Journal of Neurotrauma

DOI: 10.1089/neu.2019.6692

Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial.

Authors:

Joan Stilling, MD, MSc[1,2,3] , Eric Paxman, MSc [1,4] , Leah Mercier[1,2] , Liu Shi Gan, PhD [1,2] , Meng Wang, MSc [1,2] , Farnaz Amoozegar, MD, MSc, FRCPC [1,2,3] , Sean P. Dukelow, MD, PhD, FRCPC [1,2,3] , Oury Monchi, PhD[1,2,3] , Chantel Debert, MD, MSc, FRCPC [1,2,3]

Affiliations:

[1] University of Calgary, Calgary, Alberta, Canada

[2] Hotchkiss Brain Institute, Calgary, Alberta, Canada

[3] Department of Clinical Neurosciences, Cumming School of Medicine, Calgary, Alberta, Canada

[4] University of Alberta, Department of Medicine, Edmonton, Alberta, Canada

Corresponding Author:

Joan Stilling, MD, MSc: joan.stilling@ahs.ca

Department of Clinical Neurosciences,

Division of Physical Medicine and Rehabilitation,

University of Calgary,

1403-29 St. NW Calgary, AB, Canada T2N 2T9

Ph: 587-894-0660

Co-Authors:

Eric Paxman: epaxman@ualberta.ca

Department of Medicine, University of Alberta,

13-103 Clinical Sciences Building,

11350 – 83 Avenue, Edmonton, AB, Canada T6G 2G3

Ph: 403-915-5625

Leah Mercier: leah.mercier@mail.mcgill.ca

Department of Clinical Neurosciences,

University of Calgary,

1403-29 St. NW Calgary, AB, Canada T2N 2T9

Ph: 403-944-5358

Liu Shi Gan: liushi.gan@ahs.ca

Hotchkiss Brain Institute,

HSC 2954, 3330 Hospital Dr NW, Calgary, AB, Canada T2N 4N1

Ph: 403-220-2807

Meng Wang: meng.wang1@ucalgary.ca

Department of Clinical Neurosciences,

University of Calgary,

3280 Hospital Drive NW Calgary, AB, Canada T2N 4Z6

Ph: 403-210-7210

Farnaz Amoozegar: farnaz.amoozegar@ahs.ca

Department of Clinical Neurosciences,

Division of Neurology,

University of Calgary,

South Health Campus, 4th Floor, Rm 480043,

4448 Front Street S.E. Calgary, AB, Canada T3M 1M4

Ph: 403-956-2460

Fax:403-956-2992

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Sean P. Dukelow: sean.dukelow@ahs.ca
Department of Clinical Neurosciences,
Division of Physical Medicine and Rehabilitation,
University of Calgary,
3330 Hospital Dr. NW, Calgary, AB, Canada T2N 4N1
Ph: 403-944-2368

Oury Monchi: oury.monchi@ucalgary.ca
Hotchkiss Brain Institute,
Department of Clinical Neurosciences and Radiology,
University of Calgary,
3330 Hospital Dr. NW, Calgary, AB, Canada T2N 4N1
Ph: 403-220-8048

Chantel Debert: chantel.debert@ahs.ca
Department of Clinical Neurosciences,
Division of Physical Medicine and Rehabilitation,
University of Calgary,
1403-29 St. NW Calgary, AB, Canada T2N 2T9
Ph: 403-944-1580

Running title: rTMS for persistent post-traumatic headache.

Table of Contents title: Treatment of persistent post-traumatic headache using rTMS: a pilot RCT.

Abstract word count: 299[1]

[1] The results from this study were presented by author J.S. (oral conference lecture) at the 13th World Congress on Brain Injury, International Brain Injury Association, Toronto, Canada, March 2019, and an abstract is available in the conference proceedings. [53]

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Number of tables/figures: 7

Number of references: 53

Supplementary Data: Consort Checklist

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

ABSTRACT

Persistent post-traumatic headache (PTH) following mild traumatic brain injury (mTBI) is one of the most prominent and highly reported persistent post-concussion symptoms (PPCS). Non-pharmacologic treatments, including non-invasive neurostimulation technologies, have been proposed for use. Our objective was to evaluate headache characteristics at one-month following repetitive transcranial magnetic stimulation (rTMS) treatment in participants with PTH and PPCS. A double-blind, randomized, sham-controlled, pilot clinical trial was performed on twenty participants (18-65 years) with persistent PTH (ICHD-3) and PPCS (ICD-10). Ten sessions of rTMS therapy (10Hz, 600 pulses, 70% resting motor threshold amplitude) were delivered to the left dorsolateral prefrontal cortex (DLPFC). The primary outcome was a change in headache frequency or severity at one-month post-rTMS. Two-week long daily headache diaries and clinical questionnaires assessing function, PPCS, cognition, quality of life, and mood were completed at baseline, post-treatment, and at one-, three-, and six-months post-rTMS. A two-way (treatment x time) mixed ANOVA indicated a significant overall time effect for average headache severity [$F(3,54)= 3.214$, $p=0.03$] and a reduction in headache frequency at one-month post-treatment (#/two-weeks: REAL -5.2 (SD=5.8), SHAM -3.3 (SD=7.7)). Secondary outcomes revealed an overall time interaction for headache impact, depression, post-concussion symptoms, and quality of life. There was a significant reduction in depression rating in the REAL group between baseline and one-month post-treatment, with no change in the SHAM group (PHQ-9; REAL -4.3 (SD=3.7, $p=0.020$), SHAM -0.7 (SD=4.7, $p=1.0$), Bonferroni corrected). In the REAL group, 60% returned to work while only 10% returned in the SHAM group ($p=0.027$). This pilot study demonstrates an overall time effect on headache severity, functional impact, depression, PPCS, and quality of life following rTMS treatment in participants with persistent PTH, however, findings were below clinical significance thresholds. There was a 100% response rate, no dropouts, and minimal adverse effects, warranting a larger phase II study. Clinicaltrials.gov: NCT03691272. **Key Words:** transcranial magnetic stimulation, post-traumatic headache, post-concussion syndrome, brain trauma, randomized controlled trial.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

INTRODUCTION

It is estimated that 2.8 million people in the United States experience a traumatic brain injury (TBI) annually.[1] Up to 90% of these treated brain injuries are classified as mild (mTBI).[2,3] Patients with mTBI may experience a number of symptoms, such as headaches, fatigue, insomnia, anxiety, depression, and cognitive deficits, which typically resolve within three months following injury. However, recent data suggests that more than 40% of patients will experience persistent post-concussive symptoms (PPCS) beyond the three-month period, which contribute to significant functional impairment and disease burden.[4] These symptoms persist up to one year in 80% of participants with PPCS and greater than 20% remain functionally impaired.[5] To date, current treatment for PPCS entails symptom-based management with medications, physical therapy, behavioral interventions, and lifestyle modifications based on evidence-based therapies. However, despite current management approaches, many individuals continue to experience ongoing symptoms. Consequently, there is a significant need for new treatments targeted at improving functional impairment and reducing disease burden associated with PPCS.

