Randomized trial of rTMS in traumatic brain injury: improved subjective neurobehavioral symptoms and increases in EEG delta activity

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Abstract

While repetitive transcranial magnetic stimulation (rTMS) has shown efficacy for cognitive difficulties accompanying depression, it is unknown if it can improve cognition in persons with traumatic brain injury. Using a sham-controlled crossover design, we tested the capacity of high frequency rTMS of the prefrontal cortex to improve neuropsychological performance in attention, learning and memory, and executive function. Twenty-six participants with cognitive complaints and a history of mild to moderate traumatic brain injury were randomly assigned to receive first either active or sham 10 Hz stimulation for 20 minutes (1200 pulses) per session for 5 consecutive days. After a one week washout, the other condition (active or sham) was applied. Pre- and post-treatment measures included neuropsychological tests, cognitive and emotional symptoms, and EEG. Results indicated no effect of treatment on cognitive function. Subjective measures of depression, sleep dysfunction, post-concussive symptoms (PCS), and executive function showed significant improvement with stimulation, retaining improved levels at two week follow up. EEG delta power exhibited elevation one week after stimulation cessation. While there is no indication that rTMS is beneficial for neuropsychological performance, it may improve PCS and subjective cognitive dysfunction. Long term alterations in cortical oscillations may underlie the therapeutic effects of rTMS.

Keywords

transcranial magnetic stimulation, cognition, traumatic brain injury, military and veterans, resting EEG

Introduction

In chronic mild to moderate traumatic brain injury (mTBI), cognitive difficulties are a common persistent concern, but established treatment options are limited. Cognitive rehabilitation therapy is the standard of care, but largely relies on compensatory strategies, with only weak evidence for improving cognition itself. Numerous pharmacologic agents have been proposed to address the underlying cognitive impairment, but randomized trials have been universally disappointing, including stimulants (Rabinowitz & Levin, 2014; Rabinowitz & Watanabe, 2020). Therefore alternative treatments for cognitive difficulties after TBI are needed.

Repetitive transcranial magnetic stimulation (rTMS) is an intriguing potential avenue for treating cognitive difficulties after TBI. rTMS to the prefrontal cortex (PFC) is well-established for depression and has been approved by the FDA since 2008 (Moore, 2008). Recently, it has also been approved by FDA for the treatment of obsessive compulsive disorder (FDA, 2020). High frequency rTMS of the PFC has also shown preliminary evidence of improvement in cognition. For instance, a review of 15 sham-controlled trials of high-frequency rTMS for depression found that active rTMS led to significant cognitive improvement in 7 studies (Guse et al., 2010), with another review reporting significant improvement in 5/13 controlled studies (Demirtas-Tatlidede et al., 2013).

Many of the clinical trials of rTMS have been in participants with depression (and sometimes with comparison healthy groups), but the intervention may potentially benefit other disorders with cognitive impairment. Recent reviews of rTMS for cognitive deficits after TBI describe positive case reports but mostly negative results with controlled trials; however, high heterogeneity, strong placebo effects, and small studies indicate this area of study is in its infancy and firm conclusions cannot yet be drawn (Dhaliwal et al., 2015; Hara et al., 2021; Oberman et al., 2020).

In addition to cognitive complaints, neurophysiological changes have been reported after mTBI. EEG, which measures cortical oscillations, might reflect long-term changes in the brain after injury. Our previous study found increases in right prefrontal low frequency power associated with chronic mTBI (Franke et al., 2016), and similar increases in low frequency oscillations after TBI have been reported using MEG (Huang et al., 2014; Li et al., 2015; Salat et al., 2017). Increases in low frequency power correlate with declining vigilance over the course of an attention task (Paus et al., 1997), as well as reduced level of consciousness (Schiff et al., 2014). Therefore it is possible that the persistent EEG changes after mTBI are indicative of long term alterations in attention and arousal networks, and rTMS to these right prefrontal regions have positively impacted performance in tests of attention and learning (Nadeau et al., 2014)

rTMS can alter EEG oscillations in the hours following stimulation. Reduced delta power in the DLPFC region of stimulation (Woźniak-Kwaśniewska et al., 2014) and in the contralateral DLPFC (Kamp et al., 2016) have been reported. Using the logic that increased right hemisphere low frequency oscillations altered in chronic mTBI are also correlates of reduced arousal state, and can be suppressed by rTMS, it was hypothesized that targeting the right prefrontal brain with rTMS could lead to increased arousal and improved cognition alongside a reduction in low frequency oscillations.

The objectives of this study were 1) provide preliminary data on efficacy of rTMS for poor cognition in TBI, 2) determine how EEG delta oscillations change with rTMS stimulation in TBI, and 3) determine the relationship between performance improvements and EEG delta oscillations.

Materials and methods

The present study was a single-center, prospective, sham-controlled, double-blinded, sequence randomized cross-over trial with one-week washout. All procedures were approved by the Institutional Review Boards of the McGuire VA Medical Center and Virginia Commonwealth University, and the trial was registered at clinical trials.gov with identifier NCT03642158.

Participants

Veterans and servicemembers receiving care within the McGuire VA were recruited from inpatient clinics and via mailings. Eligibility inclusion criteria were as follows: a history of mild to moderate TBI within the past 1-20 years, as determined by structured interview (Walker et al.), subjective cognitive difficulties as measured by a score >1 (mild level of impairment) on the TBI QOL Cognitive Concerns measure, stable medication use, aged between 18 and 65. Exclusion criteria were history of severe or penetrating TBI, of seizure in self or in family members, of severe neuropsychiatric illness, intracranial surgery, of skull fracture, current ferrous implant or implantable device, medications that reduce seizure threshold, and pregnancy. A total of twenty-eight participants were enrolled and began the study; twenty-six completed the study (see Figure 1). One participant withdrew after randomization due to headaches, and one due to non-study related medical issue.

