

Interventional neurorehabilitation for glioma patients: A systematic review

Justyna O. Ekert[✉], Anshit Goyal, Jacob S. Young, Shawn L. Hervey-Jumper[†], and Mitchel S. Berger^{†,✉}

All author affiliations are listed at the end of the article

[†]These authors are co-first authors.

Corresponding Author: Justyna O. Ekert, MBBS, PhD, Department of Neurological Surgery, University of California, 505 Parnassus Avenue, San Francisco, CA 94117, USA (justyna.ekert.14@ucl.ac.uk).

Abstract

Harnessing the neuroplastic potential of the human brain is being increasingly recognized as an important neuro-oncological paradigm to facilitate safe resection of brain tumors while preserving neurological function and quality of life. Interventional neurorehabilitation, employing both invasive and noninvasive neuromodulation techniques, represents an important emerging therapeutic strategy to induce or enhance neural plasticity to promote functional recovery in brain tumor patients. This study aimed to conduct a comprehensive review of interventional neurorehabilitation techniques for glioma patients.

Methods. In accordance with PRISMA guidelines, searches of Medline, Embase, Web of Science, APA PsycINFO, and Cochrane were undertaken from database inception to November 28, 2023. Studies reporting on neuromodulation applied to glioma patients were included.

Results. Seven studies reporting findings from 118 patients met the inclusion criteria. Three neuromodulation techniques were identified and included transcranial magnetic stimulation (TMS) reported in 5 out of 7 (71.4%) studies; transcranial direct current stimulation (tDCS); and continuous cortical electrical stimulation (cCES) using grid electrodes, reported in one study each. All studies applying noninvasive stimulation to ameliorate postoperative deficits demonstrated an improvement on at least one outcome measure. The 2 studies applying tDCS and cCES to induce plasticity reported evidence of functional reorganization.

Conclusions. There is emerging evidence of benefits of neuromodulation to improve postoperative outcome in glioma patients. In the current literature, noninvasive stimulation has shown to have a favorable safety profile. Large-scale, double-blind, sham-controlled trials are warranted to further investigate the effectiveness of these interventions for modulating different cognitive networks in patients undergoing glioma surgery.

Keywords

cognition | glioma | motor | rehabilitation | transcranial magnetic stimulation (TMS)

The goal of glioma surgery is to remove as much tumor as possible while minimizing the risk of postoperative deficits that could affect the patient's quality of life. Achieving this delicate equipoise remains a neurosurgical challenge and a major concern for patients and their families.¹ When quality of life and length of life are viewed as a trade-off, patients with incurable malignancies, especially those of older age and declining physical health prefer living better than living longer.²

Several studies investigated the association between surgical morbidity and survival in glioma patients. A case series

of 228 patients with isocitrate dehydrogenase wild-type glioblastoma demonstrated that the presence of new postoperative neurological impairments was a significant predictor of overall survival.³ Patients who did not develop new deficits after surgery were found to have a median survival of 28.4 months, compared to 11.6 months in patients who suffered from at least one new impairment. Similarly, another study of glioblastoma patients by Rahman et al.⁴ concluded that, in their series, any survival benefits from achieving a 95% extent of resection were abrogated by the development of de novo

postoperative deficits. This evidence highlights the importance of preserving or improving neurological status even beyond the quality of life measures.

Interventional neurorehabilitation techniques, including both invasive and noninvasive neuromodulation methods, aim to harness the neuroplastic potential of the human brain to promote functional recovery. Repetitive transcranial magnetic stimulation (rTMS) utilizes an electromagnetic coil to stimulate neuronal circuits.⁵ Depending on the protocol, it can have a long-lasting inhibitory or excitatory effect on brain networks, resembling the long-term depression and potentiation, respectively.⁶ For example, when considering the frequency of stimulation, high-frequency (5, 10, or 20 Hz), but not low-frequency rTMS produced analgesic effects in patients with chronic neuropathic pain.^{7–9} Currently, there is no standardized definition of high- or low-frequency rTMS; however, frequencies of ≤ 1 Hz are typically regarded as inhibitory, while 10–20 Hz as excitatory.¹⁰ Similarly, theta burst stimulation (TBS) is a form of rTMS that involves the application of short bursts of low-intensity pulses with inner high frequency delivered every 200 ms.¹¹ While the applicability of theta-gamma coupling has not yet been proved in glioma circuits, it is thought that intermittent theta burst pulse stimulation has an excitatory effect, while continuous theta burst pulse stimulation has an inhibitory role.¹² rTMS has been trialed for the treatment of a range of neurological and psychiatric conditions with encouraging results.^{13–15} High-frequency rTMS of ipsilesional M1 was granted level A evidence of efficacy for promoting motor recovery after stroke according to the guidelines on the therapeutic use of transcranial magnetic stimulation (TMS).¹⁶ Favorable outcomes have also been demonstrated for treating aphasia,¹⁷ improving upper limb function and motor recovery,¹⁸ and spasticity after stroke.¹⁹ The widely documented effectiveness of rTMS for facilitating stroke recovery makes it a promising treatment that could be utilized in neuro-oncology patients.

