underlying cause is addressed, the motor and neuropsychiatric symptoms would resolve and significantly improve QoL. This is the first demonstration of parcel-guided, personalized rTMS treatment that targets multiple regions and treats several symptoms at once in brain tumor patients.

Our ability to target numerous symptoms and anomalous regions at once takes advantage of the idea that networks are sensitive to influences from remote cortical areas [18]. Even if a brain region is resected, changing remote cortical regions may ameliorate the effects of resection. Patients with infratentorial brain resections, regions that are often difficult to target with rTMS, were able to improve QoL after rTMS to supratentorial regions of the brain. This was observed in patients 4, 6, and 10 who had tumors in thalamus, cerebellum, and insula respectively. We have also shown the potential for inter-network modulation in patient 12 who developed severe hypobulia following a craniotomy that resected areas of the right salience network. Previous reports have shown that abulia after brain tumor resection can be prevented by sparing the cingulum tract of the prefrontal cognitive initiation “axis,” a network of connections between the Default Mode Network (DMN), salience network, and the SMA via the cingulum and frontal aslant tract [19, 20]. Two of the three rTMS targets for this patient were within this “axis”. These examples support the notion of remote cortical regions inter-communication and show how targeting regions away from the immediate resection site can improve post-craniotomy motor and psychiatric deficits caused by the resection.

Traditionally, rTMS studies for motor deficits utilize high frequency rTMS to increase cortical excitability to the motor cortex of the lesion hemisphere and low frequency rTMS to decrease cortical excitability in the contra-lesion hemisphere [21–24]. In the present study, the use of inhibitory or excitatory rTMS corroborates with the use of cTBS in the contra-lesion hemisphere and iTBS in the ipsi-lesional hemisphere. While our model does not predict the use of rTMS on the motor cortex for patients with motor deficits, at least one of the targets of choice are within the sensorimotor network. The complexity of this treatment paradigm is higher than simply targeting motor cortices, as we found that the premotor cortex may have the potential to serve as rTMS targets as well [25].

Quality-of-life and neuropsychiatric disorders following rTMS

In this study, we have shown that personalized, parcel-guided rTMS may improve physical and psychiatric symptoms experienced post-craniotomy. The magnitude of improvement in QoL was not affected by gender or age. However, patients who received rTMS therapy within 1 year of brain resection had significantly greater increase in quality of improvement than those who received rTMS after 1 year of surgery. While it may appear that people treated remotely from the surgery did not improve based on the EQ-5D, they still derived neurological improvements as seen in patient 1 and 2.

We have previously reported improvements in language and motor strength using the Agile Method for rTMS in post-surgical glioma patients [10]. Rather than measuring motor strength, we assess motor skill based on a functional scale. Function is important to assess as it contributes directly to improved activities of daily life. In addition to motor function, QoL is assessed with the EQ-5D, which have been shown to be correlated with survival for patients with glioblastoma following craniotomy [26].

The presence of neuropsychiatric disorders may worsen QoL as much as motor deficits. Depression has been reported by the GOP to be significantly increased in patients following craniotomy [1, 2]. For the patient who experienced post-surgical depression, BDI was reduced by 88% during follow-up after rTMS. This may suggest that the personalized, parcel-guided approach to rTMS treatment could decrease depressive symptoms following craniotomy. TMS has already been approved by the FDA as a treatment for depression [9]. There have also been numerous randomize-controlled studies on the treatment of depression with parcel-guided and fRMI-guided rTMS targeting the DMN [27–29]. To our knowledge, there has not been any study focused on rTMS interventions to improve psychiatric symptoms post-craniotomy. Patients with previous brain surgeries are often excluded from rTMS trials [30]. However, with a sample size of one, it is difficult to draw conclusions on the efficacy of this approach in craniotomy-exacerbated depression. Further investigation must be done to show whether this preliminary finding persists in a larger cohort of individuals, as well as for other neuropsychiatric symptoms following craniotomy.

