

Repetitive TMS does not improve cognition in patients with TBI

A randomized double-blind trial

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Neurology® 2019;93:1-10. doi:10.1212/WNL.0000000000007748

Abstract

Objective

To determine whether high-frequency repetitive transcranial magnetic stimulation (rTMS) improves cognition in patients with severe traumatic brain injury.

Methods

A single-center, randomized, double-blind, placebo-controlled study of rTMS was conducted in patients aged 18–60 years with chronic (>12 months postinjury) diffuse axonal injury (DAI). Patients were randomized to either a sham or real group in a 1:1 ratio. A 10-session rTMS protocol was used with 10-Hz stimulation over the left dorsolateral prefrontal cortex (DLPFC). Neuropsychological assessments were performed at 3 time points: at baseline, after the 10th rTMS session, and 90 days after intervention. The primary outcome was change in executive function evaluated using the Trail Making Test Part B.

Results

Thirty patients with chronic DAI met the study criteria. Between-group comparisons of performance on TMT Part B at baseline and after the 10th rTMS session did not differ between groups ($p = 0.680$ and $p = 0.341$, respectively). No significant differences were observed on other neuropsychological tests. No differences in adverse events between treatment groups were observed.

Conclusions

Cognitive function in individuals with chronic DAI is not improved by high-frequency rTMS over the left DLPFC, though it appears safe and well-tolerated in this population.

ClinicalTrials.gov identifier

NCT02167971.

Classification of evidence

This study provides Class II evidence that for individuals with chronic DAI, high-frequency rTMS over the left DLPFC does not significantly improve cognition.

MORE ONLINE

→ Class of Evidence

Criteria for rating therapeutic and diagnostic studies

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by the authors.

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Glossary

DAI = diffuse axonal injury; DLPFC = dorsolateral prefrontal cortex; RMT = resting motor threshold; rTMS = repetitive transcranial magnetic stimulation; TBI = traumatic brain injury; TMS = transcranial magnetic stimulation; TMT-B = Trail Making Test Part B.

Diffuse axonal injury (DAI) causes extensive brain dysfunction and is a major cause of neurologic sequelae in patients, affecting about 40% of those who sustain severe traumatic brain injuries (TBIs).¹⁻³

DAI is a common mechanism of injury from brain trauma and is associated with cognitive impairments and emotional and behavior disorders.⁴ These cognitive impairments after DAI can be persistent, especially in moderate and severe TBI cases, and commonly involve deficits to executive function, judgment, verbal fluency, information, and attentional processing and memory impairments.^{5,6}

Although many studies have reported positive effects of cognitive rehabilitation therapies in these patients, the literature with regard to therapy for DAI and TBI remains inconclusive.⁷⁻⁹ Within this framework, noninvasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS), have emerged as promising tools. Most studies that examine cognitive rehabilitation with TMS have evaluated effects in patients with dementia and most notably Alzheimer disease, as well as depression. More specifically, dorsolateral prefrontal cortex (DLPFC) stimulation has been associated with improvements in cognitive performance.¹⁰⁻¹³ Few studies have evaluated the effect of repetitive TMS (rTMS) as a tool to help clinical recovery in patients with severe TBI,¹⁴ most of which are case reports investigating heterogeneous conditions linked to TBI, such as cognition enhancement, depression, tinnitus, auditory hallucinations, neurobehavioral gains during coma recovery, and postconcussion symptoms.¹⁵⁻²⁰

According to the International Federation of Clinical Neurophysiology committee report, Clinical TMS Society consensus, and European evidence-based guidelines,²¹⁻²³ there is solid evidence that left DLPFC is a safe target to stimulate using high-frequency rTMS in many neurologic and psychiatric conditions. For this reason, we hypothesized that left DLPFC would be a safe and promising target for TBI. Safety issues concerning rTMS over subcortical targets and other protocols are under evaluation. Thus, the present randomized clinical trial aimed to investigate the effects of high-frequency rTMS of the left DLPFC on the cognitive functions of patients with DAI, focusing on the efficacy and safety of this method.