Other techniques such as transcranial direct current stimulation (tDCS) have also reported beneficial effects. This noninvasive stimulation technique involves emission of a low-amplitude electrical current through the scalp.²⁰ A traditional tDCS setup involves placement of 2 electrodes on the scalp, with one being the target and the other a reference electrode.²¹ During stimulation, current flows between the 2 electrodes while passing through the brain, and most is shunted through the scalp. Direction of current flow differentiates between anodal and cathodal stimulation with the former considered excitatory due to membrane depolarization and the latter being, conversely, inhibitory.²² The exact mechanism of action remains incompletely understood and complex, ranging from modulation of resting membrane potential to alteration in cortical excitability, neuronal firing rates, and oscillatory patterns.^{23–31} A randomized controlled trial (RCT) showed that tDCS over left Wernicke's area resulted in improved accuracy on the picture-naming task and shorter naming latencies in both healthy participants and 3 patients with chronic poststroke aphasia compared to sham stimulation.³² Significant tDCS effects on a range of cognitive functions, including working memory, inhibition, flexibility, and theory of mind, have been demonstrated in a meta-analysis of 69 studies of both healthy and clinical populations.³³

Although reports of invasive neuromodulation outside of the neurosurgical literature are sparse, these methods might allow for more precise targeting of cortical areas.³⁴ In a study of 5 glioma patients, a contoured subdural grid was positioned over the residual tumor, the craniotomy site was closed and cables externalized.³⁵ The grid electrodes were then used to perform extraoperative stimulation mapping. Once the presence of functional sites was confirmed, patients underwent continuous cortical electrical stimulation (cCES) to induce mild behavioral disturbances. To promote reorganization of brain networks, the stimulation parameters were adjusted daily until no further deficits were observed.

Several potential pharmacological and nonpharmacological treatments for amelioration of impairments in brain tumor patients have been highlighted in a recent systematic review. As the majority of included studies suffered from methodological limitations, their benefit remains unclear.³⁶ Considering the limited progress in physical and cognitive therapy over the last 3 decades, there is a need for new approaches. Interventional neurorehabilitation with the use of neuromodulation could be a useful tool in the neuro-oncological armamentarium.

In this review, we aim to draw together the available evidence on interventional neurorehabilitation techniques used to induce or enhance plasticity, thereby promoting functional recovery in glioma patients.

Methods

This review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.³⁷ The protocol was registered with the International Prospective Registry of Systematic Reviews (PROSPERO; registration no. CRD42023483875).

Search Strategy

A systematic search of electronic databases of PubMed, Web of Science, Embase, Cochrane, and PsychINFO was performed from their inception to November 28, 2023. The search strategy combined the 3 broad content areas—brain tumor (eg, glioma), neuromodulation, and plasticity. These 3 content areas were combined using the Boolean operator “AND.” The PsychINFO search was limited to peer review. Reference lists of identified studies were also reviewed to identify additional relevant studies. The full search strategy is presented in [Supplementary Table 1](#).

Eligibility Criteria

The eligibility criteria were as follows:

Study design.—RCTs, controlled clinical trials, cohort studies, and case series were included. Case reports, review articles and meta-analyses, editorials, letters, commentaries, opinion papers, conference abstracts, clinical trial protocols, theses, and book chapters were excluded. Non-English articles were also excluded.

Population.—Adult patients (≥ 18 years) with a suspected or confirmed diagnosis of a hemispheric glioma were included. Studies incorporating mixed pathologies were also included, provided that glioma patients were part of the study population.

Intervention.—Neuromodulation (eg, TMS, tDCS, cCES) targeting the brain to induce or enhance plasticity, thereby promoting functional recovery. Studies reporting neuromodulation with permanent implants were excluded.

Study Selection

Titles and abstracts were screened against the predefined eligibility criteria by 2 independent reviewers (J.O.E. and A.G.). Any disagreements were resolved through discussion or further adjudication by a third reviewer (J.S.Y.).

For each study, the authors' institutions and data collection period were reviewed in detail to avoid multiple counting. In the event of multiple publications analyzing the same cohort of patients, the publication with the largest sample size was included.

Data Extraction and Synthesis

The following variables were extracted from the studies that meet the eligibility criteria: (1) general study information (the name of the first author, year of publication, study design, and country, where the study was conducted); (2) characteristics of the patient population (number of participants, demographics); (3) tumor characteristics (laterality, pathology); (4) details of the neuromodulation protocol; and (5) outcome measures.

Due to significant heterogeneity in outcome measures, meta-analysis was not deemed possible, and a qualitative synthesis was conducted. The synthesis involved a summary of the frequencies for each reported variable.

Risk of Bias Assessment

Two independent authors (J.O.E. and A.G.) evaluated the risk of bias in included studies using the Joanna Briggs Institute (JBI) checklist for case series³⁸ (10-item checklist) and RCTs³⁹ (13-item checklist). The total scores obtained for each study can be categorized as low risk of bias (80%–100%), moderate risk of bias (50%–80%), and high risk of bias (20%–50%).

Results

The systematic search identified 4770 articles (Figure 1). After deduplication, 3190 papers remained for title/abstract screening, of which 3141 were excluded. The full texts of 49 publications were reviewed. Seven studies with 118 patients met the eligibility criteria for inclusion. The flow chart of the selection process is shown in Figure 1.

