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Navigated repetitive transcranial magnetic stimulation improves the outcome of postsurgical paresis in glioma patients – A randomized, double-blinded trial

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ABSTRACT

Background: Navigated repetitive transcranial magnetic stimulation (nrTMS) is effective therapy for stroke patients. Neurorehabilitation could be supported by low-frequency stimulation of the non-damaged hemisphere to reduce transcallosal inhibition.
Objective: The present study examines the effect of postoperative nrTMS therapy of the unaffected hemisphere in glioma patients suffering from acute surgery-related paresis of the upper extremity (UE) due to subcortical ischemia.
Methods: We performed a randomized, sham-controlled, double-blinded trial on patients suffering from acute surgery-related paresis of the UE after glioma resection. Patients were randomly assigned to receive either low frequency nrTMS (1 Hz, 15 min) or sham stimulation directly before physical therapy for 7 consecutive days. We performed primary and secondary outcome measures on day 1, on day 7, and at a 3-month follow-up (FU). The primary endpoint was the change in Fugl-Meyer Assessment (FMA) at FU compared to day 1 after surgery.
Results: Compared to the sham stimulation, nrTMS significantly improved outcomes between day 1 and FU based on the FMA (mean [95% CI] +31.9 [22.6, 41.3] vs. +4.2 [-4.1, 12.5]; P = .001) and the National Institutes of Health Stroke Scale (NIHSS) (−5.6 [-7.5, −3.6] vs. −2.4 [-3.6, −1.2]; P = .02). To achieve a minimal clinically important difference of 10 points on the FMA scale, the number needed to treat is 2.19.
Conclusion: The present results show that patients suffering from acute surgery-related paresis of the UE due to subcortical ischemia after glioma resection significantly benefit from low-frequency nrTMS stimulation therapy of the unaffected hemisphere.
Clinical trial registration: Local institutional registration: 12/15; ClinicalTrials.gov number: NCT03982329

Abbreviations: nrTMS, Navigated repetitive transcranial magnetic stimulation; UE, upper extremity; FU, 3-month follow-up; FMA, Fugl-Meyer Assessment; NIHSS, National Institutes of Health Stroke Scale; EOR, extent of resection; QOL, quality of life; TCI, transcallosal inhibition; PT, physical therapy; BMRC, British Medical Research Council; DWI, diffusion-weighted imaging; MEP, motor evoked potential; rMT, resting motor threshold; NHPT, Nine Hole Peg Test; JTHFT, Jebsen-Taylor Hand Function Test; KPS, Karnofsky Performance Status.

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Introduction

Achieving maximum extent of resection (EOR) while preserving functionality is a crucial step for the optimal oncological treatment of patients suffering from brain glioma [1,2]. In particular, microsurgical glioma resection within or adjacent to eloquent brain regions might lead to new surgery-related functional deficits. Previous studies showed that most surgery-related deficits originate from subcortical ischemia rather than eloquent brain tissue resection [3]. Postoperative motor function loss greatly impairs patients' quality of life (QOL). Moreover, patients' overall survival and potential recovery is limited due to glioma recurrence and transformation. Hence, reducing time spent on neurorehabilitation to address new functional deficits has tremendous potential to enhance QOL in this group of patients.

From stroke patients we know various ipsilesional mechanisms supporting motor recovery from such damage and the subsequent functional disability [4,5]. Moreover, we know from studies of stroke patients that even the contralesional hemisphere is involved in ipsilesional recovery by transcallosal inhibition (TCI) [6,7]. In the healthy brain, upper extremity (UE) movement needs to be coordinated via communication between the hemispheres. Both primary motor cortices interact with the one of the other hemisphere to avoid mirror movements but also to facilitate uni- and bi-manual movement [8]. In the injured brain, however, TCI is altered which might impair motor recovery and is very well researched in stroke patients [9,10]. In case of ipsilesional hemisphere's damage TCI is enhanced. Thereby, the unaffected hemisphere pathologically inhibits the affected hemisphere and as a consequence also its recovery from damage. Thus, approaches include non-invasively down-regulating the contralesional motor cortex to reduce TCI [11].

Transcranial magnetic stimulation (TMS) is a safe, reliable, and standardized non-invasive brain activity modulation technique [12,13]. Repetitive TMS (rTMS) can be used to up-regulate or down-regulate cortical excitability. In particular, low-frequency rTMS can down-regulate the ipsilateral motor cortex and enhance the cortical excitability of the contralateral hemisphere [14,15]. Meanwhile, low-frequency rTMS of the contralesional motor cortex has been applied successfully and repeatedly and has proven beneficial in patients suffering from strokes [16–19].

For the present randomized, double-blinded, sham-controlled trial, we hypothesized that low-frequency navigated rTMS (nrTMS) applied to the contralesional hemisphere and combined with physical therapy (PT) in glioma patients suffering from acute surgery-related paresis of the UE due to subcortical ischemia improves UE motor outcomes as measured by the FMA upper extremity section more than does sham stimulation combined with PT.

Methods

Ethics

The local ethics board reviewed and approved the trial plan (registration number: 12/15; ClinicalTrials.gov number: NCT03982329). We performed the trial in accordance with the Declaration of Helsinki. All included patients provided written informed consent prior to randomization.