Stimulation protocol

All participants received sham and active stimulation, but order of presentation (sham first week or active condition first week) was block randomized. The first week, each participant received once daily stimulation (or sham) sessions for each of 5 consecutive days. Stimulation protocol for each session was 10Hz stimulation for two seconds followed by no stimulation for 20 seconds, for a total duration of 20 minutes. Eight participants underwent an alternative schedule of 4 days of stimulation at 25 minutes, due to holiday and weather conflicts; the total time and pulse number was the same as the original schedule. Stimulation was set at 80% of each participant's resting motor threshold (RMT) for the first day, and 100% thereafter. Stimulation was applied using the NextStim NBS4 Figure-of-8 (double) coil system to the right dorsolateral prefrontal cortex, identified for each participant using structural magnetic resonance imaging at 3T (Philips Ingenia 3.0 Tesla Scanner). Sham stimulation consisted of stimulation set at 25% of RMT, and with the coil tilted 90 degrees from the scalp rather than perpendicular for the active stimulation. An eight-day washout period followed, after which the participant received the stimulation condition not received the first week. Stimulation condition, active versus sham, was known only to the technician applying stimulation. Both the participants and outcome assessors were blinded to the order of stimulation condition.

Measures

Neurocognitive measures were selected to address the primary cognitive domain of interest: attention control and learning. These included the Ruff 2 and 7 Selective attention test, the DKEFS Verbal Fluency Test, the California Verbal Learning test II. PTSD status was evaluated for each participant at baseline using Clinician administered PTSD scale 5 (CAPS-5). Participants self-administered the following symptom inventories: Neurobehavioral symptom inventory (NSI), Pittsburgh Sleep quality index (PSQI), Patient health questionnaire (PHQ-9), McGill Pain questionnaire short form, Traumatic brain injury

quality of life (TBI-QOL) Cognitive Concerns, Executive Function, Positivity, and Anxiety scales, and General Self-efficacy scale (GSE). Success of blinding was evaluated by questionnaire ("do you believe you received active or sham stimulation?").

Assessment took place at 5 time points: baseline, post-treatment for first condition (active or sham), pre-treatment for second condition, post-treatment for second condition, and at a two week follow up point (Figure 2).

EEG data collection and processing

EEG was collected from a 64-channel electrode cap with standard 10-20 system based layout using the Compumedics Neuroscan Synamps RT system. Baseline and pre-treatment EEGs were collected before stimulation, while post-treatment EEG was collected from participants 1-2 hours following rTMS. Data collection and processing were performed with Neuroscan Curry 7 software. Data were recorded at 500 Hz. All impedances were verified to be below 5 kΩ, except for occasional individual channels which were later removed from analysis. Participants were instructed to sit quietly with eyes closed for 10 minutes. Offline, data were baseline corrected, filtered with a low pass filter at 70 Hz and Hanning window, then reviewed visually for bad channels or motion artifact. Bad channels were removed using interpolation of 4 nearest channels, and motion artifacts were removed by deletion of the segment. Further artifacts were removed using an amplitude threshold filter set at +/-200 uV for all channels. At least 75 clean epochs (4 seconds in length) were required for inclusion; all sessions met this criterion. FFT was performed on retained epochs, and values were averaged over retained epochs to generate a power spectra. Power measures (uV^2) extracted from the spectra for the following frequency bands: delta (0.5-3.8 Hz), theta (4-7.8 Hz), alpha (8-12 Hz), beta (12.5-35 Hz) and gamma (35+ Hz); only results for delta are presented here.

Data Analysis

Data for participants who completed at least one assessment were included in analysis. For each neuropsychological test, specific scores were chosen a priori for statistical analysis from among the many outcome measures generated. Raw (unadjusted) scores were used for analysis. For neuropsychological test scores, symptom measures, and delta power, change scores were created for pre-post treatment differences for the sham and the active conditions. Nine 9 prefrontal, frontocentral, and lateral temporal sites were evaluated: FP1, FPz, FP2, F3, Fz, F4, T7, Cz, and T8. T-tests for change scores between active and sham conditions were performed. Post-hoc analyses were also conducted on between-treatment delta power changes 1-2 weeks after the cessation of the intervention. To test these post-hoc hypotheses, "elevation" change scores were computed as the difference between the session following the post-stimulation assessment and the post-stimulation assessment. Delta power "elevation" scores were evaluated using repeated measures ANOVA with factors of site and treatment. Greenhouse-Geisser corrections were employed for violations of sphericity. The relationship between symptom change and delta power elevation from last treatment session to next data collection session was evaluated using simple correlation.

Results

The demographics of the sample are shown in Table 1. Blinding was successful in that participants were only 50% accurate in guessing the stimulation protocol they had received.

Neuropsychological tests

Mean change and results of statistical tests for neurocognitive tests and symptom inventories are shown in Table 2. There were no significant group differences in neurocognitive performance for any of the measures tested. The Ruff 2 and 7 test exhibited an effect of time, attributable to practice effects as participants became faster and more accurate for both the automatic and controlled conditions.

Symptom measures

Four self-report measures exhibited significant improvement with active vs sham stimulation: PHQ-9, Executive Function, NSI, and the PSQI (see Figure X). Mean percent improvements relative to initial score were: PHQ-9: 9% (PHQ-9), 6% (EF), 15% (NSI), and 16% (PSQI).

The symptom measure improvement was maintained or continued to improve at the two week follow up (see Figure 3).

EEG power

There was no significant effect of stimulation on delta power change scores pre- and post-intervention at any of the 9 sites. However, delta power elevation in the session following the post-intervention assessment was observed. Post-hoc analysis showed that this delta power elevation was significantly higher in the active vs sham condition; there was a significant effect of treatment ($F_{(8,104)}$= 4.276, p=0.022) . Across all sites, delta power increased a mean of 13.190 uV^2 at the session recorded after the cessation of active stimulation, significantly different from sham at a mean of 0.188 uV^2, . There was a significant interaction between treatment and site ($F_{(8,104)}$=3.601, p=0.03), with the treatment effect on delta power increase observed only at prefrontal sites FP1, FPz, and FP2 (see Figure 4).