Study Characteristics

The included studies were case series ($n = 5$)^{35,40–43} and randomized, sham-controlled, double-blinded trials ($n = 2$)^{44,45} (Table 1). Patient sex was reported in all studies, 50.4% ($n = 59$) were male and 49.6% ($n = 58$) were female. The participants' age was reported as the mean in 6 out of 7 studies, and median in one study.⁴¹ The overall pooled mean age was 51.1 years. Tumor pathology was reported for 117 patients, and included World Health Organization (WHO) Grade I ($n = 6$, 5.1%), Grade II ($n = 7$, 6.0%), Grade III ($n = 15$, 12.8%), Grade IV ($n = 41$, 35.0%), other glioma ($n = 9$, 7.7%), metastases ($n = 5$, 4.1%), and other ($n = 4$, 3.4%). Poologaindran et al.⁴¹ reported the total number of patients with WHO grade II–IV tumors ($n = 30$, 25.6%). Tumor laterality was reported in 5 out of 7 (71.4%) studies for 53 patients. Tumors were located in the left hemisphere in 31 (58.5%) patients and in the right hemisphere in 22 (41.2%) patients.

Three neuromodulation techniques were identified and included TMS ($n = 5$, 71.4%), cCES ($n = 1$, 14.3%) with grid electrodes, and tDCS ($n = 1$, 14.3%). Interventional neurorehabilitation was applied postoperatively in 5 out of 7 (71.4%) studies, between 1st and 2nd surgery in one study (14.3%), and preoperatively in one study (14.3%). The indications for neuromodulation were the presence of a motor deficit ($n = 3$, 42.9%); motor and/or language deficit ($n = 1$, 14.3%); induction of plasticity in the motor and/or language networks ($n = 2$, 28.6%); language deficit ($n = 1$, 14.3%); motor, cognitive, and psychological deficits ($n = 1$, 14.3%).