Eligibility criteria

We enrolled patients 18 years and older who underwent microsurgical glioma resection at our department and developed an acute surgery-related paresis of the UE. The patients had British Medical Research Council (BMRC) scale scores of 3 or below when compared to their preoperatively examined motor status and a new subcortical infarct within the corticospinal tract (CST) as shown by diffusion-weighted imaging (DWI) in postoperative MRI scan. Exclusion criteria were general TMS exclusion criteria (pacemaker, brain electrodes, and cochlear implants), as well as MRI exclusion criteria [20]. We did not include patients who underwent biopsy rather than microsurgical resection. Patients without preserved motor evoked potential (MEP) responses as measured by postoperative navigated TMS (nTMS) motor mapping were not included in the randomized trial. Eligibility criteria were assessed on day 1 (Fig. 1).

To perform a valid analysis of the effect of nrTMS, we calculated the sample size before the start of the trial. Due to the lack of prior studies on glioma patients, we based the sample size calculation on comparable studies that examined the effect of nrTMS stimulation in patients suffering from strokes. The calculation indicated an optimal sample size of 39 patients (26 nrTMS group, 13 sham group) [21].

Trial protocol

Patients who met the inclusion criteria received a new navigational cranial MRI scan, including a three-dimensional (3-D) gradient echo sequence with intravenous contrast administration, the day after surgery. After examining the participants' initial motor status and general neurological status, we performed postoperative nTMS motor mapping of the ipsilesional and contralesional hemisphere [22].

In case of preserved MEPs, patients were then randomly assigned to the nrTMS group or the sham group. Patients assigned to the nrTMS group received low-frequency nrTMS stimulation of 1 Hz for 15 min (900 pulses) at an intensity of 110% resting motor threshold (rMT, defined as the lowest TMS intensity capable of eliciting a 50 μV MEP amplitude). The rMT was measured at day 1 after surgery. This stimulation was applied to the contralesional hemisphere's motor hot spot. For nrTMS stimulation, the stimulation coil was handled perpendicular to the gyrus due to the orientation of pyramidal cells in the central sulcus. Patients in the sham group received sham stimulation at a stimulation intensity of 5% rMT with 1 Hz for 15 min. This was applied to the contralesional hemisphere's motor hot spot with an angulation parallel to the gyrus in order to additionally minimize the TMS effect. Within 1 h after receiving nrTMS or sham stimulation, patients received 30 min of intensive task-oriented PT focused on the UE. This protocol was performed for seven consecutive days directly after surgery (Fig. 1).

Outcome measures

We used the change in FMA at FU compared to day 1 after surgery as primary outcome measure because its reliability and validity is well-demonstrated [23,24]. Secondary outcome measures were the Nine Hole Peg Test (NHPT) and the Jebsen-Taylor Hand Function Test (JTHFT) [25,26]. To examine the patients' general neurological status, we used the National Institutes of Health Stroke Scale (NIHSS) [27]. Because we included only patients suffering from glioma, we applied the Karnofsky Performance Status (KPS) scale as a general oncological outcome scale to provide information on eligibility for adjuvant therapy [28].

Primary and secondary outcome measures were performed before day 1, directly after the last treatment on day 7, and at FU (Fig. 1). Due to potential tumor progression and other therapy-related confounders, the trial only assessed a 3-month period after surgery.

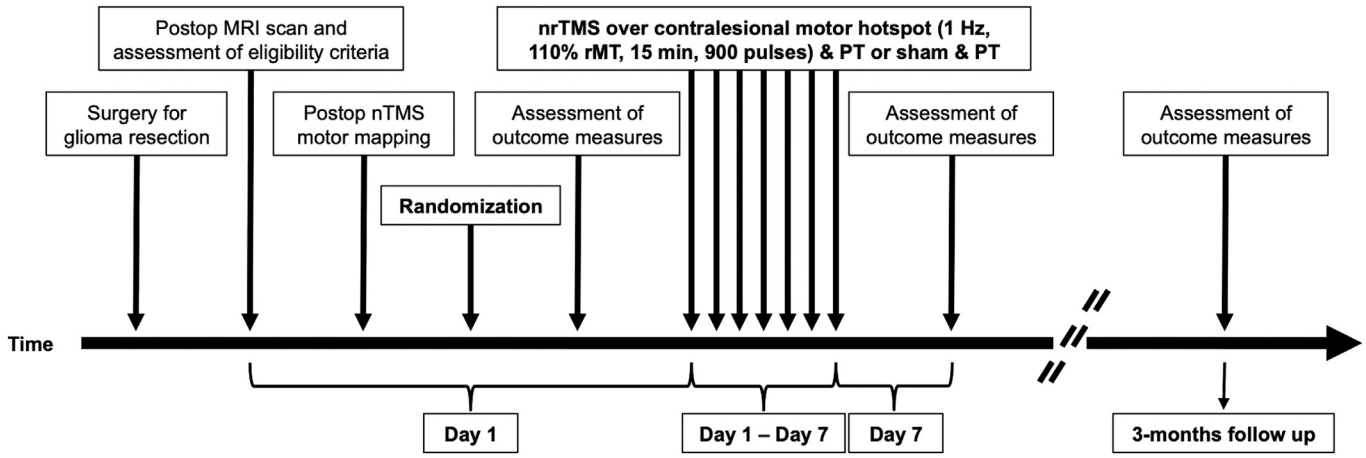

Fig. 1. Trial Time Course. nrTMS = navigated repetitive transcranial magnetic stimulation for therapy; nTMS = navigated transcranial magnetic stimulation for motor mapping; PT = physical therapy; rMT = resting motor threshold.

Randomization and blinding

After postoperative nTMS motor mapping in order to evaluate preservation of MEP responses, included patients were randomly assigned to receive either nrTMS stimulation combined with PT (= nrTMS group) or sham stimulation combined with PT (= sham group) in a 2:1 ratio. Randomization was performed by the use of standardized envelopes ensuring random treatment assignment as defined by the trial protocol.