Methods

Classification of evidence

This study seeks to address the following research questions with the associated classification of evidence:

1. Does high-frequency rTMS improve executive functions, assessed using the Trail Making Test Part B (TMT-B), in patients with chronic DAI (Class II)?
2. Does high-frequency rTMS improve other cognitive functions, including attention and memory, and motor functions, in patients with chronic DAI (Class II)?
3. Is high-frequency rTMS safe and well-tolerated in patients with severe TBI (Class II)?

Standard protocol approvals, registrations, and patient consents

Our university's ethical standards committee on human experimentation approved all the experiments conducted in the present study. The study protocol was approved by the local ethics committee (institutional review board no. 193.985/13) and all patients provided written, informed consent before enrolling. This prospective, single-center, randomized, parallel-group controlled trial was also registered at clinicaltrials.gov (NCT02167971) on June 17, 2014.²⁴

Data availability statement

All individual, de-identified participant data will be shared upon request, including data regarding participant outcomes and cognitive testing, the study protocol, and statistical analyses. The data will be made available for a period of 5 years and can be accessed upon request made to the corresponding author via email.

Participants and setting

Individuals were eligible if they were between 18 and 60 years of age, sustained a nonpenetrating TBI >12 months prior to enrollment, and had a clinically and radiologically based diagnosis of DAI. The study was completed at the Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, Brazil.

Patients with the following were excluded: (1) current addictive behavior or severe psychiatric illness; (2) uncontrolled epilepsy; (3) implanted metallic or electronic device carriers, such as a cardiac pacemaker, stents, epidural or deep brain electrodes, cochlear implants, drug infusion systems, or intracranial clips; (4) current pregnancy; (5) severely damaged left DLPFC as evaluated using MRI.

A clinical diagnosis of DAI was defined as coma after severe TBI, lasting for at least 6 hours. In the acute phase of TBI, all patients underwent head CT scans, a standardized procedure for the hospital care of patients with moderate and severe TBI,

which confirmed DAI after exclusion of intracranial lesions with significant ischemic or mass effects (TBI-associated hematomas $>25 \text{ cm}^3$ or midline shift $>5 \text{ mm}$). In addition, all patients underwent brain MRI to identify typical DAI lesions and left DLPFC integrity, as well as to rule out other brain injuries that could justify their diagnosis, the latter being performed after stabilization of the acute injury or during outpatient follow-up. All medications were on stable dosing for at least 1 month prior to enrollment with no plans to change during the 90-day study period.

Interventions

Demographic, medical history, and injury data were collected and verified via interview and medical record review. After confirmation of eligibility and baseline assessments, participants were randomly allocated at a 1:1 ratio to either the sham or real rTMS group.

Neuropsychological evaluations were performed at 3 time points: baseline (evaluation 1 [E1]), following the last (10th) rTMS session (evaluation 2 [E2]), and at 90 days after rTMS (evaluation 3 [E3]).

TMS

rTMS was applied using a magnetic stimulator (MagPro X100; MagVenture A/S, Farum, Denmark) connected to a figure-of-8 coil. Two different coils were used: (1) an active (real) coil (110 mm external diameter, MC-B70; MagVenture Tonika Elektronik, Farum, Denmark) and (2) a sham coil (MC-P-B70; Magventure Tonika Elektronik).

The sham coil was very similar in terms of shape, color, and sound production. Stimulation intensity was set to 110% of each participant's resting motor threshold (RMT), defined as the lowest intensity at which the machine (measured as a percentage of its maximum power) was capable of evoking a motor evoked potential larger than 50 microvolts in 5 of 10 consecutive attempts.²⁵ The first dorsal interosseous muscle was used to determine the RMT.

TMS was performed with the figure-of-8 coil, positioned tangentially to the convexity of the head above the left DLPFC. The target location was identified on the first day on which rTMS was administered and was based on the International 10/20 System for EEG and aided by a tool developed by Beam et al.²⁶ for left DLPFC identification.

Trains of rhythmic high-frequency (10 Hz) rTMS were delivered for short periods (5 seconds duration), separated by longer, no-stimulus periods (25 seconds), during each daily session. A total of 2,000 pulses were applied each day (50 stimuli/train, 40 trains) for a total of 10 sessions.

Outcomes

The primary endpoint of the study was executive function assessed by the TMT-B. We hypothesized that the real group would demonstrate improvement between baseline (evaluation 1)

and early post-treatment assessment (evaluation 2) of $>1 \text{ SD}$ on the TMT-B over the sham group.