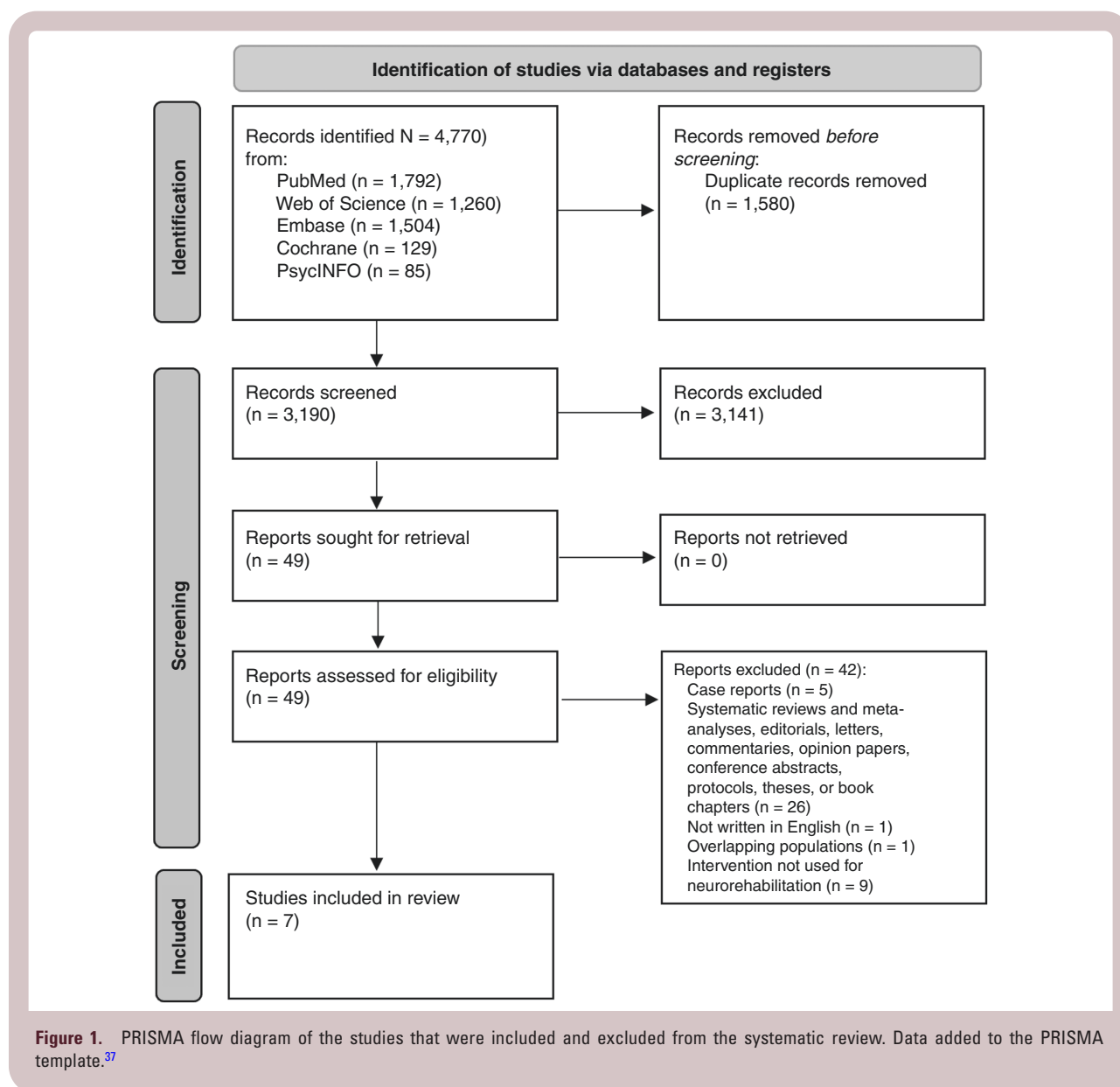
Risk of Bias Assessment

In the risk of bias assessment with the JBI checklist for case series, 4 studies were rated as 9 out of 10 and one study as 7 out of 10. The 2 RCTs attained a score of 12 out of 13 on the JBI checklist for RCTs. For individual ratings, see Supplementary Table 2.

Intervention Details

Protocols and targets.—The most frequently utilized neuromodulation protocol was low-frequency rTMS in 3 studies (42.9%), followed by high-frequency TBS in 2 studies (28.6%) (Table 2). Across the 5TMS studies, the median number of stimulation sessions per treatment was 7, delivered over 7 days. cCES with grid electrodes was performed for a median number of 16 days (range 15–25 days) until no functional deficits were induced.

The most frequently targeted network was the motor network in 6 out of 7 studies (85.7%), followed by the language network in 3 studies (42.9%). The primary motor cortex (M1) was the most common cortical target within the motor network. Tang et al.⁴² modulated the activity of the sensorimotor, language, central executive, salience, limbic and paralimbic, multiple demand, and default mode network (DMN) using connectomics-driven targets. Specifically, these targets were identified from a patient-specific anomaly matrix and had to be part of a network



implicated in the presenting symptoms. Continuous theta burst pulse stimulation (ctBS) was applied to areas that were hyperconnected on the anomaly detection matrix, while intermittent theta burst pulse stimulation (iTBS) to hypoconnected regions.

Additional interventions.—In 5 out of 7 studies (71.4%), patients received an additional intervention such as physical therapy, speech therapy, or rehabilitative therapy. Rehabilitative measures were not standardized across studies in terms of the type or duration of intervention. For instance, in the study by Ille et al.⁴⁵ patients underwent 30 minutes of task-oriented physical therapy focused on the upper extremity. In comparison, patients included in the tDCS study by Lang et al.⁴⁰ completed a music rhythm task of manual dexterity that required them to engage in a piano playing task.

Outcome measures

Motor function.—In studies investigating the effect of neuromodulation on motor function, 4 studies reported the findings of clinical examination on the Medical Research Council (MRC) scale.^{35,41,43,44} Two studies utilized the Fugl-Meyer Assessment (FMA).^{44,45} Less consistently reported measures of motor function included: the Nine Hole Peg Test, the number of finger taps with the paretic finger in 10 seconds, the National Institutes Stroke Scale (NIHSS), Jepsen-Taylor Hand Function Test, activities of daily living (ADL) using upper limb, the National Institute of Neurological Disorders and Stroke reflex scale, and upper and lower extremity functional scales (UEFS and LEFS).

Language.—Measures of language function included the Boston Diagnostic Aphasia Examination, the Token

Table 1. Summary of the Included Studies (N = 7)

First author, Year	Country	Study design	Sample size	Age (y)	Sex		Tumor type, <i>n</i> (%)	Tumor laterality		Main intervention	Timing	Indication
					M	F		L	R			
Motor												
Engelhardt, 2023 ⁴⁴	Germany	RCT	30	52	17	13	IV, 17 (57); Other glioma, 9 (30); Other, 4 (13)	NR	NR	rTMS	Postoperative	Motor deficit
Ille, 2021 ⁴⁵	Germany	RCT	22*	53 (rTMS) 61 (Sham)	12	9	II, 1 (5); III, 6 (29); IV, 14 (67)	9	12	rTMS	Postoperative	Motor deficit
Vitulli, 2023 ⁴³	UK	Case Series	7	56	2	5	I, 1 (14); IV, 1 (14); Metastasis, 5 (71)	4	3	rTMS	Postoperative	Motor deficit
Lang, 2020 ⁴⁰	Canada	Case Series	8	47	4	4	II, 2 (25); III, 2 (25); IV, 4 (50)	8	0	tDCS	Preoperative	Induction of plasticity in the motor network
Motor and language												
Poologaindran, 2022 ⁴¹	Australia	Case Series	34	58†	14	20	I, 4 (12); II–IV, 30 (88)	NR	NR	rTMS	Postoperative	Motor and language deficits
Rivera-Rivera, 2017 ³⁵	Spain	Case Series	5	41	3	2	II, 2 (40); III, 3 (60)	5	0	cCES	Between 1st and 2nd surgery	Induction of plasticity in the motor and language networks
Other												
Tang, 2022 ⁴²	Australia	Case Series	12	50	7	5	I, 1 (8); II, 2 (17); III, 4 (33); IV, 5 (42)	5	7	rTMS	Postoperative	Motor, cognitive, and psychological deficits

Notes: cCES = continuous cortical electrical stimulation; NR = not reported; RCT = randomized clinical trial; rTMS = repetitive transcranial magnetic stimulation; tDCS = transcranial direct current stimulation. *Baseline characteristics were reported for 21 study participants. †Median age reported. Patient was treated with radiotherapy without tissue diagnosis.