Symptom improvement for executive function and depression were not significantly related to the amount of delta power increase after the cessation of active stimulation. However, the size of the correlations varied substantially: for subjective executive function: R=0.408, p=0.117, and for depression, R=0.299, p=0.26, while for the NSI improvement R=0.003, p=0.992, and for Sleep R=0.033, p=0.90. Only 16/26 cases had complete EEG data for this analysis.

Discussion

No cognitive benefit

The present study failed to demonstrate a benefit for any neurocognitive measure for rTMS after TBI. This finding is in keeping with recent reports: a controlled study in severe TBI found no efficacy for cognition (Neville et al., 2019), neither was one found for mild to moderate TBI (Adamson et al., 2019). As described earlier, even in some larger studies of depression, no significant cognitive benefit is observed. This may be attributable to the heterogeneity of test types and domains and/or limited effect size if any. In a recent meta-analysis, tDCS and rTMS of DLPFC were both effective for working memory, while tDCS but not rTMS was effective for attention, and no effects of stimulation were observed in any other cognitive domain (executive function, processing speed, verbal fluency, verbal learning, and social cognition) (Begemann et al., 2020). Very small pooled effect sizes were reported for both techniques

(g<0.2). A corroborating meta-analysis addressed brain stimulation effects on the n-back working memory task specifically, and also found a significant but small pooled effect of around 0.2 (Brunoni & Vanderhasselt, 2014). These meta-analyses indicate that DLPFC stimulation selectively affects working memory tasks with a small effect, and so a test battery chosen to comprehensively evaluate cognition for safety purposes (e.g. Neville 2019) or simply focuses on other domains (e.g. Adamson 2019 and the present study) may miss these. This is perhaps not surprising considering the central role of the DLPFC in working memory (Barbey et al., 2013).

Measurement of cognitive effects of DLPFC stimulation may also be missed because some cognitive processes it mediates are not evaluated by standard neuropsychological tests. For instance, the right DLPFC is associated with cognitive insight or meta-cognition: "A more accurate level of trait/ability-based insight was related to increased signal change in the right anterior dorsal prefrontal cortex (PFC). The results suggest that one's post-injury level of self-referential insight is related to a network inclusive of the medial and right dorsal PFC." (Schmitz et al., 2006). "

Despite a lack of cognitive benefit, there is clinical significance in the present results. The present study is the first sham controlled study to report improvement in PCS symptoms – pilot studies were promising but lacked a control (Koski et al., 2014; Meek et al., 2021). Blinding in the present study was successful, and statistically significant improvements in PCS, sleep, depression, and executive function were observed in the active condition. The size of these improvements (from 9 to 16% of starting score) could be considered clinically significant. For the NSI, the amount of improvement was about half of that observed after 4weeks of inpatient rehabilitation (Dretsch et al., 2016), and subjective sleep improvements were similar to those observed with 16 weeks of moderate intensity exercise training (King et al., 1997). Further, it appeared that symptom levels remained at the improved level or continued to improve at the two week follow up assessment.

Despite not observing improvement in objective cognition, the improvement in subjective functioning may be clinically important. Across many studies of mTBI, neurobehavioral and psychological symptoms are elevated but are not well-correlated with neurocognitive performance. Subjective functioning is a midlife predictor of poor outcomes in aging. Additionally, the most prominent physiologic event-related brain signal in chronic mTBI is strongly associated with depression and anxiety symptoms (Franke et al., under review). Poor subjective functioning may be an indicator of reduced general ability rather than a specific cognitive domain impairment: subjective cognitive symptoms are more strongly related to global measures of cognitive performance rather than individual tests (Rijsbergen et al., 2017).

In conclusion, while no clear benefit for attention, learning, or executive function may be concluded, rTMS may benefit subjective well-being after mTBI, especially for those with PCS, depression, and/or sleep disorders.

EEG changes after rTMS.

We did not observe the predicted decrease in EEG power following active stimulation. We did observe a delayed increase, as well as significant symptom improvement, indicating that the lack of EEG change was not due to an excessively low dose of the intervention. Our hypothesis was not confirmed that rTMS would decrease EEG delta power, despite previously being demonstrated across a variety of stimulation frequencies (Woźniak-Kwaśniewska et al., 2014). One possible explanation is that the importance of stimulation parameters may be underappreciated. Even a small difference in stimulation parameters

(intensity of stimulation) elicited the opposite effect in a different study, increasing delta oscillations (Griškova et al., 2007).

Another potential factor may be the timing of the post-intervention recording. If the delta decrease is very short-lived (less than 30 minutes), then the changes may have been missed by recording more than 30 minutes after stimulation. The timing of the increase (1-2 weeks after cessation of active protocol) suggests the speculation that there was a temporary increase as hypothesized, yet we only observed its rebound. While a delta rebound this long after stimulation has not been reported previously, the 1-2 week EEG observation point after stimulation is not typical. In contrast, most EEG power shifts reported in the literature were assessed concomitantly or immediately following stimulation. Short delay EEG rebound effects after rTMS are known, however. One study reported a power change followed seconds later by an opposing rebound of EEG activity in connected cortical regions after M1 stimulation (Manganotti et al., 2013) across all frequency bands. Thus, EEG effects of rTMS are dynamic, evolving over time after stimulation.

The timeframe of the change observed in the present study is on the timescale (days to weeks) of synaptic long-term potentiation and so may be a network level summation of this process. Indeed, induction of hippocampal LTP is correlated with changes to low frequency cortical EEG in experimental animals (Whitlock et al., 2006). Additionally, low frequency cortical EEG oscillations are related to general neuronal inhibitory processes (Contreras & Steriade, 1995), and so the effect may be a late rebound of cortical inhibition after rTMS 10 Hz excitation.