Persistent headache attributed to traumatic injury to the head (ICHD-3), also referred to as persistent post-traumatic headache (PTH), is the most common and often the most prominent symptom in PPCS.[6] Persistent PTH can remain beyond five years following injury, significantly impacting daily activities.[7] In a prospective cohort study by Lucas et al., there was a 91% cumulative incidence of headache over the course of a year following mTBI.[8]

The pathophysiology of persistent PTH is poorly understood. Defrin et al. reported how damage to cortical pain modulation systems and central sensitization may be contributing factors to the development of persistent PTH.[9] Another study by Leung et al. proposed that alterations in pain modulation in participants with persistent PTH may be related to a functional connectivity deficit in the prefrontal cortex,[10] while a study performed by Obermann et al. demonstrated gray matter changes in the prefrontal cortex.[11] Specifically, decreased gray volume was observed in the DLPFC and anterior cingulate in participants with chronic PTH after three months.[11] They reported subsequent improvement in volume at one year, which correlated with symptom resolution. This suggests that the DLPFC may play a role in the pathophysiology of PTH.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

One potential approach for treating persistent PTH involves using non-pharmacologic interventions, such as neuromodulation therapy, which has the goal of normalizing cortical activity. Repetitive transcranial magnetic stimulation (rTMS) is one such method currently being explored as a treatment option.[12-14] TMS is a non-invasive neurostimulation procedure in which cerebral electrical activity is influenced by a pulsed magnetic field. The magnetic field is generated by an electric current briefly passing through a copper-wire coil. When this coil is placed on the head, its magnetic field induces small currents in an area of the brain directly under the coil. In rTMS, repeated single magnetic pulses of similar intensity are delivered over a targeted brain region. Numerous studies using rTMS to treat other central nervous system disorders such as stroke,[15] addiction,[16] and depression[17] have shown much promise. In the United States, TMS is currently FDA approved for prevention and acute treatment of migraine with aura[18] and treatment-resistant depression.[17,19]

The pathophysiological mechanism of action for treatment of persistent PTH remains largely unknown, despite studies suggesting rTMS may be an efficacious treatment for PTH.[12,13,20] However, looking at primary headache literature, Brighina et al. demonstrated high frequency rTMS over the left DLPFC for participants with chronic migraine to be superior to placebo in reducing headache frequency.[21] They suggested that rTMS may relieve migraines through sustained changes in neuronal excitability or modulation of neurotransmitters and subsequent suppression of central pain perception. Another study, employing rTMS to the left DLPFC in treatment resistant depressed participants, reported an increase in gray matter volume in areas involved in decision making and emotional experience.[22] This suggests that rTMS may have an influence on changes in brain architecture; however, the exact pathophysiology of neuromodulation is still unidentified.

Consequently, there was an opportunity to look specifically at the effect of rTMS in the treatment of persistent PTH. We hypothesized that rTMS to the left DLPFC in participants with persistent PTH and PPCS would lead to an improvement in headache parameters (i.e. frequency, severity), and other post-concussion symptoms such as cognition, mood, function, and quality of life.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

MATERIALS AND METHODS

A double-blind, sham-controlled, randomized pilot clinical trial was completed from May 2017- September 2018. Twenty participants aged 18-65 years were recruited from the Calgary Brain Injury Program (CBIP), Calgary Headache Assessment and Management Program (CHAMP), and Calgary Chronic Pain Centre (CPC), in Calgary, Alberta, Canada from May 2017 – February 2018 (**Figure 1**). The study was approved by the University of Calgary Conjoint Health Research Ethics Board (REB16-2377). Trial protocol was registered on clinicaltrials.gov under NCT03691272. Written informed consent was obtained from all participants.

Inclusion criteria

Participants aged 18-65 years old, with a diagnosis of persistent headache attributed to traumatic injury to the head based on the ICHD-3 criteria and PPCS based on the ICD-10 criteria for at least three months to a maximum of five years were included. They had to be stable on preventative headache pharmacologic medication doses prior to starting the treatment protocol and could not change management throughout the intervention.

Exclusion criteria

Subjects were excluded if they had a prior history of TMS therapy, TMS-related contraindications (i.e. pacemaker, metallic implant), history of chronic headache (≥15 days/month for >3 months) or migraine (ICHD-3) prior to most recent trauma, other medical conditions such as structural brain disease, previous seizure, psychotic disorders (i.e. schizophrenia, bipolar disorder), liver or kidney disease, malignancy, uncontrolled hypertension or diabetes, and pregnancy. Prescribed pharmacologic management was not altered from baseline to 3 months following treatment (i.e. tricyclic antidepressants, anti-seizure medications, opioids), however subjects were permitted to take PRN or "as needed" medications (i.e. triptans, acetaminophen, non-steroidal anti-inflammatories) throughout the study with documentation in a daily headache diary. Participants undergoing onabotulinumtoxinA (Botox) treatment underwent rTMS intervention six to eight weeks following their injection, which is around the time of peak Botox efficacy[23] and one month prior to their next scheduled Botox dose.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

CLINICAL ASSESSMENTS

Demographic information was collected two to four weeks prior to starting the study, including age, sex, education, past medical history, medication use, allergies, social and family medical history (**Table 1**). TBI history, in accordance with World Health Organization (WHO) criteria[24] for mild TBI, was obtained. Headache history was collected including frequency, severity, medication-use, quality of headache, associated symptoms (i.e. neck pain, photophobia, phonophobia, nausea, vomiting) and headache triggers.

The primary outcome was defined as a change in headache frequency or severity at 1-month post-treatment. This was determined through a two-week headache diary, which was completed by participants before treatment, during treatment, following rTMS, and at the one-, three-, and six-month follow up assessments (twelve weeks total diary). Headache frequency was documented as a headache being present in the morning, afternoon, or evening each day. Summing these frequencies accounted for a maximum possible total of forty-two headaches/two-weeks. Headache severity was graded based on the numeric pain rating scale (NPRS), which is an 11-point scale from 0-10, where "0" indicates no pain and "10" suggests the most severe pain imaginable. Severity was only documented when a headache was present. Baseline questionnaires, assessing secondary outcomes, included the headache impact test – 6 (HIT-6), Rivermead PPCS questionnaire (RPSQ), British Columbia post-concussion symptom inventory (BC-PSI), Montreal cognitive assessment (MoCA), quality of life after brain injury questionnaire (QOLIBRI), participant health questionnaire-9 (PHQ-9), generalized anxiety disorder scale-7 (GAD-7) and the post traumatic stress disorder checklist for DSM-5 (PCL-5). Participants were reassessed at the completion of their rTMS treatment (day 14), and at one-, three-, and six-months post-treatment. The questionnaires including: HIT-6, Rivermead PPCS questionnaire, BC-PSI, MoCA, QOLIBRI, PHQ-9 and GAD-7 were completed at all follow-up visits.

Randomization and Blinding

Participants were randomized with a computer random number generator to receive either REAL or SHAM rTMS. Allocation, performed by an independent research assistant, was concealed using opaque, sequentially numbered, sealed envelopes. All individuals involved in the study, except research assistants administering the rTMS (Authors E.P.,

L.M., L.G.), were blinded to the treatment protocol. Investigators involved in the generation of random sequences, participant recruitment (J.S., C.D.), follow up assessments (J.S.), and data analysis (M.W., J.S.) were blinded. Investigators and participants were unblinded when all twenty participants had competed their six-month follow up visit and all data had been collected.

TMS PROTOCOL

Participants engaged in a two-week treatment protocol. Sessions were delivered at the same time once a day, from Monday to Friday, for a total of 10 sessions. A Magstim Super Rapid2 (Magstim, UK) stimulator connected to a figure-of-eight cooled air-film coil was used. Electromyography (EMG) electrodes were attached to the right abductor digiti minimi (ADM) muscle. The TMS stimulation coil was placed over the left motor cortex (M1), and the optimal location for activation of the ADM muscle and resting motor threshold (RMT) was determined. The RMT was defined as the minimal single TMS pulse stimulation intensity required to elicit motor-evoked response of 50 microvolts peak-to-peak amplitude in at least five out of ten consecutive trials of the ADM (contralateral to stimulation).[25] Participant clinical anatomical T1 weighted MR brain scans were loaded and processed using TMS neuronavigation software (Brainsight2, Rogue, Montreal). To find the left DLPFC, Montreal Neurologic Institute (MNI) coordinates (mid-DLPFC: x = -48; y = 20; z = 34) were used.[26] Stereotaxic data for localization of the TMS stimulation site was determined through a co-registration method between the TMS coil position and the projected site on the MR brain scan. Once the left DLPFC was localized, an inverse version of the native-to-stereotaxic transformation matrix reverted the MRI images to the participant's native brain coordinate space. When MRI was not available (3 participants), a standardized average brain with MNI coordinates was used for navigation[2]. The air-cooled 70-mm rTMS coil was placed tangentially at 45° over the left DLPFC target. Stimulation was completed at 10 Hz and 70% RMT amplitude for a total of 600 pulses (10 trains of 60 pulses/train, 45 second inter-train interval (ITI)).[27-33] In the SHAM condition, a SHAM air-film coil was applied to the scalp after the RMT was determined, using the same location,

[2] Post-hoc validation between patient MRI and MNI atlas coordinates revealed a maximum 1 cm difference between localization methods.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

localization method, and stimulation protocol (10Hz, 600 pulses, 45s ITI). Participants were able to hear the sound and feel the vibration of the SHAM coil. Previous studies have demonstrated efficacy of the blinding method used.[34] To monitor for adverse effects, participants filled out a TMS tolerability questionnaire immediately before and after each treatment session.