Table 2. Intervention Details

First author, Year	Protocol	Hz (% rMT) /mA	Total <i>N</i> pulses	<i>N</i> session (days)	Duration of session	Target		Other interven- tion		Outcome measure	Result
						Network	Motor	Cortical	tion		
Engelhardt, 2023 ⁴⁴	rTMS	LF	900	7 (7)	15 min		Motor	CL M1	PT	Primary: Motor functioning domain of FMA at 3 months postoperatively; Secondary: FMA at 7 days and 1 month postoperatively, NHPT, number of finger taps achieved with the paretic index finger in 10 s, KPS, MRC, NIHSS, EORTC-QLQ-C30	FMA: No significant difference between groups at 3 months postoperatively (<i>P</i> = .63); MRC: Improved scores at 1 month postoperatively in the rTMS group at 1 month (<i>P</i> = .05) compared to the sham group; NIHSS: Lower scores in a subgroup of patients with motor eloquent ischemia at postoperative day 7 (<i>P</i> = .04), month 1 (–4.4 [–8.12; 0.64]; <i>P</i> = .02) and month 3 (–3.8 [–7.57; 0.097]; <i>P</i> = .045).
	Sham	NR	NR	7 (7)	15 min		Motor	CL M1	PT		
Ille, 2021 ⁴⁵	rTMS	LF	900	7 (7)	15 min		Motor	CL M1	PT	Primary: ΔFMA at FU compared to day 1 after surgery Secondary: NHPT, JTHFT, NIHSS, and KPS	FMA: Statistically significant mean improvement from 31.9 points in the rTMS group compared to 4.2 (<i>P</i> = .00) points in the sham group and the NIHSS (–5.6 vs. –2.4; <i>P</i> = .02).
	Sham	1 Hz (5%)	NR	7 (7)	15 min		Motor	CL M1	PT		
Vitulli, 2023 ⁴³	rTMS	LF	900	7 (7)	15 min		Motor	CL M1	–	Clinical examination of motor function (MRC scale), Performance Status	Six patients recovered to their preoperative functional status and one patient with improved from being hemiplegic before and immediately postoperatively to motor power 3/5 in upper and lower limbs.
Lang, 2020 ⁴⁰	tDCS	2 mA	–	8 (4)	20 min		Motor	Anode: IL M1; Cathode: SL SOA	Motor training	Δinterhemispheric, global and local connectivity of M1 at 24 h postintervention on rs-fMRI	Subjective improvement in motor performance on the task; rs-fMRI: Increased local and global left M1 connectivity
Poologaindran, 2022 ⁴¹	rTMS	cTBS iTBS	NR	25 (5)	NR		Motor Language	Mixed Mixed	Rehabilitative Therapy	Clinical examination of motor function (MRC scale), ART	An improvement in motor and language function was noted in 19/21 and 12/13 patients, respectively, at 1 week post-TMS

Table 2. Continued

First author, year	Protocol	Hz (% rMT) /mA	Total <i>N</i> pulses	<i>N</i> session (days)	Duration of session	Target Network	Cortical	Other intervention	Outcome measure	Result
Rivera-Rivera, 2017 ³⁵	cCES	130 Hz 4.1–10.5 mA	Continuous (16*)	Continuous	Language	Mixed	SLT/PT	Boston Naming task, Token Test, Verbal fluency, Clinical examination of motor function (MRC scale), AfMRI activation	Boston Naming task: At 2–3 months postsurgery, naming ability improved or was maintained in all cases; Token Test: comprehension was maintained or improved in all cases, except in Case 2; Verbal fluency: maintained; Motor performance: maintained. Other cognitive functions: a slight worsening in memory, executive function, and attention in Cases 2, 4, and 5.	
Tang, 2022 ⁴²	rTMS	cTBS iTBS	50 Hz (80%–120%) 50 Hz (80%–120%)	1800 1200	25–26 (5)	NR	Language, Sensorimotor, Limbic and paralimbic, Salience, Central executive, DMN	-	EuroQoL (EQ-5D), BDI (patient with mild depression), LEFS, and UEFS (patients with motor deficits).	EQ-5D: increased scores after TMS ($P = .00$) and during follow-up ($P = .00$) compared to baseline. UEFS and LEFS: A 9-point improvement in >50% patients at follow-up. BDI: An 88% reduction in depressive symptoms in one patient with depression at follow-up.