All randomized patients, their treating physicians, trial investigators, and outcome raters, as well as administrative staff, including nurses, physiotherapists, and the patients' relatives, remained blinded to the randomization results and the following treatment protocol throughout the entire trial. Only the nrTMS system operator was informed of the randomization results and the assigned treatment protocol.

Statistical analysis

An interim analysis after the inclusion of half of the optimal sample group was predefined. To evaluate the trial's safety comprehensively, we selected a deterioration of overall performance to discuss stopping the trial.

We considered a p-value of less than 0.05 statistically significant. No specific plan was outlined initially for the management of missing data. No imputations were planned or performed. The plan for analysis was to compare the two randomized groups regarding changes of outcome measures between the time points of assessments and total differences of outcome measures at the time points of assessments. The plan for analysis included the following comparisons for all outcome measures:

- Change of outcome measures between day 1 and 3-months follow up
- Change of outcome measures between day 1 and day 7
- Change of outcome measures between day 7 and 3-months follow up
- Difference of outcome measures at day 7
- Difference of outcome measures at 3-months follow up

The baseline characteristics of the two groups were compared using independent t-tests for continuous variables and Fisher's exact or chi-square test for categorical variables. A p-value of less than 0.05 was considered significant. Initially, Gaussian distribution was tested for all measures. Due to the small cohort size, Gaussian distribution was tested using the Shapiro-Wilk-Test. In case of rejecting the null hypothesis based on a P-value <.05, further calculations for the tested data were performed using the Mann-Whitney Test. In case of no rejection of the null hypothesis based on a P-value >.05, further calculations for the tested data were performed using both parametric and non-parametric tests. In these cases, the manuscript and tables show P-value results of the T-test. Mean values including 95% confidence interval (95% CI) were calculated for all outcome measures. An interim analysis was performed after the inclusion of 50% of patients. No changes were made in the statistical analysis plan after the study was stopped.

We based our number needed to treat (NNT) calculation on publications defining the respective thresholds [29,30]. An improvement of more than 10 points on the FMA was defined as a minimal clinically important difference (MCID) [29]. The NNT for NIHSS results was based on the stroke severity score, which is scaled using NIHSS measures (0 = no stroke symptoms, 1–4 = minor stroke, 5–15 = moderate stroke, 16–20 = moderate to severe stroke, 21–42 = severe stroke). We defined a score of 0–4 as a favorable outcome and a score of more than 4 as an unfavorable outcome [31]. We defined a NIHSS motor arm score of 0–2 as a favorable outcome. We defined a favorable oncological outcome as a KPS of ≥70 [30]. All analyses were performed using R 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

Between June 2015 and May 2019, 39 patients met the randomized trial's inclusion criteria. In accordance with the trial protocol, 14 patients did not undergo randomization due to missing MEPs in the postoperative nTMS mapping. Three patients who met the inclusion criteria declined to participate in the trial. One patient assigned to receive nrTMS stimulation withdrew his consent to participate in the trial during the stimulation period due to psycho-oncological distress (Fig. 2). This patient left the hospital to recover at home with his family. No patient suffered from adverse events related to nrTMS or sham stimulation during or after the treatment period. Especially no seizures occurred during or after nrTMS or sham stimulation.

According to the trial randomization protocol, we assigned 16 patients (72.7%) to receive nrTMS stimulation therapy combined

with PT and assigned six patients (27.3%) to receive sham stimulation combined with PT. Apart from tumor hemisphere, baseline patient characteristics were well balanced between the groups (Table 1). In the nrTMS group and the sham group, one patient was lost to follow-up due to general status (nrTMS group) or death (sham group) (Fig. 2).

Outcome measures

The mean *absolute* values, including 95% CI, for FMA, NIHSS, KPS, NHPT, and JTHFT on day 1, on day 7, and at FU are shown in Supplementary Table 1.

Supplementary Table 2 shows the mean *changes*, including 95% CI, for FMA, NIHSS, KPS, NHPT, and JTHFT.

3-Month follow-up

The primary outcome parameter as defined by the *change* in FMA between day 1 and FU was statistically significant showing mean improvement from 31.93 [95%CI 22.6, 41.25] points in the rTMS group while it was 4.2 [95%CI -4.14, 12.54] points in the sham group (Supplementary Table 2; P = .001). To achieve the minimal clinically important difference (MCID) of more than 10 points on the FMA scale, the NNT is 2.19 (P < .01). Additionally, even the mean *absolute* values of the FMA were much better at FU in the rTMS group (42.14 [95%CI 31.74, 52.54]) compared to the sham group (13.20 [95%CI 3.64, 22.76]) (Supplementary Table 1; P = .002).

Figs. 3 and 4 as well as Supplementary Figures 1 to 5 show the differences between the nrTMS and the sham group for all primary and secondary outcome measures, as well the course of outcome measures.

7-Day follow-up

Except for the sham group's KPS difference between day 1 and day 7, all primary and secondary outcome measures improved for patients of both groups according to mean values between day 1 and day 7. Neither the absolute mean values at day 7 nor the changes of mean values between day 1 and day 7 for primary and secondary outcome measures showed statistically significant differences between the nrTMS group and the sham group.

For secondary outcome measures, the change in values between day 7 and FU were statistically significant for the FMA and the NIHSS. Likewise, the change in values between day 1 and FU was statistically significant for the NIHSS, and the change in values between day 1 and day 7 was statistically significant for KPS.

Further changes in values for secondary outcome measure did not show statistical significance.