Statistical Analysis

The present study examined a convenience sample of 20 participants (10 REAL, 10 SHAM) recruited through poster advertisements in hospital clinics and from patient encounters in the Calgary brain injury, headache, and chronic pain programs. Baseline sample characteristics were assessed using descriptive statistics and frequency distributions. Chi-square tests, Fisher's exact tests, and Wilcoxon-Mann-Whitney tests were used to compare the REAL and SHAM groups wherever appropriate. Two-way (treatment × time) mixed Analysis of Variance tests were performed at the primary endpoint of one month to determine if there were treatment (REAL and SHAM) by time interaction effects, time effects, and group effects for continuous outcomes (headache severity, function, post-concussion symptoms, depression, and quality of life). When the normality assumption was violated, only descriptive analyses were conducted (headache frequency, cognition, anxiety, PTSD). Results were considered statistically significant with a p-value of less than 0.05. Simple effects testing using a Bonferroni correction was performed when a significant group by time interaction was detected. Integrity of blinding was assessed through a chi-squared test and Bang's blinding index.[35] Analyses were conducted with guidance from biostatisticians (Authors M.W. and T.F.) using SPSS v 25. Individual participant de-identified data can be provided by request to qualified investigators.

RESULTS

Sample Characteristics

All pre-defined outcome data was obtained for the twenty participants. There were no dropouts. The average age of our group was 36.0 (SD=11.4) years. The majority were female (18/20; 90%) and living in urban centres (19/20; 95%). Educational level varied from less than grade 12 to post-graduate training. Eight participants were on disability

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

insurance (seven long-term, one short-term). The majority of subjects sustained their injury secondary to motor vehicle collisions (9), while sports (6), falls (2), and other (2) accounted for the remainder. The average number of previous concussions was 2.06 (SD=1.16) and the average time from the most recent concussion was over 2.5 years [32.5 (SD=13.9) months]. Headache features were mixed in nature, with all subjects demonstrating migrainous features[3] (20/20), some having neck pain characteristics (11/20), and the remainder reporting tension type features[4] (4/20). There were no statistically significant differences between the REAL and the SHAM groups for any of the baseline demographic or clinical outcome characteristics (**Table 1**).

Primary Outcomes

The primary outcome was defined as a change in headache frequency or severity at one-month post-intervention. Results from a two-way (time x treatment) mixed ANOVA are reported in **Table 2**. Headache frequency, cognition, anxiety, and PTSD outcomes were not included in the analysis as residual distributions analyzed after the two-way mixed ANOVA assessment were non-normal.

A two-way (time × treatment) mixed ANOVA demonstrated a statistically significant overall time effect for headache severity at the primary outcome time point (one-month) with $F(3,54)=3.214$, $p=0.030$ (**Table 2**). Between baseline and one-month assessment, the average severity of the REAL group decreased from 4.42 (SD=1.20) to 4.21 (SD=1.64), and from 5.09 (SD=0.62) to 4.68 (SD=1.17) in the SHAM group (small effect size: Hedges' g = 0.182, 95% CI [-0.691, 1.066]) (**Figure 2**). Simple effects analysis demonstrated a mean difference between baseline and post-treatment assessment in the REAL group of -0.619 ($p=0.045$ LSD, $p=0.269$ Bonferroni correction). However, these changes were below the minimal clinically important difference on the numeric pain rating scale (MCID = 2).[36]

Headache frequency was modeled descriptively as the results were non-parametric. Between baseline and the primary outcome time point (one-month) assessment, the

[3] Throbbing/pounding quality, phonophobia/photophobia, nausea, emesis, mod-high severity.
[4] Bilateral, pressing/tigh quality, low-mod severity.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

average frequency of REAL group decreased from 35.4 (SD=8.4) to 30.2 (SD=12.6), while the average frequency of SHAM group changed from 28.5 (SD=11.9) to 25.2 (SD=14.6) (small effect size: Hedges' g = -0.267, 95% CI [-1.16, 0.61]) (**Figure 3**).

Secondary Outcomes

A two-way (time × treatment) mixed ANOVA was performed on all secondary outcomes (**Table 2**). There was a significant time effect as measured by the HIT-6, indicating functional improvement [F (2,36)=12.074 p=0.00]. Simple effects analysis with Bonferroni correction indicated a significant difference in means between baseline and both post-treatment [-5.5 (SEM=1.8), p=0.021] and 1 month [-5.6 (SEM=1.4), p=0.002] follow-ups for the REAL group, and between post-treatment and one-month for the SHAM group [-3.7 (SEM=1.38), p=0.046] (**Figure 4**). This was below the minimal clinically important difference (MCID) on the HIT-6, which is defined as a change of 8 points.[37]

There was also a significant time effect on the Rivermead post-concussion symptom questionnaire (RPSQ-3 [F(2,36) =9.990, p=0.000] and RPSQ-13 [F(2,36) =6.032, p=0.006]). Simple effects analysis with Bonferroni correction indicated a significant difference in means between baseline and post-treatment in the SHAM group [-2.0 (SEM=0.556), p=0.006] and between baseline and one-month in the REAL group [-1.6 (SEM=0.560), p=0.031] on the RPSQ-3 (**Figure 4**).

Finally, there was a significant time effect for depression (PHQ-9; F(2,36) =4.200, p=0.023) and quality of life (QOLIBRI; F(2,36) =4.395, p=0.020). Simple effects analysis with Bonferroni correction indicated a significant difference in means between baseline and one-month for depression in the REAL group [-4.30 (SEM=1.40), p=0.020] (**Figure 4**).

There were no significant interactions, time effects, or treatment effects for the British Columbia Post-concussion Symptom Inventory (BCPSI). Cognition (MoCA), anxiety (GAD-7) and post-traumatic stress disorder (PCL-5) were not included in **Table 2**, as normality assumptions for using ANOVA were not met based on residual analysis.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

A descriptive analysis was performed for return to work and medication changes from before to completion of the study. In the REAL group, 6/10 participants returned to either part- or full-time work, while only 1/10 participants returned in the SHAM group (Fisher's exact; p=0.027). Assessment of medication changes demonstrated 3/10 participants stop or decrease preventative medications in the REAL group, as opposed to none in the SHAM (Fisher's exact; p=0.21). In addition, three participants stopped onabotulinumtoxinA (Botox) treatment (1 REAL, 2 SHAM) (Fisher's exact; p=1.0) (**Table 3**).

Adverse Effects

A pre- and post-treatment tolerability questionnaire was completed at each session. Adverse effects during rTMS sessions across all participants included mild aggravation of headache [4.23% (SD=14.32)], scalp discomfort [0.96% (SD=8.92)], toothache [0.675% (SD=4.14)], and dizziness [0.30%, (SD=9.70)]. Minor improvements in muscle twitching, tinnitus, fatigue, and concentration were reported immediately following rTMS [0.69% (SD=6.12), 0.39%, (SD=4.09), 1.75% (SD=14.11), 1.55% (SD=10.87), respectively]. There were no serious adverse effects such as seizures. One participant in the SHAM group experienced a facial sensation change on the side contralateral to that of stimulation. In general, the treatment was very well tolerated in a globally symptomatic patient population. There were no dropouts from the study and all participants were adherent to completion of a baseline assessment, ten TMS sessions, four follow-up appointments and all outcome questionnaires.