Note: ART = Aphasia Rapid Test; aTBS = accelerated Theta burst stimulation; BDI = Beck's Depression Inventory; BL = bilateral; cCES = continuous cortical electrical stimulation; CL = contralesional; CST = corticospinal tract; DMN = default mode network; FMA = Fugl-Meyer Assessment; ICA = independent component analysis; IL = ipsilesional; LE = lower extremity; LEFS = lower extremity functional scale; LF = low frequency; M1 = Primary motor cortex; MRC = Medical Research Council; NHPT = Nine Hole Peg Test; NIHSS = National Institutes of Health Stroke Scale; OT = occupational therapy; PT = physical therapy; rMT = resting motor threshold; rs-fMRI = resting state functional magnetic resonance imaging; SLT = speech and language therapy; SOA = supraorbital area; TBS = theta burst stimulation; UE = upper extremity; UEFS = upper extremity functional scale.

*Median, range = 15–25.

Test, verbal fluency, and clinical examination of speech. Poologaindran et al.⁴¹ used the Aphasia Rapid Test to define language impairment as a score greater than 3.

Other.—Other measures of efficacy included neuroimaging correlates such as postintervention alterations in connectivity of M1 and changes in independent component analysis of rs-fMRI. Functional performance status was evaluated with the Karnofsky Performance Scale (KPS) in 2 studies,^{44,45} and quality of life with EuroQoL (EQ-5D) in one study.⁴² One study reported the Beck's Depression Inventory scores.⁴²

Outcomes

Motor.—All 5 studies applying TMS to ameliorate motor deficits reported an improvement on at least one outcome measure. Engelhardt et al.⁴⁴ demonstrated a significant improvement in MRC scores in the rTMS compared to the sham group at 1 month postoperatively ($P = .049$). There was no significant difference in FMA between groups at 3 months postoperatively. In contrast, the RCT by Ille et al.⁴⁵ that found a statistically significant mean improvement on the FMA of 31.9 points in the rTMS group compared to 4.2 points ($P = .001$) in the sham group, as well as the NIHSS ($P = .02$). The same study reported that to achieve a minimal clinically important difference (MCID) of 10 points on the FMA scale, the number needed to treat (NNT) was 2.19. The low NNT indicates that 2.19 patients would need to be treated with rTMS to demonstrate a 10-point improvement on the FMA scale. In a study of 9 patients with motor deficits, over 50% demonstrated a 9-point improvement on the UEFS or LEFS.⁴² Beneficial effects of rTMS on clinical examination have been shown in the remaining 2 studies.^{41,43}

Lang et al.⁴⁰ and Rivera-Rivera et al.³⁵ used tDCS and cCES, respectively, to induce plasticity in the motor network. Four days of tDCS combined with a piano playing task led to a subjective improvement on the task and increased M1 connectivity.⁴⁰ cCES facilitated more extensive resections by successful induction of plasticity.³⁵ The number of functional electrodes on extraoperative cortical stimulation mapping (ECSM) in a patient with motor deficits decreased from 6 to 2 after 22 days of cCES, and in another case with motor and language impairments from 10 to 1 after 15 days.²⁴

Language.—Two studies examined the effect of neuromodulation on language outcomes. In the study by Poologaindran et al.,⁴¹ 12 out of 13 patients demonstrated an improvement in language scores following rTMS. In the study by Rivera-Rivera et al.,³⁵ patients underwent cCES to promote plasticity within the language network. On the 2nd ECSM, the number of positive electrodes was reduced in all 4 patients. Displacement of function was confirmed on fMRI. At 2–3 months after the 2nd surgery, neuropsychological testing revealed either improved or maintained naming ability (4/4 patients); comprehension (3/4 patients); and verbal fluency (3/3 patient).

Other.—The effect of individualized rTMS on quality of life, motor, and psycho-cognitive assessments was evaluated in a series of 12 patients.⁴² EQ-5D scores were increased following rTMS ($P = .002$) and at follow-up ($P = .004$) compared to baseline. Greater benefits in quality of life were noted in patients who underwent rTMS within 1 year of surgery compared to more than 1 year postsurgery at baseline ($P = .03$) and during follow-up ($P = .02$). Moreover, a patient with postoperative depression showed a 47% and 88% reduction in depressive symptoms after rTMS and at follow-up, respectively, compared to baseline.

Adverse Events

The most common adverse effects associated with noninvasive stimulation were headache in 3 studies^{41,42,44}; followed by nausea,^{41,44} dizziness/lightheadedness,^{41,44} and tingling or itching sensation^{40,41} in 2 studies each; scalp discomfort at the stimulation site⁴² and facial twitching due to stimulation⁴² in one study each. No side effects were reported in the rTMS study by Ille et al.⁴⁵

In the invasive stimulation study using cCES (sample size, $n = 5$), the following complications were reported: focal seizures ($n = 3$); infections ($n = 2$), including osteomyelitis of the bone flap and an epidural abscess associated with transient deterioration of language and motor abilities that required evacuation; occasional finger twitching ($n = 1$); a subdural hematoma over the cortical grid that led to complete motor aphasia and right-sided paralysis, and had to be surgically evacuated ($n = 1$).³⁵ This patient exhibited almost complete recovery in motor function with persistence of mild dysphasia, and underwent a pseudomeningocele repair 1 year following the index surgery.