Although examinations show better mean values for all outcome measures on day 7 for the nrTMS group as compared to

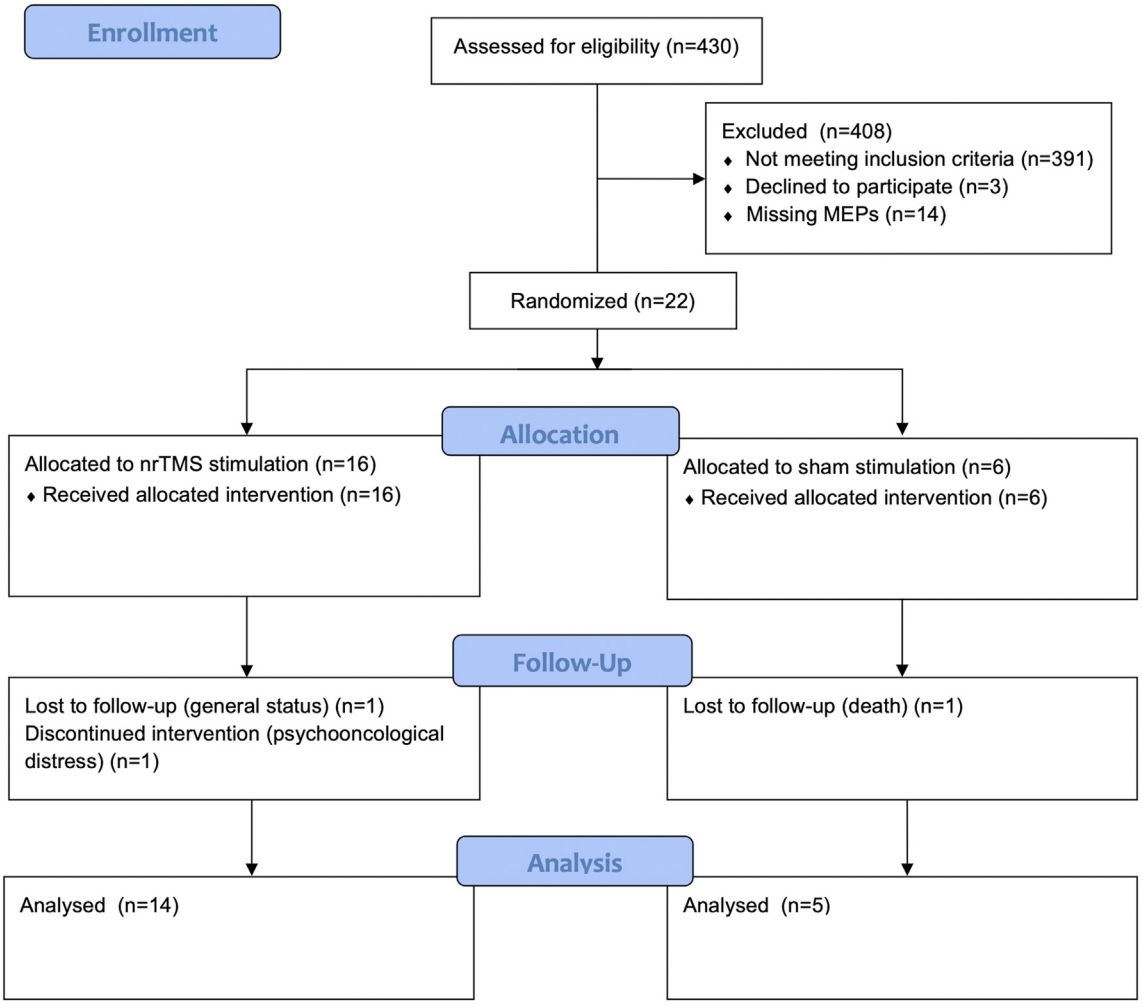

Fig. 2. Eligibility, Randomization, and Follow-Up. MEP = motor evoked potential; nrTMS = navigated repetitive transcranial magnetic stimulation for therapy; nTMS = navigated transcranial magnetic stimulation for motor mapping; PT = physical therapy.

Table 1
Patients' baseline characteristics.

1 Characteristic		nrTMS Group (N = 15)	sham Group (N = 6)
Age - yr		52.9 ± 15.2	61.4 ± 16.1
Gender	male - no. (%)	7 (47)	5 (83)
	female - no. (%)	8 (53)	1 (17)
Preoperative KPS[a] - %		87.3 ± 4.6	76.7 ± 12.1
Preoperative motor deficit	yes - no. (%)	8 (53)	5 (83)
	no - no. (%)	7 (47)	1 (17)
Hemisphere	left - no. (%)	4 (27)	5 (83)
	right - no. (%)	11 (73)	1 (17)
Lobe	frontal - no. (%)	5 (33)	1 (17)
	parietal - no. (%)	8 (53)	2 (33)
	temporal - no. (%)	2 (13)	3 (50)
Surgery	first - no. (%)	10 (67)	4 (67)
	recurrence - no. (%)	5 (33)	2 (33)
AED[b]	yes - no. (%)	10 (67)	5 (83)
	no - no. (%)	5 (33)	1 (17)
Corticosteroids	yes - no. (%)	1 (7)	3 (50)
	no - no. (%)	14 (93)	3 (50)
Subcortical ischemia size (cm^3)		5.2 ± 2.7	5.5 ± 2.4
EOR[c]	GTR - no. (%)	10 (67)	5 (83)
	STR - no. (%)	5 (33)	1 (17)
IDH[d] mutation	yes - no. (%)	6 (40)	1 (17)
	no - no. (%)	9 (60)	5 (83)
WHO[e]	II - no. (%)	1 (7)	0
	III - no. (%)	5 (33)	1 (17)
	IV - no. (%)	9 (60)	5 (83)
Recurrence/Progress at FU[f]	yes - no. (%)	2 (14)	1 (20)
	no - no. (%)	12 (86)	4 (80)