Intriguingly, in a previous study where EEG was collected a median of 4 hours after rTMS stimulation, the investigators also observed a power increase (delta, theta, and alpha) that was correlated with clinical improvement in depression (Noda et al., 2013). The present study observed a similar pattern with noteworthy correlations between depression and executive function symptom improvement and delta power increase; while these were nonsignificant, the small sample size of complete EEG data may have led to type 2 error. The present study thus provides corroborating evidence that delta-band oscillations play a role in emotional-psychological state, and so may be important biomarkers of the therapeutic effect of rTMS that appears to center on well-being. This is consistent with a broader literature linking delta oscillations with approach/avoidance mechanisms such as motivation (Knyazev, 2012), reward (Cavanagh, 2015), and placebo analgesia (De Pascalis & Scacchia, 2019). In addition to these emotion-motivation processes, delta waves increase with cognitive processes that share the domain of internal representation: inward-directed attention and working memory (Harmony, 2013). Because no improvements in the neuropsychological measures of attention were observed, no conclusions concerning the relationship between the rTMS dependent delta band changes and attention and learning can presently be made, but further analyses are planned to address these issues in more depth.

While previous studies of rTMS in TBI have failed to support cognitive benefits, evidence suggests that the intervention can alter brain structure. In one study there may have been an alteration in propensity for neural growth as measured by levels of brain-derived neurotrophic factor (BDNF) (Adamson et al., 2019). BDNF genetic polymorphisms impact brain stimulation response (Cheeran et al., 2008; Kleim et al., 2006). Also, a TMS paradigm designed to assess neuroplasticity in the DLPFC revealed that depressed patients exhibited weaker neuroplastic changes than non-patients (Noda et al., 2018). There is reason to believe that the elevated resting delta observed after rTMS in the present study may be an indicator of

neuroplastic processes. A BDNF polymorphism associated with reduced neuroplastic response after motor training (valmet66; (Kleim et al., 2006), is associated with EEG power abnormalities; specifically elevated resting low frequency activity (Gatt et al., 2008; Soltész et al., 2014). A recent review details findings of EEG delta waves being altered in several paradigms of normal and pathophysiological neuroplasticity (Assenza & Di Lazzaro, 2015). The delta rebounds observed in Manganotti et al (Manganotti et al., 2013) were in brain regions connected to the stimulation regions, suggesting Hebbian (coincident activity dependent) neuroplasticity.

Irrespective of the underlying mechanism, the timing of the delta increase suggests long term alterations in large scale cortical oscillations may underlie the therapeutic effects of rTMS. Therapeutic effects may continue to gain at the same interval (two weeks later). The effect and its hypothesized neuroplasticity correlates should be replicated/established in future studies. In conclusion, the present study did not find evidence of neuropsychological benefit for rTMS after TBI. However, subjective improvements in cognition and PCS, as well as EEG changes theoretically linked to neuroplasticity were observed, supporting the promise of the intervention for rehabilitation research. Continued study is warranted.

Acknowledgments

Funding for this study was provided by the Virginia Department of Aging and Rehabilitative Services Commonwealth Neurotrauma Initiative Fund, award # A262-76756. The authors wish to thank the study participants, as well as Sheryl Underwood, Padraic Flynn, and Tiffany Lewis for their efforts in recruitment and data collection.

declaration of interest statement

The authors report no conflict of interest.

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Tables

Table 1: Demographics and baseline symptom and neuropsychological test scores. Baseline scores include all randomized participants. Values in bold indicate significant group differences at p<0.05 (no measures were different between groups at baseline).

	Overall	**A**	**B**
n	28	14	14
Age	45.57 (10.01)	45.07 (11.31)	46.07 (8.92)
Gender (%)			
missing	1 (3.6)	0 (0.0)	1 (7.1)
Female	3 (10.7)	1 (7.1)	2 (14.3)
Male	24 (85.7)	13 (92.9)	11 (78.6)
Race (%)			
American Indian or Alaska Native	2 (7.1)	2 (14.3)	0 (0.0)
Asian	1 (3.6)	1 (7.1)	0 (0.0)
Black / African American	11 (39.3)	4 (28.6)	7 (50.0)
Other	4 (14.3)	1 (7.1)	3 (21.4)
White	10 (35.7)	6 (42.9)	4 (28.6)
Ethnicity (%)			
Not Hispanic or Latino	24 (85.7)	11 (78.6)	13 (92.9)
College graduate (%)	14 (50.0)	8 (57.1)	6 (42.9)
Time since worst injury in years (mean (SD))	12.04 (6.80)	11.43 (3.50)	12.64 (9.11)
TBI QOL Cognitive Concerns (mean (SD))	27.96 (8.85)	27.50 (9.36)	28.43 (8.63)
Headaches (mean (SD))	22.04 (10.24)	22.07 (10.16)	22.00 (10.71)
Fatigue (mean (SD))	27.68 (10.04)	28.00 (10.61)	27.36 (9.83)
TBI QOL Executive Function (mean (SD))	35.75 (8.43)	34.14 (8.71)	37.36 (8.14)
TBI QOL Anxiety (mean (SD))	23.04 (8.80)	24.14 (9.73)	21.93 (7.96)
TBI QOL Positivity (mean (SD))	32.07 (7.69)	33.21 (7.69)	30.93 (7.80)
NSI (mean (SD))	30.04 (15.78)	31.00 (17.27)	29.07 (14.73)
TBI QOL Emotional Control (mean (SD))	22.36 (7.22)	22.21 (7.90)	22.50 (6.76)
PSQI (mean (SD))	19.21 (7.09)	20.21 (7.98)	18.21 (6.20)

PHQ-9 (mean (SD))	10.07 (5.33)	10.64 (5.88)	9.50 (4.88)
McGill Pain (mean (SD))	12.57 (7.19)	13.29 (7.49)	11.86 (7.08)
GSE (mean (SD))	30.79 (5.98)	30.50 (6.41)	31.07 (5.76)
Ruff Automatic Detection Speed TScore (mean (SD))	46.14 (10.26)	43.86 (9.55)	48.43 (10.78)
Ruff Automatic Detection Accuracy TScore (mean (SD))	45.96 (10.98)	44.93 (12.17)	47.00 (9.98)
Ruff Controlled Detection Speed TScore (mean (SD))	44.57 (10.35)	41.79 (8.72)	47.36 (11.39)
Ruff Controlled Accuracy TScore (mean (SD))	44.94 (11.86)	41.92 (14.20)	50.36 (7.24)
CVLT Trial 1-5 Learning TScore (mean (SD))	47.79 (12.07)	47.50 (14.20)	50.5 (9.84)
DKEFS Letter Fluency Standard Score (mean (SD))	10.89 (3.15)	11.07 (2.59)	11.29 (3.73)

Table 2: Results of Neurocognitive test and symptom change scores and t-tests of interventions.Values in bold indicate significant group differences at p<0.05.