The secondary endpoints that we analyzed included performance on the other neuropsychological tests and in the cognitive domains evaluated, and the safety and tolerability of rTMS in patients in the chronic phase of DAI.

Measures

All cognitive tests and subtests were grouped into 4 cognitive domains as described in table 1. Participant scores for each of these tests were transformed into a Z score according to a SD and T score to percentile conversion table.²⁷ The score for each of the 4 cognitive domains assessed was the result of the mean of all Z scores for the included tests in a given domain. Each cognitive test/subtest was included in only one cognitive domain. Neuropsychological disability was established when at least one test score was below a Z score cutoff of -1.4 on the basis of results obtained in a sample of normal participants, adjusted for age, sex, and education. Upon completion of rTMS sessions at day 10, participants were questioned about their opinion about whether or not they belonged to a given group.

Safety issues

Prior to the first rTMS session, all participants answered a standardized screening questionnaire with safety-related questions adapted from Rossi et al.²⁸ Before every session, all participants were assessed by the investigators to determine the occurrence of any adverse events. Any spontaneous complaints reported by patients were also recorded.

Sample size

Given a desired difference of 1 SD in TMT-B, 80% power, and an α of 5%, a minimum of 15 participants were required to achieve sufficient statistical power for each group. Three additional patients per group were added to compensate for possible loss during the follow-up period. Given this, a total of 18 patients were allocated to each group.

Randomization

Randomization was conducted via a web-based tool (randomization.com) that generated a list of block sizes of 4. The principal investigator was in charge of randomizing participant allocation, enrollment, and assignment to interventions.

Blinding and allocation concealment committee

Patients were randomly assigned to a real or sham rTMS group using opaque, sealed, sequentially numbered envelopes. The TMS deliverer and the neuropsychologist (outcome assessor) had no role in the randomization process or in patient recruitment.

For proper blinding, the coils were of a similar shape, size, color, and weight, and emitted very similar sounds. Participants, their relatives, and the neuropsychologist were unaware of group

Table 1 Cognitive tests and their respective domains

Neuropsychological domains	Neuropsychological tests
Executive functions	Trail Making Test Part B, COWAT, Stroop Test, Five-Point Test, Digit Span Test (Backwards)
Attention	Trail Making Test Part A, Digit Span Test (Forward), Symbol Digit Test
Memory	Hopkins Verbal Learning Test, Brief Visuospatial Memory Test
Motor function	Grooved Pegboard Test

Abbreviation: COWAT = Controlled Oral Word Association Test.