Integrity of Blinding

A blinding questionnaire was completed at each participant's six-month follow-up assessment. In the REAL group, only 3/10 correctly identified treatment (Bang's BI = -0.4, 95% CI [-0.579, -0.221]), in contrast to 2/10 in the SHAM group (Bang's BI = -0.6, 95% CI [-0.757, -0.443]). The blinded investigator correctly identified 6/10 in the REAL group (Bang's BI = 0.2, 95% CI [0.008, 0.392]) and 7/10 in the SHAM group (Bang's BI = 0.4, 95% CI [0.22, 0.58]). Blinding efficacy was similar in the two groups (participants: $\chi 2$ (1)=0.267, p=0.606; investigator: $\chi 2(1)=0.220$, p=0.639). Eighty-five percent (17/20) of participants

stated that they would recommend rTMS to others and 65% (13/20) reported that they had the impression that rTMS helped them.

DISCUSSION

The Relationship Between the DLPFC and PTH

To the best of the authors knowledge, there are currently only three studies that have looked at the treatment effects of rTMS in headache attributed to traumatic injury to the head.[12,13,20] Two of these investigations stimulated the motor cortex (M1) with rTMS,[12,13] while our trial investigated stimulation of the DLPFC. This is an area of the cortex involved in pain perception and regulation, with connections to other pain inhibitory regions such as the anterior cingulate cortex (ACC) and the periaqueductal gray (PAG).[38] Serving as a key node in numerous brain networks, the DLPFC is thought to play a role in modulation of sensory (i.e. pain), affective (i.e. emotional regulation), and cognitive processing (i.e. attention, working memory).[39] As an inhibitory top-down or descending pain modulation pathway is suggested to be one of the mechanisms of analgesic control in the brain,[40] the DLPFC, rostral ACC, and PAG pathway is proposed to play a strong role in placebo analgesia.[41] Interestingly, Niu et al. recently demonstrated that this modulation pathway may be diminished in patients with PTH.[42] Leung et al. also reported decreased levels of Blood Oxygen Level Dependent activity in the DLPFC using fMRI in participants with mTBI and headaches as compared to controls, when exposed to a heat pain stimuli.[43] This suggests that individuals with persistent PTH following mTBI may have diminished pain modulatory function.

Repetitive Transcranial Magnetic Stimulation Treatment for Persistent PTH in Patients with PPCS

One recent study by Leung et al. looked at the benefits of rTMS treatment to the DLPFC in participants with mTBI related headache.[20] Similar to our results, they reported an average daily persistent headache intensity reduction at both one and four weeks following rTMS when compared to baseline. In addition, they found a significant reduction in the depression rating score at one week compared to SHAM. We also found a significant time effect for depression. In particular, there was a significant decrease in

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

depression (PHQ-9) between baseline and one-month in the REAL group, however there was no between group significance. Differences amongst the two studies could be related to alternative patient populations (military veterans vs. general population in our trial), sex (majority male vs. female), and different stimulation protocols (four sessions of 2000 pulses at 80% RMT vs. ten sessions of 600 pulses at 70% RMT).

Of our secondary outcomes measured, we found a significant decrease on the HIT-6 functional impact questionnaire between baseline and both post-treatment and one-month in the REAL group, and between baseline and one-month in the SHAM group. This correlated well with our return to work statistics. A study completed on chronic migraine participants by Shehata et al. in 2016 also reported a decrease in functional impairment measured on the HIT-6, following twelve sessions of rTMS treatment at 80% RMT to the left motor cortex.[44]

In addition, the "physical" symptoms component of the Rivermead post-concussion symptom score (RPSQ-3) demonstrated a significant time effect, with a decrease in symptom score between baseline and one-month for the REAL group. The RPSQ-3 is composed of headache/dizziness/nausea subsections of the questionnaire. This is in agreement with the observed reduction in headache severity score outlined above. Of note, the "psychosocial" component of the measure (RPSQ-13) also demonstrated a significant time effect. A recent study by Moussavi et al. investigated the treatment PPCS with rTMS.[45] Eighteen participants underwent stimulation (20 Hz, 100% RMT, 750 pulses, 10 second inter-train interval) to the left DLPFC over the course of three weeks (13 total sessions). With their primary outcome as the Rivermead post-concussion symptom questionnaire (RPSQ), they found improvement one and two months following the intervention on the RPSQ-13, primarily in individuals with <12 months of symptoms.[45]

Another study completed by Koski et al. on the use of rTMS in participants with PPCS demonstrated an improvement in headache following intervention.[14] In this open label trial, a different rTMS protocol was employed, with stimulation at 10 Hz, 110% RMT, for 1000 pulses. Twenty sessions were completed over the course of four weeks. After stimulation of the left DLPFC, headache decreased on the PCS scale and total PCS score

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

declined by 14.6 points (p=0.009). Interestingly, fMRI post-rTMS demonstrated an increase in task activation peaks over the left DLPFC following stimulation. In our study, we also saw a decrease in post-concussion symptoms as assessed through the Rivermead post-concussion symptom questionnaire as described above. However, there were no significant time, treatment, or interaction effects noted on the BCPSI post-concussion symptoms assessment. In general, scores decreased in both the REAL and the SHAM groups, however to a greater degree in the REAL cohort.

We also found a significant time effect for quality of life (QOLIBRI). Few studies have investigated quality of life as an outcome, and our data suggests an improvement following intervention. When simply assessing the results of our trial descriptively, there was a general decrease in all outcome measures following rTMS, with the REAL group generally showing a greater decline than the SHAM group (**Figure 4**).

Assessment of medication changes from before to completion of the study demonstrated three participants stopping onabotulinumtoxinA (Botox) treatment (1 REAL, 2 SHAM), and three participants decreasing or stopping at least one of their preventative medications (3 REAL, 0 SHAM) (**Table 3**). There were no serious adverse effects from treatment, participant adherence was full, and blinding integrity was maintained throughout the study.

Sham TMS Treatment Protocols

Our study highlights the importance of acknowledging literature related to the sham TMS stimulation approach. Duecker and Sack[46] outline some pitfalls of sham TMS stimulation, which include a possibility of insufficient mimicking of the sound and somato-sensory effects of active TMS, or inadequate attenuation of the magnetic field by a shield on the sham TMS coil. In addition, there is risk of a placebo response. In our trial, we did not find any significant differences between the blinding of REAL and SHAM groups. However, 8/10 participants in the SHAM group thought they were in the REAL group, suggesting a possible role for the placebo effect in our data. At the same time, 7/10 in the REAL group thought they were in the SHAM group, highlighting the risk of a nocebo effect among the REAL participants.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Possible Pathophysiologic Mechanisms of rTMS

Repetitive TMS (rTMS) stimulation of the DLPFC has been used extensively in the depression literature,[17,19] in addition to headache studies.[14,20,21,47] Despite this, the underlying mechanism of rTMS treatment response is not well understood. It has been previously suggested that high frequency rTMS may have an influence on brain architecture, with increases in gray matter volume following treatment.[22] Other theories regarding mechanism of action suggest rTMS influencing changes in the cerebral hemodynamic response[48] and functional connectivity,[49] which have been shown to be implicated in participants with PTH[42] and PPCS.[50,51] Further studies could consider the addition of a modality (i.e. fMRI, fNIRS) to be used in conjunction with rTMS, to further elucidate possible physiologic mechanisms of the technology.

We did not specifically address potential rTMS mechanisms of action in the present study, as our main objective to investigate rTMS as a treatment for persistent PTH and PPCS. Our primary outcomes demonstrated a statistically significant time effect for headache severity and a decrease in headache frequency (descriptive analysis); however, changes did not meet clinical significance thresholds. A larger randomized controlled study is needed to further assess these promising results.

Strengths and Limitations

Strengths of our trial included a year-long recruitment period, lengthy follow-up duration to six-months, and 100% response rate, with no participant drop-outs. In addition, it is the first study to our knowledge, investigating rTMS for both persistent PTH and persistent post-concussion symptoms (cognition, anxiety, depression, anxiety, post-traumatic stress, quality of life). In addition, we used the same stimulation protocol as previous studies investigating rTMS for the treatment of migraine,[27-33] allowing for comparison of our results to an alternative headache population.