Study limitations

Our study is limited by its retrospective nature. The placebo effect has been shown to be very strong for motor function as was described by a study on individuals with
Parkinson’s disease [31]. The treatment of depression with rTMS has also been shown to have a high placebo effect [32]. However, this effect usually diminishes in 11 weeks following therapy [33, 34]. The patient in our study with depression was followed up for 2 months after rTMS. Therefore, subsequent follow-up and larger sample size are warranted to study the efficacy and therapeutic duration of rTMS in treating post-craniotomy depression. Subsequent follow-ups would be beneficial for all patients to show the duration of rTMS treatment effects on improving neuro-cognitive, motor, and QoL. It is certainly possible that normal recovery would occur with time; however in our experience, especially in this pilot study, we observed immediate improvements following rTMS treatment.

It is important to acknowledge that meaningful recovery is especially difficult to assess in patients with brain tumors due to the possibility of tumor progression. One patient in our study was noted to have a decrease in UEFS at follow-up due to long-term decline. With only 12 patients in this study, the benefit of rTMS treatment can be confounded by the progression of the disease.

Conclusion

The personalized, parcel-guided rTMS approach is shown to be safe and appears to be effective in treating motor deficits and neuropsychiatric symptoms, and hence improve QoL metrics, for patients following craniotomy.

Author contributions SJT: Formal Analysis, Writing—Original Draft; Writing—Review & Editing; Visualization. JH: Conceptualization; Methodology; Data Curation; Writing—Review & Editing; Visualization; Formal Analysis. OL: Conceptualization; Writing—Review & Editing. CT: Conceptualization; Writing—Review & Editing. MS: Conceptualization; Writing—Review & Editing. JY: Conceptualization; Methodology; Formal analysis; Writing—Review & Editing; Supervision. All authors have approved the final article.

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Data availability Data is available upon request.

Declarations

Conflict of interest Charles Teo and Michael Sughrue are founders and employees of Omniscient Neurotechnology. Jonas Holle is an employee of Cingulum Health. Jacky Yeung and Olivia Lesslar are consultants of Cingulum Health but are not employees. Si Jie Tang does not report any conflicts of interest.

Ethical approval This study was approved by the Human Research Ethics Committee of the South Eastern Sydney Local Health District (2022/ETH00139).

Consent to participate Informed consent was obtained from all individual participants included in the study.

References

1. Chang SM et al (2003) Perioperative complications and neurological outcomes of first and second craniotomies among patients enrolled in the Glioma Outcome Project. J Neurosurg 98(6):1175–1181
2. Litofsky NS et al (2004) Depression in patients with high-grade glioma: results of the Glioma Outcomes Project. Neurosurgery 54(2):358–366 (Discussion 366-367)
3. Starnoni D et al (2018) Returning to work after multimodal treatment in glioblastoma patients. Neurosurg Focus 44(6):E17
4. Gehring K et al (2009) Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. J Clin Oncol 27(22):3712–3722
5. Rapp SR et al (2015) Donepezil for irradiated brain tumor survivors: a phase III randomized placebo-controlled clinical trial. J Clin Oncol 33(15):1653–1659
6. De Witt Hamer PC et al (2021) Functional outcomes and health-related quality of life following glioma surgery. Neurosurgery 88(4):720–732
7. Peng Z et al (2018) Mechanism of repetitive transcranial magnetic stimulation for depression. Shanghai Arch Psychiatry 30(2):84–92
8. Hoyer EH, Celnik PA (2011) Understanding and enhancing motor recovery after stroke using transcranial magnetic stimulation. Restor Neurol Neurosci 29(6):395–409
9. Cohen SL et al (2022) A visual and narrative timeline of US FDA milestones for Transcranial Magnetic Stimulation (TMS) devices. Brain Stimul 15(1):73–75
10. Poologaindran A et al (2022) Interventional neurorehabilitation for promoting functional recovery post-craniootomy: a proof-of-concept. Sci Rep 12(1):3039
11. Yeung JT et al (2021) Changes in the Brain Connectome Following Repetitive Transcranial Magnetic Stimulation for Stroke Rehabilitation. Cereus 13(10):e19105-e
12. Jung J et al (2021) The immediate impact of transcranial magnetic stimulation on brain structure: Short-term neuroplasticity following one session of cTBS. Neuroimage 240:118375
13. Huang YZ et al (2005) Theta burst stimulation of the human motor cortex. Neuro 45(2):201–206
14. Sonmez AI et al (2019) Accelerated TMS for Depression: A systematic review and meta-analysis. Psychiatry Res 273:770–781
15. Chesworth BM et al (2014) Reliability and validity of two versions of the upper extremity functional index. Physiother Can 66(3):243–253
16. Binkley JM et al (1999) The Lower Extremity Functional Scale (LEFS): scale development, measurement properties, and clinical application. Phys Ther 79(4):371–383
17. Gutner CA et al (2016) Emergence of transdiagnostic treatments for PTSD and posttraumatic distress. Curr Psychiatry Rep 18(10):95
18. Adachi Y et al (2012) Functional connectivity between anatomically unconnected areas is shaped by collective network-level effects in the macaque cortex. Cereb Cortex 22(7):1586–1592
19. Briggs RG et al (2021) The frontal aslant tract and supplementary motor area syndrome: moving towards a connectomic initiation axis. Cancers (Basel) 13(5):1116
20. Dadario NB et al (2021) Reducing the cognitive footprint of brain tumor surgery. Front Neurol 12:711646