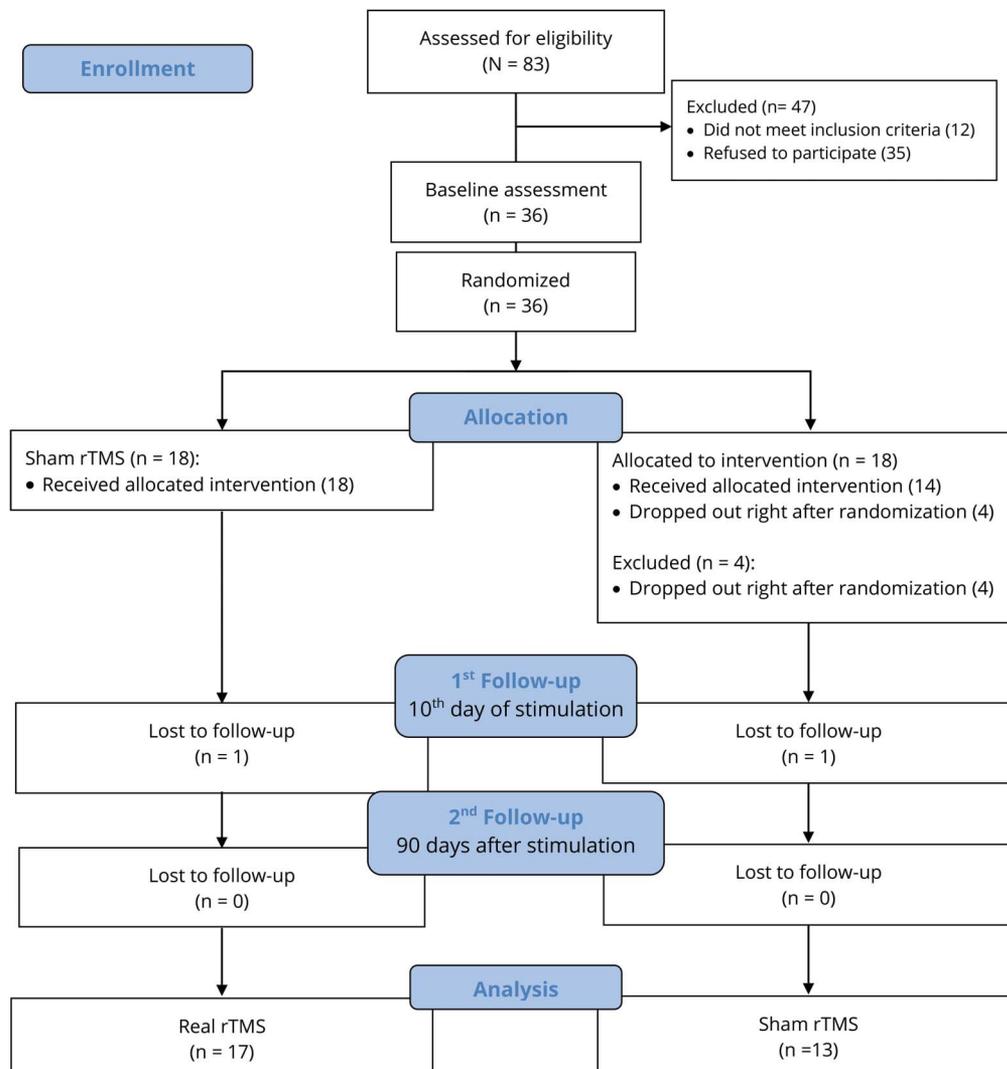
assignment. Furthermore, patients' appointments were set at different time periods to prevent loss of blinding integrity. For the persistence of allocation concealment, all evaluations were

performed using a blinded database containing groups with an "A" or "B" label. Consequently, all analyses were performed without any artifacts due to group allocation. This study involved the participation of a medical committee, members of which were not directly involved in patient group assignments and who could unblind participants should any clinical conditions arise that were relevant to group assignment, adverse events, or patient dropout.

Statistical analyses

The Kolmogorov-Smirnov test was used to test for a normal distribution. Normally distributed data are presented as means and SDs and were analyzed using independent, 2-tailed *t* tests. Nonparametrically distributed data are reported as medians and interquartile ranges and were compared using the Mann-Whitney *U* test. Categorical variables were presented as counts and evaluated using the Fisher exact test. All analyses were performed using only the cases that completed the rTMS protocol (per protocol principle).

Figure 1 Flow diagram



rTMS = repetitive transcranial magnetic stimulation.

Table 2 Comparison of demographic, injury characteristics, and neuropsychological data at baseline by treatment group

	Treatment group		p Value ^a
	Sham (n = 13)	Real (n = 17)	
Demographic data			
Male sex, n (%)	12 (92.3)	15 (88.2)	1.00 ^c
Age, y, mean ± SD	29.0 ± 10.35	32.62 ± 12.81	0.43 ^b
Education level, y, mean ± SD	10.61 ± 2.81	9.82 ± 3.00	0.47 ^b
Δ TBI and rTMS, m (range)	18.30 (13–24)	17.62 (13–26)	0.59 ^b
Automobile accidents, n (%)	11 (84.6)	15 (88.2)	1.00 ^c
GCS, mean ± SD	4.41 ± 2.54	5.00 ± 3.02	0.60 ^b
GOSE, mean ± SD	6.33 ± 1.07	6.00 ± 1.25	0.47 ^b
Neuropsychological data			
TMT (seconds)			
Part A	38.0 (29.0–55.0)	52.0 (34.0–73.0)	0.111
Part B	97.0 (83.0–269.0)	141.0 (100.0–209.5)	0.660
HVLT (score)			
Immediate recall	17.0 (15.0–19.0)	16.0 (14.0–20.5)	0.966
Delayed recall	4.0 (3.0–6.5)	5.0 (3.5–6.5)	0.554
BVMT (score)			
Immediate recall	15.0 (12.5–19.5)	15.0 (2.5–19.5)	0.600
Delayed recall	6.0 (2.5–10.0)	6.0 (0.5–9.0)	0.950
Grooved Pegboard Test (seconds)			
Dominant hand	82.0 (75.0–97.0)	86.5 (73.0–129.0)	0.827
Nondominant hand	90.0 (87.0–124.0)	96.0 (83.0–162.0)	0.736
Digit span test (score)			
Forward	5.0 (4.0–6.0)	5.0 (4.0–5.5)	0.437
Backwards	4.0 (3.0–4.0)	3.0 (3.0–4.0)	0.464
COWAT (score)			
FAS	26.0 (17.5–31.0)	23.0 (16.5–28.5)	0.529
Animals	15.0 (9.5–16.0)	13.5 (9.2–17.5)	0.859
Five-point test (score)	21.0 (13.0–28.0)	19.0 (12.0–23.5)	0.366