All group characteristics were not statistically significant except hemisphere distribution (P < .05).
[a] Karnofsky Performance Status (KPS) scale scores range from 0% to 100%. Higher scores indicate less disability and better quality of life in cancer patients.
[b] Anti-epileptic drugs (AED).
[c] Extent of resection (EOR) is subdivided into gross total resection (GTR), i.e. complete tumor resection, and subtotal resection (STR).
[d] Isocitrate dehydrogenase (IDH) mutation.
[e] The World Health Organization (WHO) grades tumors from I to IV, with higher grades indicating more malignant tumors.
[f] Status of tumor progress and/or tumor recurrence at 3-month follow-up (FU).

the sham group, we found no statistically significant differences at this time point. In contrast, at FU, mean values for the FMA and the NIHSS showed statistically significant differences (Supplementary Table 1).

Concerning the initial ischemic lesion, it did not resolve in subsequent imaging during follow-up, but did reduce in size on T1 compared to the initial DWI sequence at day 1 after surgery (mean ± SD: 5.3 ± 2.5 vs. 2.2 ± 2.4 cm^3; P = .002). There was also no difference in the initial DWI sequence at day 1 for patients who recovered (5.3 ± 2.4 cm^3) and patients who did not recover (5.3 ± 3.3 cm^3) (P = .996).

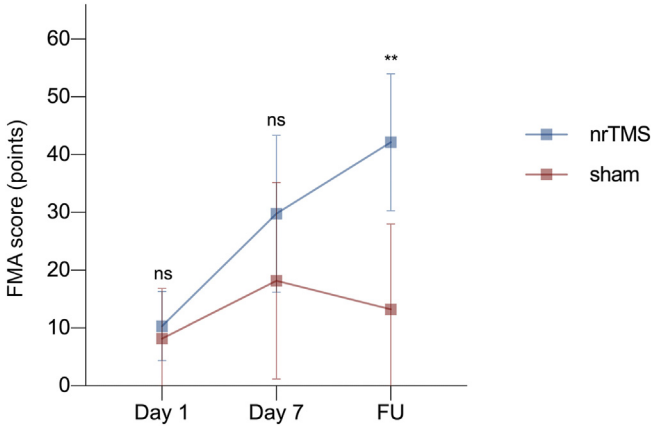

Fig. 3. Fugl-Meyer Assessment. Scores for the Fugl-Meyer Assessment (FMA) of the upper extremity range from 0 to 66, with lower scores indicating more severe disability. At all time points, the mean and 95% CI are shown. To achieve the minimal clinically important difference (MCID) of more than 10 points on the FMA scale, the NNT is 2.19 (ns = not significant, ** = P < .01, symbols refer to absolute values at timepoint).

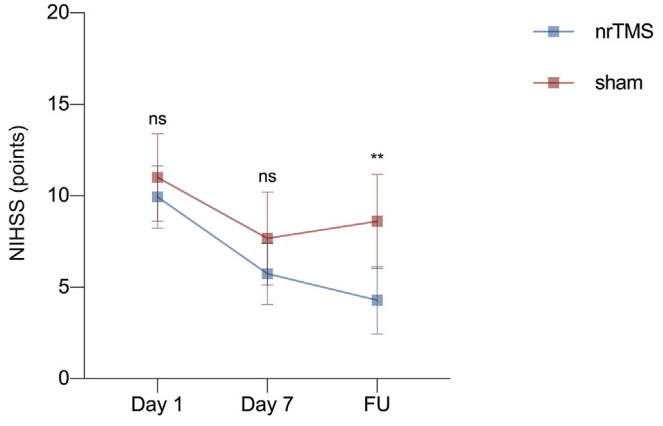

Fig. 4. National Institutes of Health Stroke Scale. National Institutes of Health Stroke Scale (NIHSS) scores range from 0 to 42, with higher scores indicating more severe disability. At all time points, the mean and 95% CI are shown. To achieve a favorable outcome on the stroke severity score, the NNT was 1.75. The NIHSS motor arm score at FU was 0–2 (favorable outcome) for 13 patients (92.9%) in the nrTMS group and two patients (40.0%) in the sham group. In contrast, an unfavorable outcome for the motor arm score was found in one patient (7.1%) in the nrTMS group and three patients (60.0%) in the sham group (P = .03) (Supplementary Fig. 4 and 5) (ns = not significant, ** = P < .01, symbols refer to absolute values at timepoint).

Number needed to treat

An improvement of more than 10 points on the FMA was found in 12 patients (85.7%) in the nrTMS group and in 2 patients (40%) in the sham group (P = .08). To achieve this MCID on the FMA scale, the NNT is 2.19 [29].

The nrTMS group's stroke severity score based on NIHSS results at FU was 0 for 2 patients (14.3%), 1–4 for 6 patients (42.9%), and 5–15 for 6 patients (42.9%). For the sham group, the stroke severity score at FU was 5–15 for all patients. In the nrTMS group, 8 patients (57.1%) showed a favorable outcome at FU, and 6 patients (42.9%) showed an unfavorable outcome. In contrast, all sham group patients showed an unfavorable outcome (P = .05).