A limitation of this study includes the small sample size, which may have been underpowered to appreciate significant changes in our outcome measures. With a larger number of participants, we may see statistically significant differences between the two groups. In addition, individual participant clinical MRI's were used as the method of neuronavigation in all but three subjects (1 REAL, 2 SHAM). In those without an MRI,

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

average brain with MNI coordinates were employed. These participants received MRI's following their rTMS to validate the localization method, and in all cases there was less than a 1cm difference between the two maps, which is within the spatial resolution of a rTMS pulse.[52] In addition, one participant missed their last treatment session due to viral illness and their treatment was delivered three days later than scheduled. The remainder of the participants attended all ten sessions as planned. Maintaining study subjects on the same medication regimen throughout the whole study was not deemed feasible; therefore, participants were permitted to change their medication doses at the three-month mark. This may have influenced our outcome scores at the six-month follow-up. In addition, our rTMS stimulation intensity was on the lower end (70% RMT) of previously reported studies, which stimulated from 80-100% or RMT.[47] Although this lower intensity may have been more tolerable for participants, further dose-response studies may be beneficial to determine if higher stimulation intensities are superior to lower intensities. Finally, a future study investigating participants with one specific headache phenotype (i.e. migrainous, cervicogenic, tension, mixed), may help to delineate possible rTMS responders from non-responders. However, as observed in this study, most PTH participants had multiple headache features (mixed) that could make this classification difficult and limit generalizability.

In summary, this pilot, double-blind, sham-controlled, randomized clinical trial was novel in its findings of rTMS influencing headache severity, frequency, functional outcomes, post-concussion symptoms, depression, and quality of life in patients with persistent PTH and PPCS. Several of our secondary outcome measures had high variances, which could be secondary to the pilot study's relatively small sample size. Overall trends toward improvement can be observed, however many outcomes were below minimal clinically important difference (MCID) thresholds. Despite this, the high return to work rate in the rTMS treatment group is very encouraging. This study demonstrated full participant adherence, with no dropouts, a 100% questionnaire response rate, no serious adverse effects, and an efficacious blinding method. As a result, a larger, appropriately powered, phase II clinical study is suggested.

ACKNOWLEDGEMENTS

Special thanks to Dr. Tak Fung for statistical analysis recommendations and Trevor Low for rTMS administration assistance. We would also like to acknowledge that results from this study were presented by author J.S. (oral conference lecture) at the 13th World Congress on Brain Injury, International Brain Injury Association, Toronto, Canada, March 2019, and an abstract is available in the conference proceedings. [53]

AUTHOR DISCLOSURE STATEMENT

There are no conflicts of interest for this manuscript. This study was funded through the University of Calgary, Cumming School of Medicine, Clinical Research Fund Grant (CRF17-0107) and the Hotchkiss Brain Institute and Department of Clinical Neurosciences Pilot fund Grant.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

CONTRIBUTIONS

Name	Location	Role	Contributions
Joan Stilling, MD, MSc	University of Calgary, Cumming School of Medicine, Hotchkiss Brain Institute, Canada.	Author	Conception and study design; data collection; data analysis and interpretation; drafting of article; critical revision of article; final approval of version to be published.
Eric Paxman, MSc	University of Calgary, Cumming School of Medicine. University of Alberta, Department of Medicine, Edmonton, Canada.	Author	Data collection; critical revision of article.
Leah Mercier	University of Calgary, Cumming School of Medicine, Hotchkiss Brain Institute, Canada	Author	Data collection; critical revision of article.
Liu Shi Gan, PhD	University of Calgary, Cumming School of Medicine, Hotchkiss Brain Institute, Canada.	Author	Conception and study design; data collection.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Meng Wang, MSc	University of Calgary, Cumming School of Medicine, Hotchkiss Brain Institute, Canada.	Author	Data analysis and interpretation; critical revision of article.
Farnaz Amoozegar, MD, MSc, FRCPC	University of Calgary, Cumming School of Medicine, Hotchkiss Brain Institute, Canada.	Author	Conception and study design; critical revision of article.
Sean Dukelow, MD, PhD, FRCPC	University of Calgary, Cumming School of Medicine, Hotchkiss Brain Institute, Canada.	Author	Conception and study design; critical revision of article.
Oury Monchi, PhD	University of Calgary, Cumming School of Medicine, Hotchkiss Brain Institute, Canada.	Author	Conception and study design; critical revision of article.
Chantel Debert, MD, MSc, FRCPC	University of Calgary, Cumming School of Medicine, Hotchkiss Brain Institute, Canada.	Author	Conception and study design; critical revision of article; final approval of version to be published.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

REFERENCES

1 Taylor, C. A., Bell, J. M., Breiding, M. J., & Xu, L. (2017). Traumatic brain injury-related emergency department visits, hospitalizations, and deaths - United States, 2007 and 2013. MMWR Surveill. Summ. 66, 1-16.

2 Cassidy, J. D., Carroll, L. J., Peloso, P. M., Borg, J., von Holst, H., Holm, L., Kraus, J., & Coronado, V. G. (2004). Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO collaborating centre task force on mild traumatic brain injury. J. Rehabil. Med. 43 Suppl., 28-60.

3 Korley, F. K., Kelen, G. D., Jones, C. M., & Diaz-Arrastia, R. (2016). Emergency department evaluation of traumatic brain injury in the United States, 2009-2010. J. Head Trauma Rehabil. 31, 379-387.

4 Cnossen, M. C., van der Naalt, J., Spikman, J. M., Nieboer, D., Yue, J. K., Winkler, E. A., Manley, G. T., von Steinbuechel, N., Polinder, S., Steyerberg, E. W., & Lingsma, H. F. (2018). Prediction of persistent post-concussion symptoms after mild traumatic brain injury. J. Neurotrauma 35, 2691-2698.

5 McMahon, P., Hricik, A., Yue, J. K., Puccio, A. M., Inoue, T., Lingsma, H. F., Beers, S. R., Gordon, W. A., Valadka, A. B., Manley, G. T., Okonkwo, D. O., Casey, S. S., Cooper, S. R., Dams-O'Connor, K., Menon, D. K., Sorani, M. D., Yuh, E. L., Mukherjee, P., Schnyer, D. M., & Vassar, M. J. (2014). Symptomatology and functional outcome in mild traumatic brain injury: results from the prospective TRACK-TBI study. J. Neurotrauma 31, 26-33.

6 Gladstone, J. (2009). From psychoneurosis to ICHD-2: an overview of the state of the art in post-traumatic headache. Headache 49, 1097-1111.

7 Stacey, A., Lucas, S., Temkin, N., Dikmen, S., Bell, K., Brown, A., Brunner, R., Diaz-Arrastia, R., Watanabe, T. K., Weintraub, A., & Hoffman, J.M. (2017). Natural history of headache five years after traumatic brain injury. J. Neurotrauma 34, 1558-1564.

8 Lucas, S., Hoffman, J. M., Bell, K. R. & Dikmen, S. (2014). A prospective study of prevalence and characterization of headache following mild traumatic brain injury. Cephalalgia 34, 93-102.

9 Defrin, R., Riabinin, M., Feingold, Y., Schreiber, S. & Pick, C. G. (2015). Deficient pain modulatory systems in patients with mild traumatic brain and chronic post-traumatic headache: implications for its mechanism. J. Neurotrauma 32, 28-37.

10 Obermann, M., Nebel, K., Schumann, C., Holle, D., Gizewski, E. R., Maschke, M., Goadsby, P. J., Diener, H. C., & Katsarava, Z. (2009). Gray matter changes related to chronic posttraumatic headache. Neurology 73, 978-983.

11 Leung, A., Yang, E., Lim, M., Metzger-Smith, V., Theilmann, R., Song, D., Lin, L., Tsai, A., & Lee, R. (2018). Pain-related white matter tract abnormalities in mild traumatic brain injury patients with persistent headache. Mol. Pain 14, 1744806918810297.

12 Leung, A., Shukla, S., Fallah, A., Song, D., Lin, L., Golshan, S., Tsai, A., Jak, A., Polston, G., & Lee, R. (2016). Repetitive transcranial magnetic stimulation in managing mild traumatic brain injury-related headaches. Neuromodulation 19, 133-141.

13 Leung, A., Fallah, A., Shukla, S., Lin, L., Tsia, A., Song, D., Polston, G., & Lee, R. (2016). rTMS in alleviating mild TBI related headaches--a case series. Pain Physician 19, E347-354.