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21. Du J et al (2016) Effects of repetitive transcranial magnetic stimulation on motor recovery and motor cortex excitability in patients with stroke: a randomized controlled trial. Eur J Neurol 23(11):1666–1672
22. Tosun A et al (2017) Effects of low-frequency repetitive transcranial magnetic stimulation and neuromuscular electrical stimulation on upper extremity motor recovery in the early period after stroke: a preliminary study. Top Stroke Rehabil 24(5):361–367
23. Ille S et al (2021) Navigated repetitive transcranial magnetic stimulation improves the outcome of postsurgical paresis in glioma patients—a randomized, double-blinded trial. Brain Stimul 14(4):780–787
24. Kubis N (2016) Non-invasive brain stimulation to enhance post-stroke recovery. Front Neural Circuits 10:56
25. Chen W-H et al (2003) Low-frequency rTMS over lateral pre-motor cortex induces lasting changes in regional activation and functional coupling of cortical motor areas. Clin Neurophysiol 114(9):1628–1637
26. Jakola AS et al (2015) Perioperative quality of life in functionally dependent glioblastoma patients: a prospective study. Br J Neurosurg 29(6):843–849
27. Cole EJ et al (2020) Stanford accelerated intelligent neuromodulation therapy for treatment-resistant depression. Am J Psychiatry 177(8):716–726
28. Moreno-Ortega M et al (2020) Parcel-guided rTMS for depression. Transl Psychiatry 10(1):283
29. Singh A et al (2020) Default mode network alterations after intermittent theta burst stimulation in healthy subjects. Transl Psychiatry 10(1):75
30. Plewnia C et al (2021) Treatment of major depressive disorder with bilateral theta burst stimulation: study protocol for a randomized, double-blind, placebo-controlled multicenter trial (TBS-D). Eur Arch Psychiatry Clin Neurosci 271(7):1231–1243
31. McRae C et al (2004) Effects of perceived treatment on quality of life and medical outcomes in a double-blind placebo surgery trial. Arch Gen Psychiatry 61(4):412–420
32. Hoy KE et al (2019) A pilot investigation of repetitive transcranial magnetic stimulation for post-traumatic brain injury depression: safety, tolerability, and efficacy. J Neurotrauma 36(13):2092–2098
33. Li F et al (2019) Meta-analysis of placebo response in adult antidepressant trials. CNS Drugs 33(10):971–980
34. Prasser J et al (2015) Bilateral prefrontal rTMS and theta burst TMS as an add-on treatment for depression: a randomized placebo controlled trial. World J Biol Psychiatry 16(1):57–65

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