To achieve a favorable outcome on the stroke severity score, the NNT was 1.75. With regard to the primary outcome parameter and the present trial's focus on improving UE functionality, the NIHSS motor arm score at FU was 0–2 (favorable outcome) for 13 patients (92.9%) in the nrTMS group and two patients (40.0%) in the sham group. In contrast, an unfavorable outcome for the motor arm score was found in one patient (7.1%) in the nrTMS group and three patients (60.0%) in the sham group (P = .04) (Supplementary Figure 4 and 5). To achieve a favorable outcome on the NIHSS motor arm score the NNT was 1.89.

With respect to general oncological outcome as measured by KPS, a favorable outcome of ≥70% was achieved in 8 patients (57.1%) in the nrTMS group and no patients in the sham group (P = .05) [30]. The NNT for a favorable oncological outcome on KPS was 1.75.

As a result of the present interim analysis of primary and secondary outcome parameters, as well as to the trial protocol's safety criteria, we stopped the randomized trial.

Discussion

nrTMS therapy for patients with acute paresis after glioma resection

In this first, randomized, double-blinded, sham-controlled trial of patients suffering from acute paresis of the UE due to subcortical ischemia after glioma resection, the addition of low-frequency nrTMS applied to the contralesional hemisphere combined with PT was associated with significantly better UE motor outcome as assessed using the FMA than sham stimulation combined with PT. The NNT to achieve a MCID on the FMA scale is 2.19. Additionally, secondary outcome measures for general oncological (KPS) and comprehensive neurological (NIHSS) outcomes showed better outcomes at FU in the nrTMS group than in the sham group. Further secondary outcome measures for specific UE function as measured by JTHFT and NHPT showed a positive improvement trend after nrTMS therapy as compared to sham group but failed to be statistically significant.

The trial's results, including the NNTs, show for the first time that the down-regulation of the contralesional motor cortex and the suspected reduction of TCI significantly benefits glioma patients' motor recovery in case of surgery-related subcortical ischemia.

For the oncological treatment of patients suffering from high-grade, low-grade, or recurrent glioma, microsurgical resection plays a central role [32,33]. Similarly, the occurrence of surgery-related paresis in patients who undergo microsurgical glioma resection is rare [34]. The present study demonstrates nrTMS therapy's potential to improve glioma patients' functional outcomes with acute surgery-related paresis after resection. First, the results show the beneficial effects and improvement of upper extremity motor impairment as measured by the FMA, which had priority in this trial. In addition, general oncological and comprehensive neurological outcome parameters also showed statistically significant improvement with nrTMS therapy.

Treatment protocol and comparison with trials on stroke patients

The enrolled patients represent a considerably homogenous cohort due to the rigorous inclusion criteria. In order to exclude the natural process of recovery or bias, patients with obvious resection of the supplementary motor area and therefore expected recovery were excluded as well. All enrolled patients required diffusion restriction in the MRI scan at the first day after surgery within the CST plus a severe corresponding functional deficit and intraoperative MEP decline or loss. Therefore, biopsy cases were also excluded.

The present trial's small cohort must be considered a limitation. The interim analysis showed statistically significant differences, particularly for the primary outcome measure of FMA change at FU. The statistical significance at this early stage, even for this small cohort, necessitated stopping the trial after the power analysis for the primary endpoint was sufficient.

Obtaining statistically significant results for the primary endpoint with such small group sizes can also be regarded as an important strength of the study because these results represent considerable effects due to effective treatment and the appropriate choice of inclusion criteria. Nevertheless, larger multicenter trials might still be reasonable not only to confirm the present results, but to provide an extensive subgroup analysis of the enrolled patients, such as lower extremity deficits and a broader range of inclusion criteria. Since the functional motor status was the main focus of this pilot study, no further QoL questionnaires were currently assessed. We chose the upper extremity for this pragmatic pilot study since it is easier to measure finer changes in motor function. Considering functional independence, the ability to walk is maybe even more important for these patients and the lower extremity should therefore be of additional interest in a future larger trial.

Only hemispheric lateralization differed significantly between the two groups in terms of their baseline characteristics. There was no difference in the application of steroids, antiepileptic drugs, EOR or molecular patterns. Mannitol was not applied at all (Table 1). Prior studies including a large-scale analysis of high-quality data showed that there is no difference in functional outcome and recovery between patients with right- or left-hemispheric strokes [35]. Thus, based on the principle of functioning, hemispheric lesion lateralization does not influence motor recovery due to nrTMS stimulation therapy, especially not for the primary outcome measure.

The therapeutic application of rTMS to enhance motor recovery has been studied in patients suffering from stroke. Although meta-analyses are somewhat controversial when applied to the results of single trials, the use of rTMS therapy with stroke patients is widely accepted, and further scientific investigation is advised [16–19]. Various approaches to using rTMS therapy with stroke patients have been developed in the past, including down-regulating the contralesional hemisphere using low-frequency rTMS to reduce TCI, which we essentially used in the present trial [36]. Previous trials compared ipsilesional high-frequency rTMS to contralesional low-frequency rTMS, leading to partially controversial results. These studies' outcomes showed more improvement using contralesional low-frequency rTMS than ipsilesional high-frequency rTMS [37,38], the opposite [39], and similar improvement when using the two approaches [40]. A meta-analysis showed that contralesional low-frequency rTMS is more effective than ipsilesional high-frequency rTMS and that patients suffering from subcortical strokes benefit more from rTMS therapy than do cortical stroke patients [18]. Because we planned to exclusively enroll patients

suffering from paresis after glioma resection due to subcortical ischemia, the present trial's treatment protocol was low-frequency nrTMS. Additionally, we applied this approach to prevent chronification of an enhanced TCI in this cohort of patients with acute paresis of the UE. This is one strength of our approach: the immediate beginning of rTMS right after the event. Since we intended to investigate a practically feasible approach, we limited rTMS to 7 days postoperatively. We are aware that most stroke trials applied rTMS 3 weeks or longer. However, this is not realistic in an acute care hospital and would have biased the results considerably due to later rTMS onset or different treatment centers for one patient if transferred to a rehabilitation unit.