Discussion

We identified 3 neuromodulation methods across 7 studies that included TMS, tDCS, and cCES. A clinical benefit on at least one outcome measure was demonstrated in all studies applying stimulation to ameliorate deficits. To induce plasticity, tDCS or cCES were employed either preoperatively (tDCS) or between the 1st and 2nd surgeries (cCES). cCES resulted in reorganization of function, allowing for more extensive resection, while tDCS led to a subjective improvement on a task, accompanied by changes in functional connectivity. A recent nonsystematic review provided an overview of case reports of neuromodulation for inducing cortical reorganization before surgery.⁴⁶ To the best of our knowledge, this is the first systematic review examining the evidence for both invasive and noninvasive stimulation methods that could be used to induce or enhance plasticity before or after glioma surgery.

Haddad et al.⁴⁷ evaluated the most common clinical applications of TMS in the preoperative stage, including risk stratification, motor and language mapping, and recovery prognostication. Consistent with our results, they found that the side effects associated with the use of this technology tend to be minor and include pain (39%–40%),

headache (28%–40%), and high frequency hearing loss (9%).⁴⁷ An important consideration raised by the authors are TMS-associated seizures.⁴⁷ A large-scale study of the TMS safety profile by Tarapore et al.⁴⁸ reported no seizures related to TMS therapy in a cohort of preoperative neurosurgical patients. While this is reassuring, the number of stimulations delivered as part of rTMS protocols for neurointerventional rehabilitation is significantly higher. In this review, focal seizures in 3 patients were reported in the invasive stimulation study using subdural grid electrodes by Riviera-Rivera et al. (2017), despite a dose of levetiracetam (500 mg/12 hours). No seizures were documented in the noninvasive stimulation studies.³⁵

To maximize the clinical benefit of neuromodulation, it is crucial to select optimal stimulation targets. Previous studies have shown that differences in gross anatomical features such as the pattern of sulci and gyri between individuals, and therefore, orientation of neurons, might be contributing to the high variability in response to tDCS.^{49,50} Target selection is further complicated by functional variability in how our brains process stimuli. For example, certain processes such as reading aloud can take place via different cognitive routes, the lexical and sublexical route.⁵¹ Considering this high structural and functional inter-individual variability, it is clear that we need to rethink the “one-size-fits-all” approach.⁵²

At present, the standard of care rehabilitation methods following glioma surgery are limited to interventions aimed at improving the patient's quality of life and functional status such as physical, language, or occupational therapy.⁵³ As our knowledge of the neural basis of recovery is expanding, we are entering the era of neurointerventional rehabilitation. Neuromodulation techniques such as TMS or tDCS are a promising treatment that could be integrated into the treatment pathways and allow us to potentiate recovery mechanisms at a neuronal scale. Given the time-intensive nature of TMS therapy, larger-scale feasibility trials are needed. Several other challenges will need to be overcome before these interventions can be included in the treatment pathways for neuro-oncology patients in the United States. Apart from feasibility and clinical outcomes, data on cost-effectiveness, the requirement for multidisciplinary resources such as physical therapy or occupational therapy, and input from other specialties will need to be evaluated before its incorporation into clinical workflow. At present, TMS is FDA-approved for the treatment of depression and obsessive-compulsive disorders; its use as a neuro-rehabilitative measure in brain tumor patients was off-label.^{54,55}

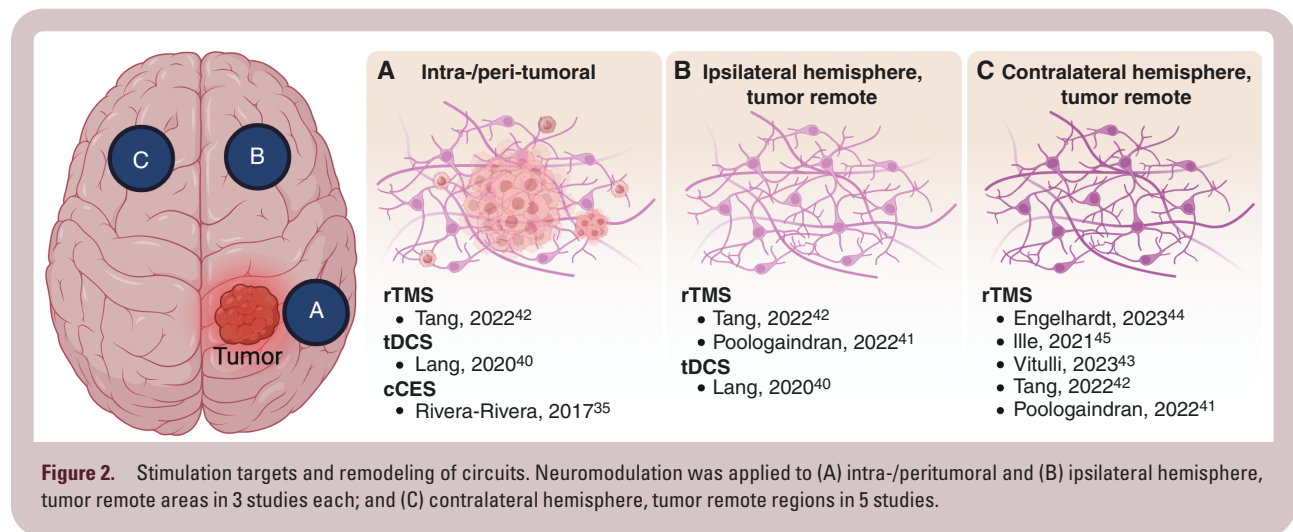
Strengths and Limitations

There were some limitations to this systematic review. First, data synthesis was qualitative given the significant heterogeneity in the outcome measures reported. Only one rTMS study reported the MCID and the number needed to treat for the FMA, but not quality of life scores.⁴⁵ The NNT is a valuable measure of clinical and statistical significance that conveys the risk-to-benefit ratio of a particular intervention.⁵⁶ To comprehensively evaluate the clinical