14 Koski, L., Kolivakis, T., Yu, C., Chen, J. K., Delaney, & S., Ptito, A. (2015). Noninvasive brain stimulation for persistent postconcussion symptoms in mild traumatic brain injury. J. Neurotrauma 32, 38-44.

15 Salazar, A. P. S., Vaz, P. G., Marchese, R. R., Stein, C. Pinto, C., & Pagnussat, A. S. (2018). Noninvasive brain stimulation improves hemispatial neglect after stroke: a systematic review and meta-analysis. Arch. Phys. Med. Rehabil. 99, 355-366.e351.

16 Diana, M., Raij, T., Melis, M., Nummenmaa, A., Leggio, L., & Bonci, A. (2017). Rehabilitating the addicted brain with transcranial magnetic stimulation. Nat. Rev. Neurosci. 18, 685-693.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

17 Brunoni, A. R., Chaimani, A., Moffa, A. H., Razza, L. B., Gattaz, W. F., Daskalakis, Z. J., & Carvalho, A. F. (2017). Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: a systematic review with network meta-analysis. JAMA Psychiatry 74, 143-152.

18 Schwedt, T. J. & Vargas, B. (2015). Neurostimulation for treatment of migraine and cluster headache. Pain Medicine 16, 1827-1834.

19 O'Reardon, J. P., Solvason, H. B., Janicak, P. G., Sampson, S., Isenberg, K. E., Nahas, Z., McDonald, W. M., Avery, D., Fitzgerald, P. B., Loo, C., Demitrack, M. A., George, M. S., & Sackeim, H. A. (2007). Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol. Psychiatry 62, 1208-1216.

20 Leung, A., Metzger-Smith, V., He, Y., Cordero, J., Ehlert, B., Song, D., Lin, L., Shahrokh, G., Tsai, A., Vaninetti, M., Rutledge, T., Polston, G., Sheu, R., & Lee, R. (2017). Left dorsolateral prefrontal cortex rTMS in alleviating mTBI related headaches and depressive symptoms. Neuromodulation 30, 30.

21 Brighina, F., Piazza, A., Vitello, G., Aloisio, A., Palermo, A., Daniele, O., & Fierro, B. (2004). rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. J. Neurol. Sci. 227, 67-71.

22 Lan, M. J., Chhetry, B. T., Liston, C., Mann, J. J., & Dubin, M. (2016). Transcranial magnetic stimulation of left dorsolateral prefrontal cortex induces brain morphological changes in regions associated with a treatment resistant major depressive episode: an exploratory analysis. Brain Stimul. 9, 577-583.

23 Dong, Y., Wu, T., Hu, X., & Wang, T. (2017). Efficacy and safety of botulinum toxin type A for upper limb spasticity after stroke or traumatic brain injury: a systematic review with meta-analysis and trial sequential analysis. Eur. J. Phys. Rehabil. Med. 53, 256-267.

24 Carroll, L. J., Cassidy, J. D., Holm, L., Kraus, J., & Coronado, V. G. (2004). Methodological issues and research recommendations for mild traumatic brain injury: the WHO collaborating centre task force on mild traumatic brain injury. J. Rehabil. Med. 43 Suppl., 113-125.

25 Khedr, E. M., Kotb, H., Kamel, N. F., Ahmed, M. A., Sadek, R., & Rothwell, J. C. (2005). Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J. Neurol. Neurosurg. Psychiatry 76, 833-838.

26 Provost, J.-S., Petrides, M., & Monchi, O. (2010). Dissociating the role of the caudate nucleus and dorsolateral prefrontal cortex in the monitoring of events within human working memory. Eur. J. Neurosci. 32, 873-880.

27 Misra, U. K., Kalita, J., & Bhoi, S. K. (2013). High-rate repetitive transcranial magnetic stimulation in migraine prophylaxis: a randomized, placebo-controlled study. J. Neurol 260, 2793-2801.

28 Misra, U. K., Kalita, J., Tripathi, G. M., & Bhoi, S. K. (2013). Is beta endorphin related to migraine headache and its relief? Cephalalgia 33, 316-322.

29 Misra, U. K., Kalita, J., & Bhoi, S. K. (2012). High frequency repetitive transcranial magnetic stimulation (rTMS) is effective in migraine prophylaxis: an open labeled study. Neurol. Res. 34, 547-551.

30 Kalita, J., Laskar, S., Bhoi, S. K., & Misra, U. K. (2016). Efficacy of single versus three sessions of high rate repetitive transcranial magnetic stimulation in chronic migraine and tension-type headache. J. Neurol 263, 2238-2246.

31 Misra, U. K., Kalita, J., Tripathi, G., & Bhoi, S. K. (2017). Role of beta endorphin in pain relief following high rate repetitive transcranial magnetic stimulation in migraine. Brain Stimul. 10, 618-623.

32 Kalita, J., Bhoi, S. K., & Misra, U. K. (2016). Effect of high rate rTMS on somatosensory evoked potential in migraine. Cephalalgia 25, 25.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

33 Tripathi, G. M., Kalita, J., & Misra, U. K. (2018). Role of glutamate and its receptors in migraine with reference to amitriptyline and transcranial magnetic stimulation therapy. Brain Res. 31, 31.

34 Broadbent, H. J., van den Eynde, F., Guillaume, S., Hanif, E. L., Stahl, D., David, A. S., Campbell, I. C., & Schmidt, U. (2011). Blinding success of rTMS applied to the dorsolateral prefrontal cortex in randomised sham-controlled trials: a systematic review. World J. Biol. Psychiatry 12, 240-248.

35 Bang, H., Ni, L., & Davis, C. E. (2004). Assessment of blinding in clinical trials. Control Clin. Trials 25, 143-156.

36 Farrar, J. T., Young, J. P., Jr., LaMoreaux, L., Werth, J. L., & Poole, R. M. (2001). Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 94, 149-158.

37 Castien, R. F., Blankenstein, A. H., Windt, D. A., & Dekker, J. (2012). Minimal clinically important change on the headache impact test-6 questionnaire in patients with chronic tension-type headache. Cephalalgia 32, 710-714.

38 Lorenz, J., Minoshima, S., & Casey, K. L. (2003). Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain 126, 1079-1091.

39 Seminowicz, D. A. & Moayedi, M. (2017). The dorsolateral prefrontal cortex in acute and chronic pain. J. Pain 18, 1027-1035.

40 Kwon, M., Altin, M., Duenas, H., & Alev, L. (2014). The role of descending inhibitory pathways on chronic pain modulation and clinical implications. Pain Pract. 14, 656-667.

41 Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., Kosslyn, S. M., Rose, R. M., & Cohen, J. D. (2004). Placebo-induced changes in fMRI in the anticipation and experience of pain. Science 303, 1162-1167.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

42 Niu, X., Bai, L., Sun, Y., Wang, S., Cao, J., Sun, C., Wang, Z., Xu, H., Gan, S., Fan, G., Huang, W., Gu, C., Yin, B., Bai, G., Xu, X., & Zhang, M. (2019). Disruption of periaqueductal grey-default mode network functional connectivity predicts persistent post-traumatic headache in mild traumatic brain injury. J. Neurol. Neurosurg. Psychiatry 90, 326-332.

43 Leung, A., Shukla, S., Yang, E., Canlas, B., Kadokana, M., Heald, J., Davani, A., Song, D., Lin, L., Polston, G. (2016). Diminished supraspinal pain modulation in patients with mild traumatic brain injury. Mol. Pain 12, 1744806916662661.

44 Shehata, H. S., Esmail, E. H., Abdelalim, A., El-Jaafary, S., Elmazny, A., Sabbah, A., & Shalaby, N. M. (2016). Repetitive transcranial magnetic stimulation versus botulinum toxin injection in chronic migraine prophylaxis: A pilot randomized trial. J. Pain Res. 9, 771-777.

45 Moussavi, Z., Suleiman, A., Rutherford, G., Ranjbar Pouya, O., Dastgheib, Z., Zhang, W., Salter, J., Wang, X., Mansouri, B., & Lithgow, B. (2019). A pilot randomised double-blind study of the tolerability and efficacy of repetitive transcranial magnetic stimulation on persistent post-concussion syndrome. Sci. Rep. 9, 5498.