	Active Mean	Sham Mean	Difference between conditions	t	p
Ruff Controlled Detection Speed	6.77	11.35	-4.58	-0.9	0.3776
Ruff Controlled Detection Accuracy	0.14	0.02	0.17	0.3	0.7977
Ruff Automatic Detection Speed	8.89	10.58	-1.69	-0.4	0.6613
Ruff Automatic Detection Accuracy	0.41	0.49	-0.08	-0.1	0.9415
CVLT-II 1-5 Learning	-3.2	6	2.85	1.2	0.2439
DKEFS Letter Fluency	0.23	0.46	-0.462	-0.3	0.7764
Cognitive Concerns	4.96	3.5	2.19	1.4	0.1749
Headaches	-2.08	-1.73	-0.35	-0.2	0.8335
Fatigue	-2.08	-0.7	-1.38	-0.9	0.3647
Executive Function	**2.23**	**-0.23**	**2.46**	**2.1**	**0.0437**
Anxiety	-2.11	-0.65	-1.46	-1.2	0.2278
Positivity	2.54	2.04	0.5	0.5	0.6237
NSI	**-4.5**	**-0.31**	**-4.19**	**-2.3**	**0.03**
Emotional Control	-2.73	-1.69	-1.04	-12	0.2461
PSQI	**-3**	**0.23**	**-3.23**	**-2.4**	**0.0248**
PHQ-9	**-1**	**-0.12**	**-0.96**	**-2.21**	**0.0367**
McGill Pain	-2.69	-0.85	-1.85	-1	0.3121
GSE	1.35	0.38	0.96	1.5	0.1446