Table 2 Comparison of demographic, injury characteristics, and neuropsychological data at baseline by treatment group (continued)

	Treatment group		p Value ^a
	Sham (n = 13)	Real (n = 17)	
Stroop test (score)			
Stroop effect	32.0 (24.5–38.0)	33.0 (26.3–45.0)	0.714
Symbol Digit Test	40.0 (28.0–50.0)	34.5 (24.8–43.0)	0.263
Cognitive domains, z score, mean ± SD			
Executive functions	-1.19 ± 0.64	-1.24 ± 0.47	0.831
Attention	-0.86 ± 0.88	-1.07 ± 0.93	0.530
Memory	-1.44 ± 0.78	-1.43 ± 1.09	0.990
Motor function	-1.48 ± 0.87	-1.43 ± 1.08	0.903

Abbreviations: BVMT = Brief Visuospatial Memory Test; COWAT = Controlled Oral Word Association Test; HVLT = Hopkins Verbal Learning Test; GCS = Glasgow Coma Scale; GOSE = Glasgow Outcome Scale Extended; rTMS = repetitive transcranial magnetic stimulation; TBI = traumatic brain injury; TMT = Trail Making Test.

Neuropsychological tests are expressed as median (Q1–Q3) of the raw scores obtained. In the TMT and Grooved Pegboard Test, the values represent the time (in seconds) to accomplish the task, whereas the other tests are expressed as score. Δ = calculated difference (in months).

^a Mann-Whitney test.

^b t Test.

^c Fisher exact test.

The primary outcome was analyzed with a Mann-Whitney test and Wilcoxon rank sum test for between-group and within-group comparisons, respectively. Mean Z scores for each cognitive domain between the groups at each of the 3 time points assessed were calculated using the generalized estimating equation model with study time point as the within-subject variable. A robust covariance matrix was created with an independent working matrix correlation and linear distribution. If main effects or interactions were found to be significant, a pairwise post hoc analysis using the Bonferroni correction was also performed.

Blinded controls were evaluated via a Cohen kappa coefficient of agreement to assess patients' predictions about whether or not they belonged to a given group.

All statistical analyses were performed using IBM SPSS version 22.0 (IBM, Armonk, NY). Significance was set to $p < 0.05$.

Results

Participants

From July 2014 to February 2017, 83 individuals were enrolled and randomized, with 36 meeting eligibility criteria (n = 18 sham and n = 18 real), as outlined in figure 1.

Table 3 Time course of cognitive domains according to treatment group

Cognitive domain	E1	E2	E3	<i>p</i> Value, group	<i>p</i> Value, time	<i>p</i> Value interaction (time × group)
Executive functions						
Sham	-1.19 ± 0.64	-1.01 ± 0.75	-0.93 ± 0.58	0.838	<0.001	0.987
Real	-1.24 ± 0.47	-1.05 ± 0.59	-0.99 ± 0.56 ^a			
Attention						
Sham	-0.86 ± 0.88	-0.71 ± 0.93	-0.10 ± 2.51	0.247	0.469	0.364
Real	-1.07 ± 0.93	-0.97 ± 0.93	-1.22 ± 2.18			
Memory						
Sham	-1.44 ± 0.78	-1.40 ± 0.94	-1.51 ± 0.97	0.593	0.216	0.409
Real	-1.43 ± 1.09	-1.14 ± 1.20	-1.25 ± 1.13			
Motor function						
Sham	-1.48 ± 0.87	-1.35 ± 1.44	-1.14 ± 1.13	0.667	0.476	0.488
Real	-1.43 ± 1.08	-1.50 ± 1.10	-1.48 ± 1.27			