Limitations

The present trial's treatment protocol was adapted from an earlier pilot study on stroke patients using a similar approach [21]. However, the study's cohort was fairly heterogeneous, as is characteristic for stroke patients. A subsequent randomized, sham-controlled multicenter trial on stroke patients failed to show differences between rTMS and sham stimulation [41]. Interestingly, both trial arms, the nrTMS group and the sham group showed significant improvement as measured by the FMA at a 6-month FU, far superior to the improvement noted in the literature. In contrast, the present trial's cohort only consists of patients with proven subcortical ischemia of the CST as confirmed by postoperative MRI. Therefore, our cohort is considerably more homogeneous and the ischemic lesions were much more circumscribed thus allowing for synaptic and functional reorganization. As already discussed by the authors of the mentioned stroke trial, the application of a special sham coil that induces a donut-shaped electric field of 10–30 V/m might have been the most likely reason for the lack of difference in both trial arms' improvement, as even low electric fields affect neuronal circuits [42]. However, we used a sham protocol of only 5% rMT stimulation intensity and an angulation parallel to the gyrus to apply minimum electric field strength and minimum stimulator output intensity; thus, active stimulation in our trial's sham group can be ruled out by two reasons: the electric field does not reach the brain through the skull and the induced current is perpendicular to the axons of the pyramidal cell which makes an action potential impossible per se.

Conclusion

This is the first study to examine the effect of nrTMS therapy in patients suffering from acute functional deficits after glioma resection. A strong treatment effect for contralesional nrTMS in the acute phase was shown for patients suffering from acute surgery-related paresis of the UE and subcortical ischemia if combined with PT. Larger trials should be done to potentially extent the indication.

Disclosure

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work.

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Credit author statement

All authors have contributed to this study in a manner to justify authorship. SI and AK performed literature search, figures, data collection, data analysis, and data interpretation. SI drafted the manuscript. AS, CN, VB, and NS participated in data collection. LA performed statistical analysis. TP and PV were participants of the scientific committee. BM was responsible for study supervision, data collection. SK was responsible for study design, study supervision, implementation of the study, data collection, data analysis, and performed data interpretation. All authors revised the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.04.026.

References

[1] Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. N Engl J Med 2008;358(1):18–27.
[2] Wijnenga MMJ, French PJ, Dubbink HJ, Dinjens WNM, Atmodimedjo PN, Kros JM, et al. The impact of surgery in molecularly defined low-grade glioma: an integrated clinical, radiological, and molecular analysis. Neuro Oncol 2018;20(1):103–12.
[3] Gempt J, Forschler A, Buchmann N, Pape H, Ryang YM, Krieg SM, et al. Postoperative ischemic changes following resection of newly diagnosed and recurrent gliomas and their clinical relevance. J Neurosurg 2013;118(4):801–8.
[4] Fridman EA, Hanakawa T, Chung M, Hummel F, Leiguarda RC, Cohen LG. Reorganization of the human ipsilesional premotor cortex after stroke. Brain : J Neurol 2004;127(Pt 4):747–58.
[5] Werhahn KJ, Conforto AB, Kadom N, Hallett M, Cohen LG. Contribution of the ipsilateral motor cortex to recovery after chronic stroke. Ann Neurol 2003;54(4):464–72.
[6] Carter AR, Astafiev SV, Lang CE, Connor LT, Rengachary J, Strube MJ, et al. Resting interhemispheric functional magnetic resonance imaging connectivity predicts performance after stroke. Ann Neurol 2010;67(3):365–75.
[7] Floel A, Hummel F, Duque J, Knecht S, Cohen LG. Influence of somatosensory input on interhemispheric interactions in patients with chronic stroke. Neurorehabilitation Neural Repair 2008;22(5):477–85.
[8] Geffen GM, Jones DL, Geffen LB. Interhemispheric control of manual motor activity. Behav Brain Res 1994;64(1–2):131–40.