Figures

Figure1: CONSORT Diagram

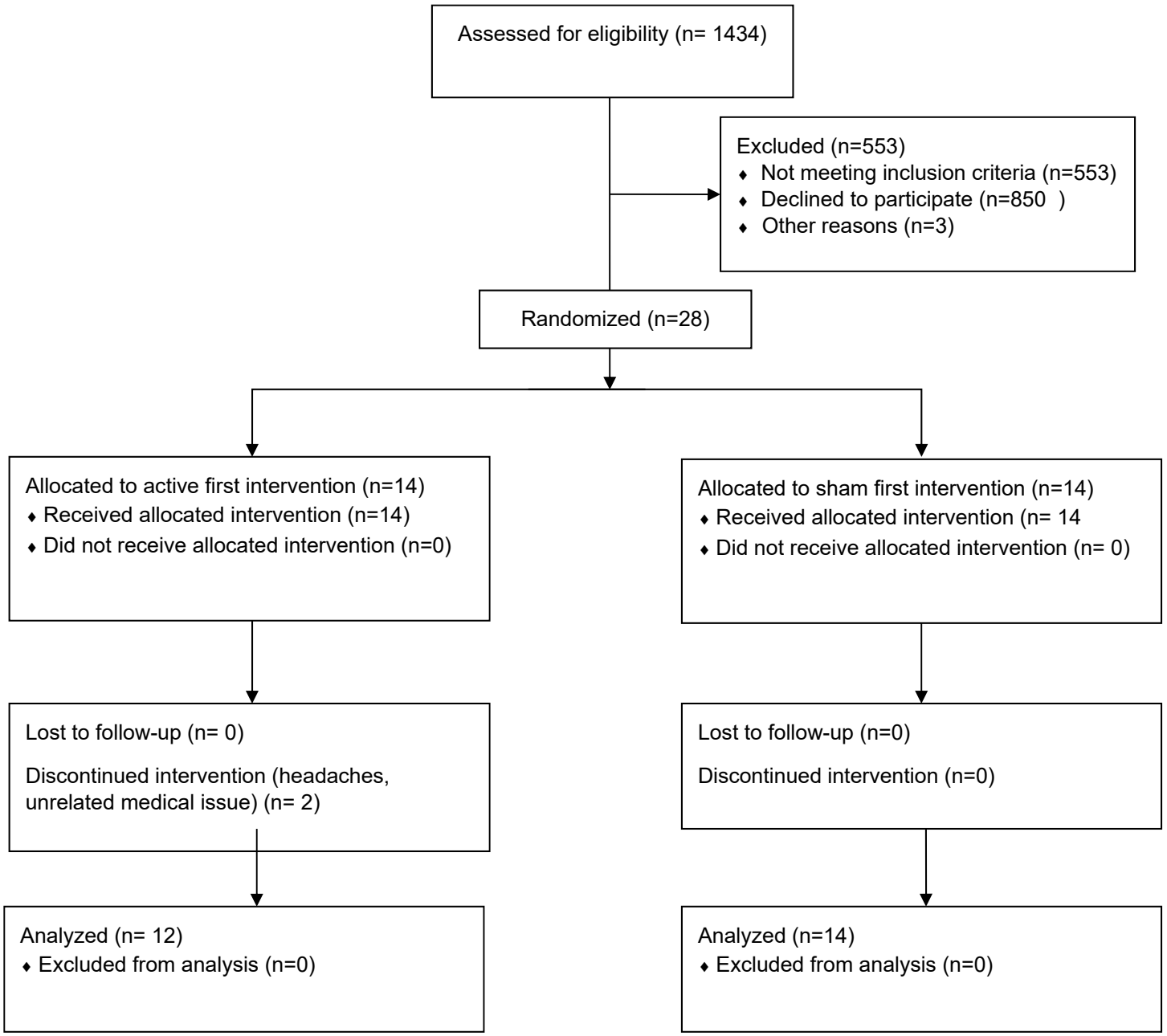


Figure 2: Study Design

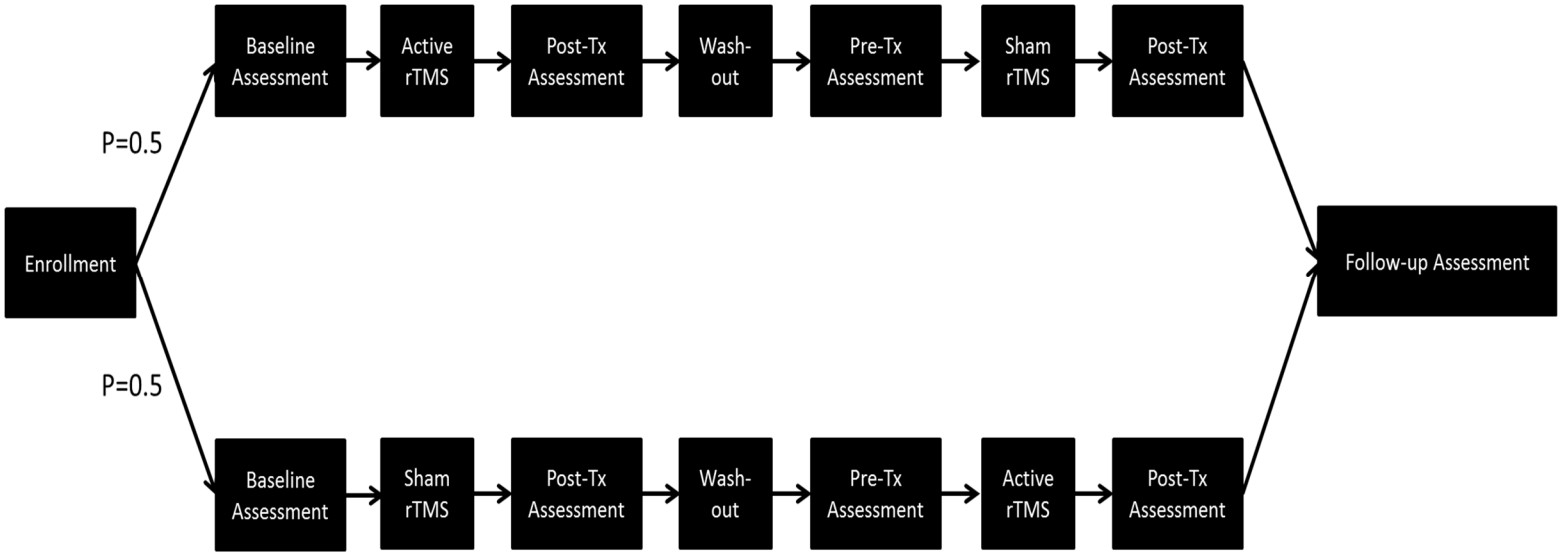
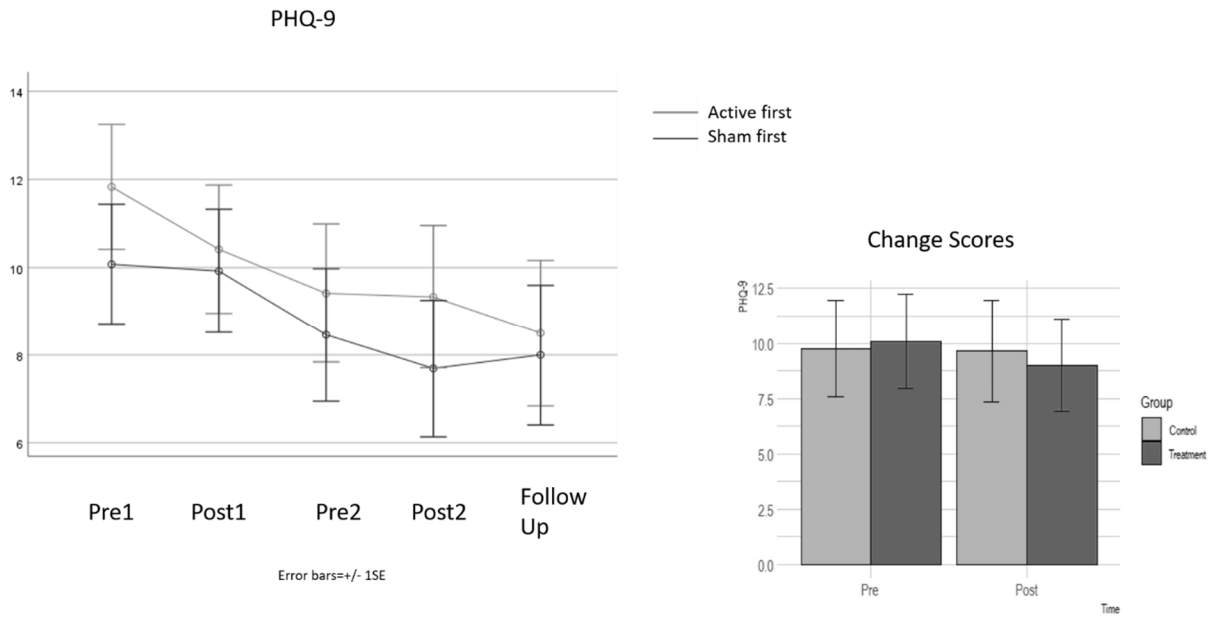


Figure 3: Symptom by treatment effects

A.