Abbreviations: E1 = evaluation 1 (at baseline); E2 = evaluation 2 (after 10th repetitive transcranial magnetic stimulation session); E3 = evaluation 3 (90 days after repetitive transcranial magnetic stimulation). Values are mean ± SD.

^a *p* < 0.05 (post hoc analysis with Bonferroni correction) within-group comparison (compared to baseline). None of the between-group comparisons at each timepoint was significant.

Compliance, defined as attendance of ≥80% of planned rTMS sessions, was high (88.2% in the real group and 92.3% in the sham group). Six participants (16.6%; 5 sham and 1 real group) did not complete the study, yielding 30 individuals to be included in the final analyses (13 from the sham group and 17 from the real group).

Table 2 summarizes and compares baseline demographic, injury characteristic, and neuropsychological data between the sham and real groups and did not reveal differences between the treatment groups.

The use of antidepressants, antiepileptics, benzodiazepines, and neuroleptic agents was very rare in the study population (6.6%, 3.3%, 3.3%, and 6.6%, respectively) and did not differ between the 2 groups (*p* > 0.05). Rates of neuropsychological disability ranged from 10% to 66.6%, depending on the cognitive test used. The proportion of participants with cognitive impairments at baseline was similar between the treatment groups.

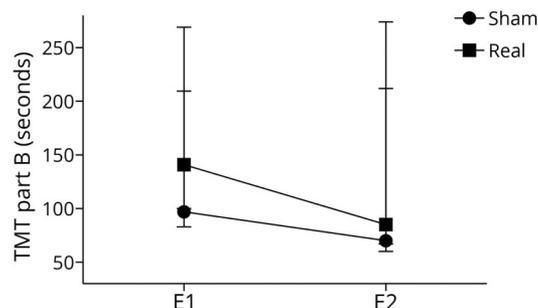
Treatment group comparison

Primary outcomes are illustrated in figure 2. Between-group comparisons of raw scores (in seconds) on TMT-B at evaluation 1 and 2 did not reveal differences between the treatment groups (*p* = 0.680 and *p* = 0.341, respectively). Within-group comparisons revealed differences only in the sham group (*p* = 0.023), indicating improvement in performance following intervention (evaluation 2).

Calculated differences in TMT-B between E2 and E1 and between E3 and E1 resulted in 2 new variables: Δ1 and Δ2,

respectively. The median Δ1 was -24.0 seconds (-47.5; -4.0) in the sham group and -27.0 seconds (-47.5; 22.5) in the real group, revealing a nonsignificant (*p* = 0.630) reduction in execution time at evaluation 2. In the sham group, the median Δ2 was -28.0 seconds (-78.5; 3.0) seconds, while it was -26.0 seconds (-50.5; 39.5) in the real group. As with Δ1, these values were not different (*p* = 0.451). There were also no differences in the interaction time × group comparisons in TMT-B (*p* = 0.450) scores between the 2 groups.

Data were grouped into 4 cognitive domains, as shown in table 3. In our comparison of E1 and E2 performance, a positive variation in Z scores (indicating performance improvement) was observed in all subgroups studied, with the

Figure 2 Mean changes in the Trail Making Test (TMT) part B at the 3 assessments in the 2 groups of patients

E1 = evaluation 1; E2 = evaluation 2.

exception of the real group in the motor function domain, although these observations were not significant. Intragroup comparisons for E1 and E3 revealed a difference only in the real group. Considering the values obtained across all 3 time points, a significant interaction between time and group was not found in any of the 4 cognitive domains evaluated, although there was a main effect due to time for the executive function domain. Between-group comparisons at all 3 time points were also nonsignificant. There was a significant effect due to time for executive function ($p < 0.001$).