46 Duecker, F. & Sack, A. T. (2015). Rethinking the role of sham TMS. Front. Psychol. 6, 210-210.

47 Stilling, J. M., Monchi, O., Amoozegar, F., & Debert, C. T. (2019). Transcranial magnetic and direct current stimulation (TMS/tDCS) for the treatment of headache: a systematic review. Headache 59, 339-357.

48 Kito, S., Hasegawa, T., & Koga, Y. (2012). Cerebral blood flow ratio of the dorsolateral prefrontal cortex to the ventromedial prefrontal cortex as a potential predictor of treatment response to transcranial magnetic stimulation in depression. Brain Stimul. 5, 547-553.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

49 Tik, M., Hoffmann, A., Sladky, R., Tomova, L., Hummer, A., Navarro de Lara, L., Bukowski, H., Pripfl, J., Biswal, B., Lamm, C., & Windischberger, C. (2017). Towards understanding rTMS mechanism of action: stimulation of the DLPFC causes network-specific increase in functional connectivity. Neuroimage 162, 289-296.

50 Hocke, L. M., Duszynski, C. C., Debert, C. T., Dleikan, D., & Dunn, J. F. (2018). Reduced functional connectivity in adults with persistent post-concussion symptoms: a functional near-infrared spectroscopy study. J. Neurotrauma 35, 1224-1232.

51 Palacios, E. M., Yuh, E. L., Chang, Y. S., Yue, J. K., Schnyer, D. M., Okonkwo, D. O., Valadka, A. B., Gordon, W. A., Maas, A. I. R., Vassar, M., Manley, G. T., & Mukherjee, P. (2017). Resting-state functional connectivity alterations associated with six-month outcomes in mild traumatic brain injury. J. Neurotrauma 34, 1546-1557.

52 Wassermann, E., Epstein, C., Ziemann, U., Walsh, V., Paus, T., & Lisanby, S. (Eds.). (2018). Oxford handbook of transcranial stimulation. Oxford University Press.

53 Stilling, J., Paxman, E., Mercier, L., Gan, L., Wang, M., Amoozegar, F., Dukelow, D., Monchi, O., Debert, C. (2019). Accepted Abstracts from the International Brain Injury Association's 13th World Congress on Brain Injury, Brain Inj. 33, 1-337.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Table 1: Demographic and baseline clinical characteristics. All baseline measures were non-significant with p >0.05. Unless otherwise specified, values are listed as mean (SD).

Characteristic	**Overall N=20**	**REAL N=10**	**SHAM N=10**	**p-value** [a]
Demographics				
Age (mean, SD)	36.0 (11.4)	40.3 (11.2)	31.6 (10.4)	0.09
Sex --- female (n, %)	18 (90%)	9 (90%)	9 (90%)	1.0
Dwelling	19 Urban, 1 Rural	10 Urban	9 Urban, 1 Rural	1.0
Marital Status	Married (9), Common-law (3), Partner (1), Single (7)	Married (7), Partner (1), Single (2)	Married (2) Common-law (3), Single (5)	0.35
Number of Children	18	12	6	0.13
Highest level of education	MD/PhD (1), Master's (2), Bachelor's (9), Trades/Vocational Ed (6), Grade 12 (1), Less than Grade 12 (1)	MD/PhD (1), Bachelor's (5), Trades/Vocational Ed (4)	Master's (2), Bachelor's (4), Trades/Vocational Ed (2), Grade 12 (1), Less than Grade 12 (1)	0.38
Disability (n)	LTD (7), STD (1)	LTD (3)	LTD (4), STD (1)	0.65
Mechanism of Injury (n)	MVC (9), Sports (6), Fall (3) Other (2)	MVC (3), Sports (3), Fall (2) Other (2)	MVC (6), Sports (3), Fall (1) Other (0)	0.34
Average number of previous concussions	2.06 (1.16)	1.78 (1.31)	2.38 (0.86)	0.26
Time from most recent concussion	32.5(13.9)	29.17 (14.79)	35.74 (12.13)	0.32

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

(months)				
Headache Type (n)	Migrainous (20), Cervicogenic (11), Tension (4)	Migrainous (10), Cervicogenic (6), Tension (2)	Migrainous (10), Cervicogenic (5), Tension (2)	0.167
OnabotulinumtoxinA (Botox) treatment (n)	10	3	7	0.18
Preventative Headache Medication Use	11	7	2	0.07
Amitriptyline		3	1	
Topiramate		1	1	
Duloxetine		2	-	
Venlafaxine		1	-	
Clinical Outcomes				
Headache Frequency (number/14 days)	31.95 (10.37)	35.40 (7.94)	28.50 (11.32)	0.15
Headache Severity (NPRS average/14 days)	4.75 (1.01)	4.42 (1.20)	5.09 (0.62)	0.16
Cognition (MoCA)	27.45 (1.50)	27.20 (1.54)	27.70 (1.42)	0.48
PCS (RPSQ-3)	7.30 (2.12)	7.20 (2.09)	7.40 (2.15)	0.84
PCS (RPSQ-13)	32.55 (9.72)	34.10 (11.27)	31.00 (7.55)	0.50
PCS (BCPSI)	33.72 (9.90)	33.33 (11.91)	34.11 (7.34)	0.92
Function (HIT-6)	66.80 (6.02)	65.90 (7.93)	67.70 (2.83)	0.53
Depression (PHQ-9)	11.90 (6.74)	11.80 (6.88)	12.00 (6.59)	0.95
Anxiety (GAD-7)	9.25 (5.81)	10.30 (6.28)	8.20 (5.10)	0.45
PTSD (PCL-5)	23.20 (16.72)	21.60 (17.78)	24.8 (15.41)	0.69
Quality of Life (QOLIBRI)	46.90 (18.87)	48.60 (21.69)	45.20 (15.35)	0.71

[a] P-values were based on chi-square tests or Fisher's exact test for categorical variables, and Wilcoxon-Mann-Whitney test for continuous variables. Abbreviations: NPRS=numeric pain rating scale; MoCA=Montreal cognitive assessment; PCS=post-concussion symptoms; RPSQ=Rivermead post-concussion symptoms questionnaire; BCPSI= British Columbia Post Concussion Symptom Inventory; HIT-6=Headache Impact Test 6; PHQ-9= patient health questionnaire-9; GAD-7=generalized anxiety disorder scale-7; PCL-5=post-traumatic stress disorder checklist for DSM-5; QOLIBRI=quality of life after brain injury questionnaire.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Table 2: Two-way (time x treatment) mixed ANOVA at the primary endpoint of 1-month. Headache severity, function (HIT-6), post-concussion symptoms (RPSQ), depression (PHQ-9), and quality of life (QOLIBRI) demonstrated significant time effects.

Outcomes	**Time effect**	**Group Effect**	**Interaction**
	F (df) [P]	*F (df) [P]*	*F (df) [P]*
Headache Severity	**3.214 (3,54) [0.030]***	1.279 (1,18) [0.273]	0.459 (3,54) [0.712]
HIT-6	**12.074 (2,36) [0.000]***	0.803 (1,18) [0.382]	0.774 (2,36) [0.469]
RPSQ-3	**9.990 (2,36) [0.000]***	0.098 (1,18) [0.758]	1.703 (2,36) [0.196]
RPSQ-13	**6.032 (2,36) [0.006]***	0.026 (1,18) [0.873]	1.593 (2,36) [0.217]
BCPSI	2.231 (2,36) [0.122]	0.086 (1,18) [0.772]	0.141 (2,36) [0.869]
PHQ-9	**4.200 (2,36) [0.023]***	0.564 (1,18) [0.462]	1.698 (2,36) [0.197]
QOLIBRI	**4.395 (2,36) [0.020]***	0.491 (1,18) [0.493]	1.736 (2,36) [0.191]

** significant at 0.05 level. Abbreviations: HIT-6=Headache Impact Test 6; RPSQ=Rivermead post-concussion symptoms questionnaire; BCPSI= British Columbia Post Concussion Symptom Inventory; PHQ-9=Personal Health Questionnaire 9; QOLIBRI=quality of life after brain injury questionnaire.*

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Table 3: **Descriptive clinical outcomes at six months following completion of rTMS intervention.**

Participant	Employment	Medications[5]
REAL		
1	Let go from work.	Maintained onabotulinumtoxinA (Botox), amitriptyline.
2	Returned to full-time work.	Weaning off venlafaxine.
3	Maintained full-time work.	Plan to decrease topiramate.
4	Returned to full-time work.	Stopped onabotulinumtoxinA and methylphenidate, decreased duloxetine and zolpidem.
5	No return to work.	None.
6	Returned to full-time school.	None.
7	Stopped full-time work; no return.	Decreased sertraline dose.
8	Returned to part-time work.	Maintained amitriptyline and lisdexamfetamine (Vyvanse), started escitalopram.
9	Returned to work after maternity leave.	Maintained duloxetine.