[9] Duque J, Hummel F, Celnik P, Murase N, Mazzocchio R, Cohen LG. Transcallosal inhibition in chronic subcortical stroke. Neuroimage 2005;28(4):940–6.
[10] Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. Ann Neurol 2004;55(3):400–9.
[11] Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet Neurol 2006;5(8):708–12.
[12] Lefaucheur JP, Andre-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol : official journal of the International Federation of Clinical Neurophysiology 2014;125(11):2150–206.
[13] Siebner HR, Rothwell J. Transcranial magnetic stimulation: new insights into representational cortical plasticity. Exp Brain Res 2003;148(1):1–16.
[14] Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin Neurophysiol : official journal of the International Federation of Clinical Neurophysiology 2000;111(5):800–5.
[15] Kobayashi M, Hutchinson S, Theoret H, Schlaug G, Pascual-Leone A. Repetitive TMS of the motor cortex improves ipsilateral sequential simple finger movements. Neurology 2004;62(1):91–8.
[16] Graef P, Dadalt MLR, Rodrigues D, Stein C, Pagnussat AS. Transcranial magnetic stimulation combined with upper-limb training for improving function after stroke: a systematic review and meta-analysis. Journal of the neurological sciences 2016;369:149–58.
[17] Hao Z, Wang D, Zeng Y, Liu M. Repetitive transcranial magnetic stimulation for improving function after stroke. Cochrane Database Syst Rev 2013;(5):Cd008862.
[18] Hsu WY, Cheng CH, Liao KK, Lee IH, Lin YY. Effects of repetitive transcranial magnetic stimulation on motor functions in patients with stroke: a meta-analysis. Stroke 2012;43(7):1849–57.
[19] Le Q, Qu Y, Tao Y, Zhu S. Effects of repetitive transcranial magnetic stimulation on hand function recovery and excitability of the motor cortex after stroke: a meta-analysis. Am J Phys Med Rehab 2014;93(5):422–30.
[20] Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol 2015;126(6):1071–107.
[21] Harvey RL, Roth HR, Tappan RS, Kermen R, Laine J, Stinear J, et al. Abstract 152: the contrastim stroke study: improving hand and arm function after stroke with combined non-invasive brain stimulation and task-oriented. Therapy - A Pilot Study 2014;45(suppl_1):A152–.
[22] Krieg SM, Lioumis P, Mäkelä JP, Wilenius J, Karhu J, Hannula H, et al. Protocol for motor and language mapping by navigated TMS in patients and healthy volunteers; workshop report. Acta Neurochir (Wien) 2017 Jul;159(7):1187–95. https://doi.org/10.1007/s00701-017-3187-z. Epub 2017 Apr 29. PMID: 28456870.
[23] Duncan PW, Propst M, Nelson SG. Reliability of the Fugl-Meyer assessment of sensorimotor recovery following cerebrovascular accident. Phys Ther 1983;63(10):1606–10.
[24] Platz T, Pinkowski C, van Wijck F, Kim IH, di Bella P, Johnson G. Reliability and validity of arm function assessment with standardized guidelines for the fugl-meyer test, action research arm test and box and block test: a multicentre study. Clin Rehabil 2005;19(4):404–11.
[25] Oxford Grice K, Vogel KA, Le V, Mitchell A, Muniz S, Vollmer MA. Adult norms for a commercially available Nine Hole Peg Test for finger dexterity. Am J Occup Ther 2003;57(5):570–3. official publication of the American Occupational Therapy Association.
[26] Jebsen RH, Taylor N, Trieschmann RB, Trotter MJ, Howard LA. An objective and standardized test of hand function. Arch Phys Med Rehabil 1969;50(6):311–9.
[27] Brott T, Adams Jr HP, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20(7):864–70.
[28] Timmermann C. Just give me the best quality of life questionnaire': the Karnofsky scale and the history of quality of life measurements in cancer trials. Chron Illness 2013;9(3):179–90.
[29] Narayan Arya K, Verma R, Garg RK. Estimating the minimal clinically important difference of an upper extremity recovery measure in subacute stroke patients. Top Stroke Rehabil 2011;18(sup1):599–610.
[30] Navarria P, Minniti G, Clerici E, Tomatis S, Pinzi V, Ciammella P, et al. Re-irradiation for recurrent glioma: outcome evaluation, toxicity and prognostic factors assessment. A multicenter study of the Radiation Oncology Italian Association (AIRO). Journal of neuro-oncology 2019;142(1):59–67.
[31] Adams Jr HP, Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, et al. Baseline NIH stroke scale score strongly predicts outcome after stroke: a report of the trial of org 10172 in acute stroke treatment (toast). Neurology 1999;53(1):126–31.
[32] Hervey-Jumper SL, Berger MS. Maximizing safe resection of low- and high-grade glioma. Journal of neuro-oncology 2016;130(2):269–82.
[33] Stummer W, Reulen HJ, Meinel T, Pichlmeier U, Schumacher W, Tonn JC, et al. Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. Neurosurgery 2008;62(3):564–76. discussion -76.
[34] De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol 2012;30(20):2559–65.
[35] Fink JN, Frampton CM, Lyden P, Lees KR. Does hemispheric lateralization influence functional and cardiovascular outcomes after stroke?: an analysis of placebo-treated patients from prospective acute stroke trials. Stroke 2008;39(12):3335–40.
[36] Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. Stroke 2005;36(12):2681–6.
[37] Khedr EM, Abdel-Fadeil MR, Farghali A, Qaid M. Role of 1 and 3 Hz repetitive transcranial magnetic stimulation on motor function recovery after acute ischaemic stroke. Eur J Neurol 2009;16(12):1323–30.
[38] Takeuchi N, Tada T, Toshima M, Matsuo Y, Ikoma K. Repetitive transcranial magnetic stimulation over bilateral hemispheres enhances motor function and training effect of paretic hand in patients after stroke. J Rehabil Med 2009;41(13):1049–54.
[39] Sasaki N, Mizutani S, Kakuda W, Abo M. Comparison of the effects of high- and low-frequency repetitive transcranial magnetic stimulation on upper limb hemiparesis in the early phase of stroke. J Stroke Cerebrovasc Dis : the official journal of National Stroke Association 2013;22(4):413–8.
[40] Du J, Yang F, Hu J, Hu J, Xu Q, Cong N, et al. Effects of high- and low-frequency repetitive transcranial magnetic stimulation on motor recovery in early stroke patients: evidence from a randomized controlled trial with clinical, neurophysiological and functional imaging assessments. NeuroImage Clinical 2019;21:101620.
[41] Harvey RL, Edwards D, Dunning K, Fregni F, Stein J, Laine J, et al. Randomized sham-controlled trial of navigated repetitive transcranial magnetic stimulation for motor recovery in stroke. Stroke 2018;49(9):2138–46.
[42] Opitz A, Legon W, Mueller J, Barbour A, Paulus W, Tyler WJ. Is sham cTBS real cTBS? The effect on EEG dynamics. Front Hum Neurosci 2014;8:1043.