Control of blinding

Agreement analysis with Cohen kappa was completed to evaluate the effectiveness of the blinding. At the end of the 10 rTMS sessions, of the 30 patients who completed the protocol, only 5 reported that they had been included in the sham group, representing 16.7% of the total participants. Patients were correct about their group assignment 66.6% (20 cases) of the time. Cohen kappa coefficient was 0.268, indicating low agreement and, therefore, positive blinding integrity.

Adverse events

High-frequency rTMS (10 Hz) was safe and well-tolerated in this population. No severe adverse events were reported. There was a greater frequency of mild adverse events in the real group (70.6% vs 46.2%, $p = 0.176$) above the sham group, though this difference was not statistically significant.

Discussion

This clinical trial evaluated the efficacy and safety of high-frequency (10 Hz) rTMS applied across 10 sessions to the left DLPFC for the purposes of cognitive rehabilitation in 30 cases of severe DAI. Participants were randomized into 2 groups: sham and real. There were no improvements in the executive functions of patients in the real group compared to the sham group, a result inconsistent with our primary hypothesis. In addition, no cognitive decline was found throughout the study regardless of treatment group. The present study is the first randomized controlled trial to evaluate the cognitive effects of rTMS in patients with pure chronic DAI.

No effect (time \times group interaction) of rTMS was found at either the early (E2) or late (E3) postintervention evaluation timepoints. In our analysis of repeated measures, an early effect of performance improvement was observed in both groups, with a reduction of approximately 40% in the median time of execution of the test in the patients in the real group and reductions of 28% in the sham group. Although there was no interaction in our between-groups comparison, a within-group analysis revealed a difference in the sham group. However, despite an improvement between E1 and E2, a decline in test performances between E2 and E3 was observed with median time increases from 85 to 161 and from 70 to 96 seconds in the active and sham groups, respectively. Nevertheless, neither $\Delta 1$ nor $\Delta 2$ differed between

the groups. Likewise, in the TMT-B assessment, pooled analyses of cognitive domain test performance also lacked differences.

No major adverse events occurred in this study and we did not observe a difference in the frequency of mild adverse events between groups. Due to a fear of adverse events in patients with TBI, especially seizure induction, the therapeutic application of TMS in this population began to be further studied^{15–20} only after publication of the last safety guidelines for TMS use in 2009.²⁸ Although this population is at increased risk for seizures, none of the patients in this trial experienced such events, suggesting that 10-Hz rTMS on the left DLPFC may be safe and well-tolerated for this population.

One hypothesis of the lack of evidence that TMS can improve clinical outcomes in patients with DAI is possibly due to the nature of the disease. Diffuse injury affects widespread cortical neural networks, leading to primary and secondary axotomy and microhemorrhages.² A longitudinal study showed that there is a progressive and significant atrophy in the total brain volume, white matter volume, and subcortical gray volume 1 year after the brain injury in patients diagnosed with DAI.²⁹ The authors suggest that the progression of the atrophy can be a continuum, possibly leading to changes on the cortical representation of cognitive areas. In this case, TMS may not be the best option for this target population due to its focality. Since we did not use a navigation system, the stimulation may have not reached the expected target as described in healthy participants, which may explain, at least in part, our negative findings.^{30,31} Although the figure-of-8 coil induces a relatively focal magnetic field over the cortex, its effects can influence nodes from large networks, generating changes in whole brain activity, as previously reported in neuroimaging and electrophysiology studies.^{32–34} Furthermore, there is robust evidence supporting the benefits of TMS in diseases that affect the brain diffusely or multifocally (e.g., depression, Alzheimer disease, pain syndromes).³⁵

A second hypothesis is that the cognitive enhancement induced by rTMS was reported in depressive patients.^{30,31,36,37} High-frequency rTMS applied over the left DLPFC has been shown to effectively treat depression, which may possibly lead to cognitive improvement as a consequence of mood amelioration. However, since the pathophysiology of TBI and depression are markedly different, the improvement observed in the latter may not be applicable in DAI cases. In fact, cognitive decline described in depression is potentially reversible and occurs due to a more focal brain dysfunction, different from the extensive brain damage seen in DAI.^{38,39}

Cognitive enhancement promoted by other noninvasive brain stimulation techniques, such as transcranial direct current stimulation, has shown promising results in patients with TBI.^{40–42} Combining neuromodulatory techniques with therapies, such as cognitive training, may be the best

option to boost and guide neuroplasticity and modulate some specific networks of interest.⁴³ In fact, noninvasive brain stimulation combined with virtual reality and brain-computer interface has been used to enhance motor recovery after stroke.^{44,45} Furthermore, this approach has also been tested for anxiety disorders, with promising results.⁴⁶ These reports support the concept of a combined and integrated approach for cognitive rehabilitation.