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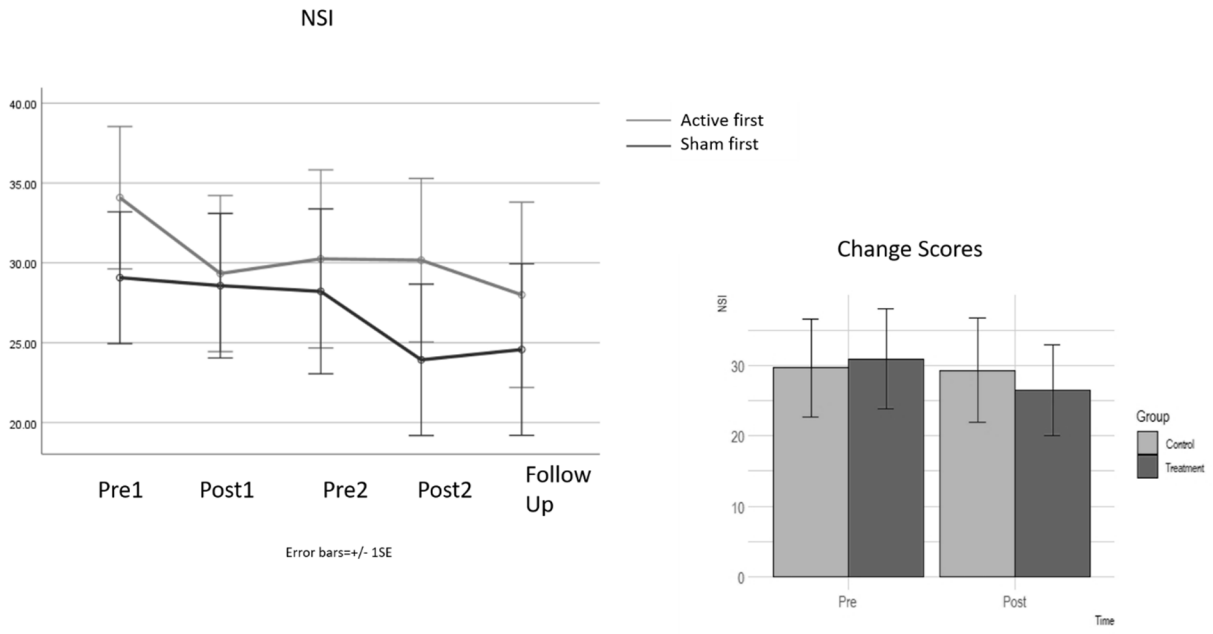
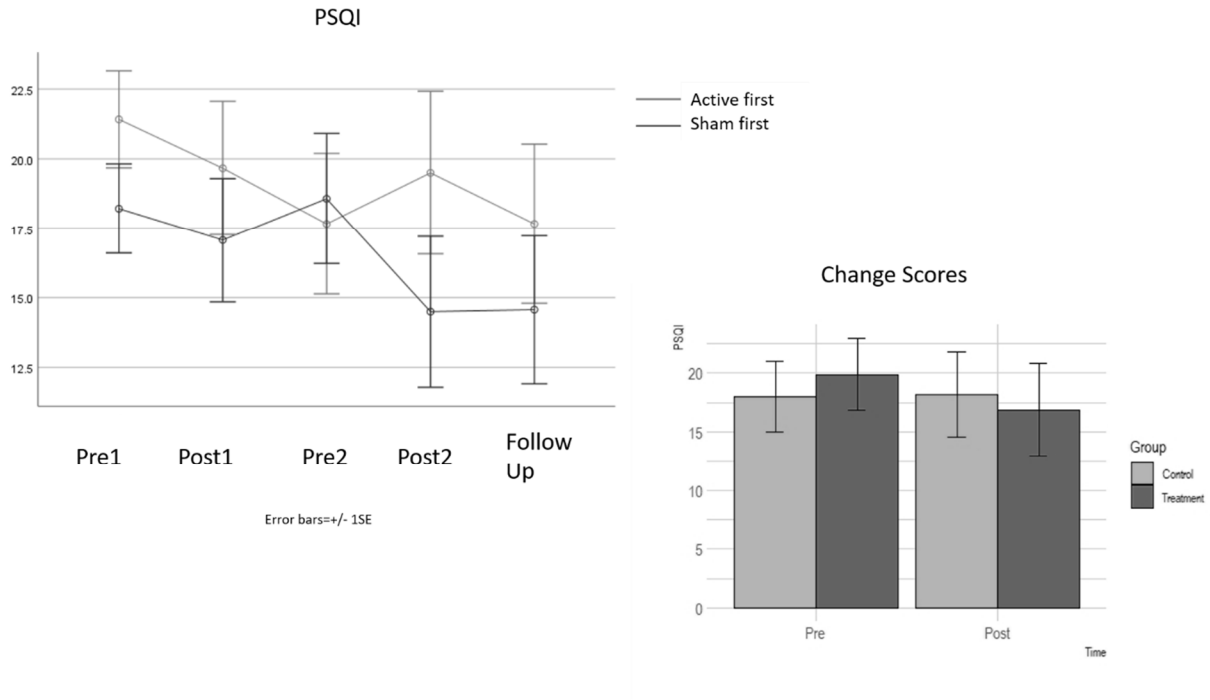


C.


PSQI
22.5
20.0
17.5
15.0
12.5
Pre1
Post1
Pre2
Post2
Follow Up
Error bars=+/- 1SE
Active first
Sham first
Change Scores
PSQI
20
15
10
5
0
Pre
Post
Time
Group
Control
Treatment

D.