relevance of neuromodulation techniques, reporting of MCID and NNT should be considered in future studies. Second, there was significant variability in stimulation types, protocols, targets, and additional interventions (eg, physical therapy, language therapy) administered as part of the study protocols. The lack of a sham control in the majority of the included studies, compounded with the implementation of additional therapies of varying duration and intensity, made it difficult to evaluate the true effect of neuromodulation on patient outcomes. Third, the overall quality of evidence was low since over 70% of the included studies were case series lacking a comparison arm. Despite this, our risk of bias assessment (see Results section) revealed low risk of bias in the majority of the included studies, with 4 case series attaining a score of 9 out of 10 and one of 7 out of 10, with points being lost due to potential bias in selection of participants into the study (questions 4 and 5).³⁸ Both RCTs were deducted one point each for the lack of blinding of those delivering the treatment (question 5). It is also interesting to note that the positive results of the RCT evaluating rTMS for motor recovery postsurgery by Ille et al.⁴⁵ were not reproduced in the RCT by Engelhardt et al.,⁴⁴ which found no significant difference in outcome between rTMS and sham stimulation. One plausible explanation for this lack of reproducibility are differences in patient selection between the 2 high-quality studies. Ille et al.⁴⁵ only recruited patients who had a radiologically proven subcortical infarct within the corticospinal tract following glioma resection. By contrast, broader inclusion criteria were utilized in the clinical trial by Engelhardt et al.⁴⁴ Therefore, larger clinical trials are required to investigate whether specific patient subgroups might benefit the most from neuromodulation.

Despite the above limitations, this remains the first analysis of literature to date for neuromodulation as an emerging rehabilitation paradigm in neurosurgical oncology. To facilitate the design of successful clinical trials with the use of neuromodulation, more fundamental science is needed to understand how cancers alter the structure and function of neurons. The stimulation protocols described in the included studies can be broadly divided into 3 groups based on the location of the regions targeted with neuromodulation in relation to the tumor: (A) intra- or peritumoral; (B) ipsilateral hemisphere, tumor remote; and (C) contralateral hemisphere, tumor remote (Figure 2). Recent work by Krishna and colleagues⁵⁷ demonstrated that glioblastomas functionally remodel brain circuits to promote tumor progression. Furthermore, it was found that patients with high intratumoral connectivity had shorter survival (71 weeks) than patients without functional connectivity (123 weeks).⁵⁷ An important consideration is whether neuromodulation is applied to normal neuronal circuits or cancer-neuron circuits. Future clinical trials should build on these concepts and investigate whether suppression of intratumoral connectivity with neuromodulation yields a survival benefit.

Another crucial aspect in designing trials for postsurgery patients is the timing of therapy. This is to ensure that interventions are administered within the window for neuroplasticity. In a study of 60 stroke survivors, Hordacre et al.⁵⁸ examined the effect of cTBS on synaptic plasticity in



the motor cortex. Greater synaptic plasticity was inferred when larger reductions in cortical excitability and motor-evoked potential amplitude were observed. It was found that the depression of cortical excitability was strongest at 2 weeks poststroke in the contralesional hemisphere, while the cTBS response in the ipsilateral hemisphere remained constant over the course of the study with no effect of time.⁵⁸ Furthermore, the Critical Period After Stroke Study (CPASS): a phase II clinical trial reported that the time of heightened motor recovery was 60–90 days poststroke.⁵⁹ Although the literature on this topic is limited to studies on stroke patients, future studies on neuromodulation in brain tumor patients should aim to elucidate the appropriate timing for intervention.

We hope that gaps in evidence identified by this review would help inform development of future RCTs and allow more widespread clinical translation.

Conclusions

This systematic review shows promising potential for neuromodulation as a neuro-rehabilitative strategy for postoperative glioma patients with deficits. TMS and tDCS were found to have a favorable safety profile in currently available literature and therefore, may be a promising tool that could be applied to promote functional recovery in glioma patients. More large-scale trials are needed to: (i) enable quantitative synthesis of outcomes, and (ii) elucidate the utility of these techniques on induction of plasticity in other networks.

Supplementary material

Supplementary material is available online at *Neuro-Oncology Practice* (<https://academic.oup.com/nop/>).

Conflict of interest statement

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Affiliations

Department of Neurological Surgery, University of California, San Francisco, San Francisco, California, USA (J.O.E., J.S.Y., S.L.H.-J., M.S.B.); Department of Neurosurgery, Mayo Clinic, Jacksonville, Florida, USA (A.G.)

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