The results of the present study are in agreement with the existing scientific evidence. An extensive review of the literature in 2010 addressing the potential cognitive effects of rTMS found that only 7 out of 30 articles reported selective improvements in TMS group participants above sham controls.⁴⁷

Several factors may be responsible for this lack of therapeutic effect of rTMS in the present study. First, all participants had severe TBI (Glasgow Coma Scale score from hospital admission in the acute phase with medians of 3 and 4 in the sham and active groups, respectively) and there was a high prevalence of neuropsychological disability among participants at baseline. Furthermore, TMT-A and -B raw scores from the real group at baseline tended to be worse, although not significant. The magnitude and multifocality of DAI brain damage, as well as a lack of synergistic cognitive rehabilitation strategies such as cognitive rehabilitation therapies, may have limited the therapeutic effect of rTMS in the present study.

The present study was the first randomized controlled trial to use rTMS in patients with severe TBI. The limitations of and lessons learned from this study are noteworthy. Our pre-specified primary outcome measure registered in clinicaltrials.gov in 2014 should have been more specific and should have clearly mentioned that our aim was to evaluate executive function (measured by TMT-B); this was later clarified in the publication of our study protocol in 2015.²⁴ The non-navigated target location method based on the International 10/20 System may have negatively affected the accuracy of coil positioning across the 10 stimulation sessions, although Beam F3 has been shown to provide a reasonable approximation to MRI-guided neuronavigation for locating the left DLPFC.^{26,48} Future studies may wish to employ additional functional neuroimaging strategies such as fMRI or SPECT to better assess of the pathophysiologic processes involved.^{34,49}

We report in this clinical trial on the effect of rTMS on cognitive functioning among patients with chronic DAI. High-frequency rTMS during 10 sessions in this population with chronic DAI appears not to be beneficial for overall cognition. The use of rTMS to enhance cognitive function is not supported by the study's findings.

Acknowledgment

The authors thank Vinicius Guirado, MD, for contributions to participant recruitment, and the Service of Interdisciplinary Neuromodulation team for support.

Study funding

Supported by Brazilian National Council for Scientific and Technological Development (#459077/2014-7) and Chamada Universal (Universal Call, #14/2014). The study sponsor had no role in the design or execution of the present study, the collection, management, analysis, or interpretation of the data, manuscript preparation, or approval of this manuscript.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* August 31, 2018. Accepted in final form March 1, 2019.

Appendix Authors

Name	Location	Role	Contribution
Iuri Santana Neville, MD, PhD	Division of Neurosurgery, Hospital das Clinicas, and Service of Interdisciplinary Neuromodulation, University of Sao Paulo, Brazil	Author	Contributed to the study conception and design, the interpretation of the data, drafting, and critical review of the article; had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis
Ana Luiza Zaninotto, PhD	Division of Neurosurgery, Hospital das Clinicas, University of Sao Paulo, Brazil; Neuromodulation Center, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA	Author	Contributed to the study conception and design, interpretation of the data, drafting, critical review of the article
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Priscila Aparecida Rodrigues	Division of Neurosurgery, Hospital das Clinicas, University of Sao Paulo, Brazil	Author	Primary outcome assessor, acquisition of the data
Ricardo Galhardoni, DDS, PhD	Service of Interdisciplinary Neuromodulation and Pain Center, Department of Neurology, University of Sao Paulo; School of Medicine, Universidade da Cidade de Sao Paulo (UNICID), Brazil	Author	Conducted training in rTMS technique, acquisition of the data

Appendix (continued)

Name	Location	Role	Contribution
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Neurology published online June 7, 2019

DOI 10.1212/WNL.00000000000007748

This information is current as of June 7, 2019

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