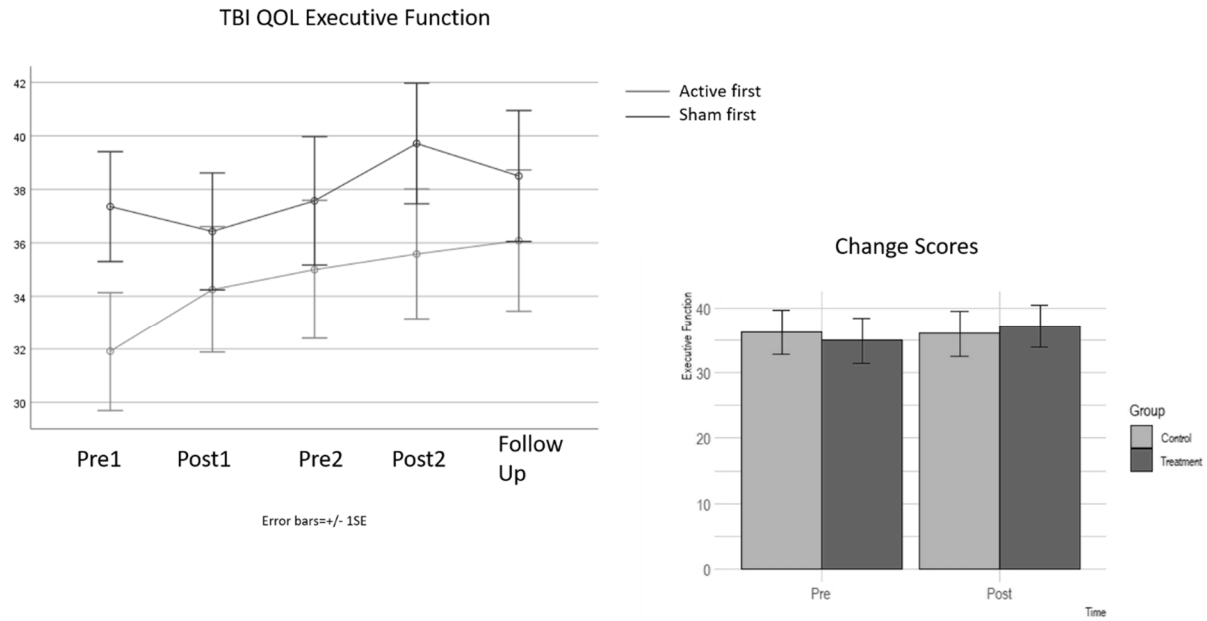

TBI QOL Executive Function
42
40
38
36
34
32
30
Pre1
Post1
Pre2
Post2
Follow Up
Error bars=+/- 1SE
Active first
Sham first
Change Scores
Executive Function
40
30
20
10
0
Pre
Post
Time
Group
Control
Treatment

Figure 4: Delta Power Change across sites, 1-2 weeks after the intervention

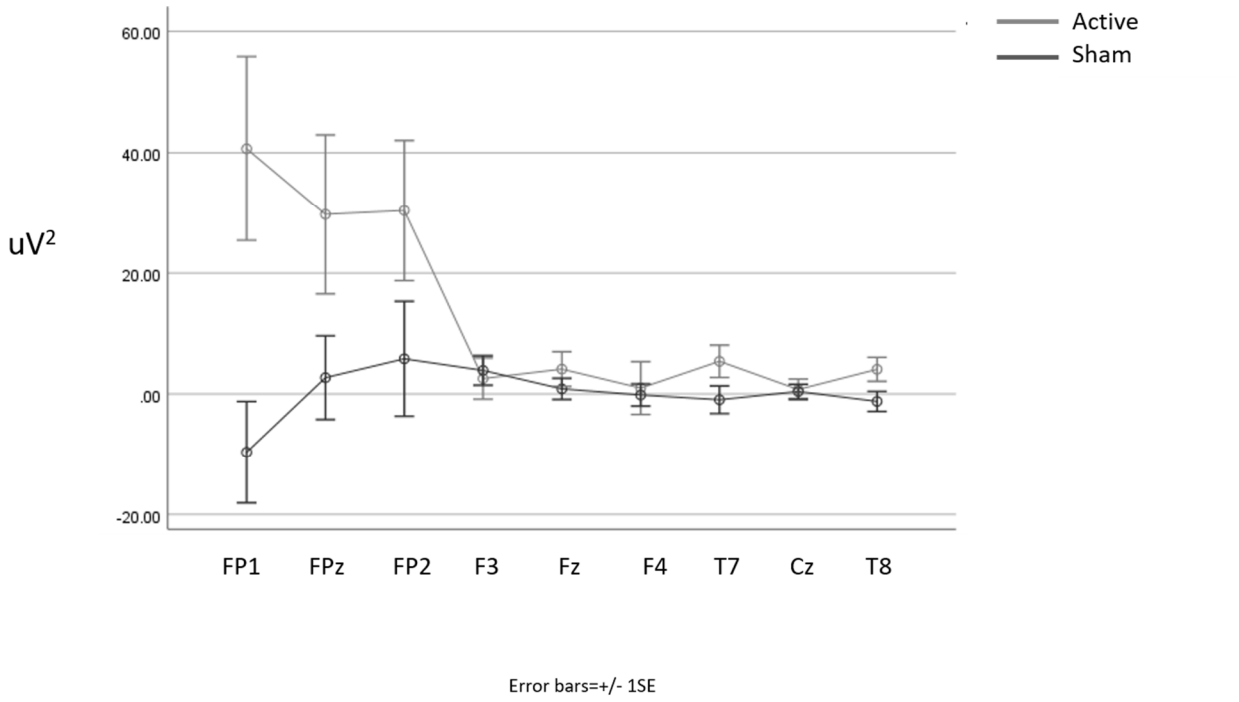


Figure Captions

Figure 2: Study Design. Stimulation/sham sessions consisted of 20 minutes at 10Hz stimulation, once per day for 5 days. Washout was 1 week, and follow-up assessments were conducted 2 weeks after the second phase of the intervention.

Figure 3: Symptom by treatment effects. Four symptom measures exhibited a significant benefit of active over sham rTMS. A) PHQ-9, b) Neurobehavioral Symptom Inventory, C) PSQI, and D) TBI-QOL Executive Function. For all scores, lower scores indicate improvement, except for Executive Function, where higher scores indicate improvement.

Figure 4. Delta power change across sites. Delta power at the post-intervention session was subtracted from the power at the next assessment session (either the pre-intervention assessment for the second phase or the follow-up assessment, depending on assigned arm). Delta power increased over the post-intervention period, with greatest gains in prefrontal sites FP1, FPz, and FP2.