[5] All participant medications were maintained stable from the baseline assessment to the three-month follow up appointment. If medications changes were needed, this occurred following the three-month assessment.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

10	Returned to part-time work; job change.	Maintained amitriptyline.
SHAM		
11	Return to part-time work.	Started trazadone.
12	Maintained part-time work; new concussion.	None.
13	No return to work.	Stopped onabotulinumtoxinA. Started baclofen, naproxen, and tramacet for back pain.
14	Maintained school.	Titrated off desvenlafaxine due to fatigue.
15	Maintained part-time work.	Maintained onabotulinumtoxinA, dextroamphetamine, eltriptan.
16	Maintained school.	Maintained onabotulinumtoxinA, amitriptyline, desvenlafaxine.
17	No return to work, maintained long-term disability insurance.	Trialed desvenlafaxine, venlafaxine, gabapentin, pregabalin, duloxetine, amitriptyline, propranolol; none helpful.
18	No return to work, switched to long-term disability	None.

	insurance.	
19	New car accident. Stopped work.	Maintained onabotulinumtoxinA, started escitalopram, pregabalin, topiramate, morphine.
20	No return to work, maintained long-term disability insurance.	Stopped onabotulinumtoxinA.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

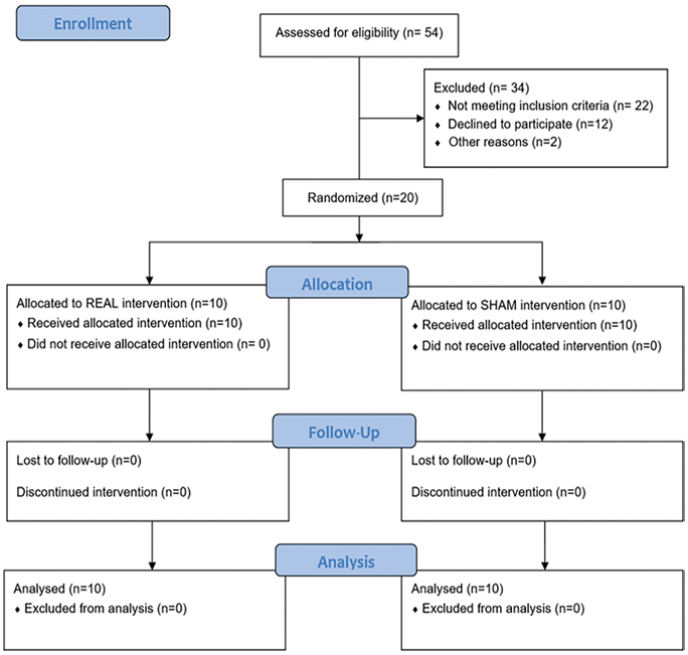
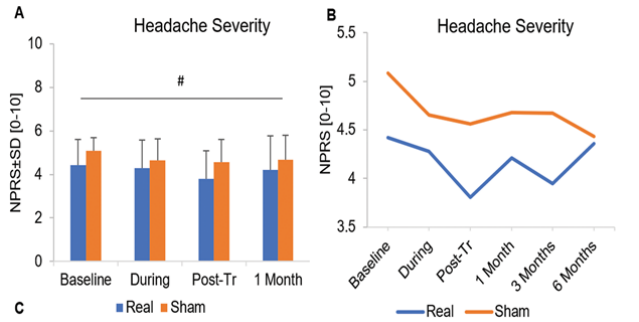


Figure 1: **Consort 2010 Flow Diagram.** Fifty-four participants were assessed for elibility and twenty were randomized into REAL and SHAM intervention groups. There were no participants lost to follow-up. We had full participant adherence and a 100% response rate was achieved.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

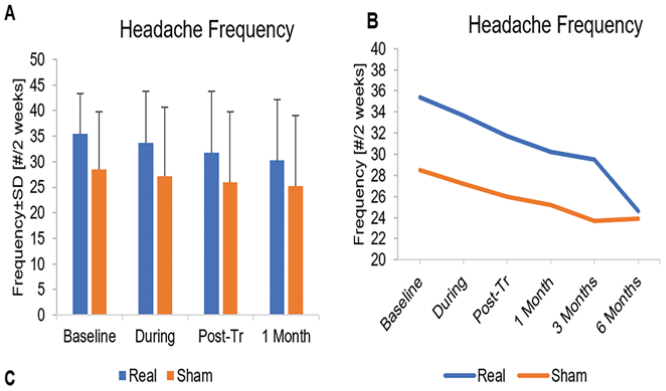


C

Headache Severity *Mean (SD, % change from baseline)*	Baseline	During	Post-Treatment	1 Month	3 Months	6 Months
REAL	4.42 (1.20)	4.28 (1.37, -3%)	3.81 (1.35, -14%)	4.21 (1.64, -5%)	3.95 (1.59, -11%)	4.36 (1.32, -11%)
SHAM	5.09 (0.62)	4.66 (1.03, -8%)	4.57 (1.10, -10%)	4.68 (1.17, -8%)	4.67 (1.23, -8%)	4.43 (1.07, -13%)

Figure 2: Headache severity distributions. A) #: A two-way (time × treatment) mixed ANOVA demonstrated a statistically significant overall time effect at the 1-month primary time point with F(3,54) =3.214, p=0.030. **B, C)** Mean changes of headache severity from baseline, during, post-treatment (day 14), 1 month, 3 months, and 6 months post rTMS. Between baseline and 1-month assessment, the average severity of REAL group changed from 4.42 (SD=1.20) to 4.21 (SD=1.64), while the average severity of SHAM group decreased from to 5.09 (SD=0.62) to 4.68 (SD=1.17); small effect size: Hedges' g = 0.182, 95% CI [-0.691, 1.066]. Abbreviations: NPRS=numeric pain rating scale; Post-Tr=post-treatment.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

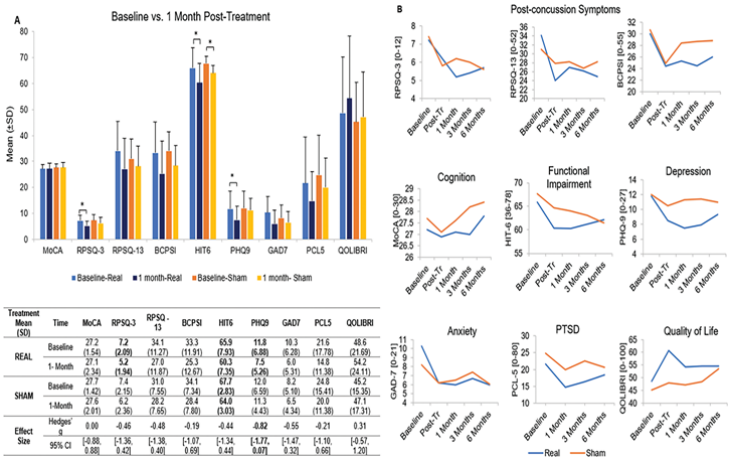


C

Headache Frequency *Mean (SD)*	Baseline	During	Post-Treatment	1 Month	3 Months	6 Months
REAL	35.4 (8.4)	33.7 (10.7)	31.7 (12.7)	30.2 (12.6)	29.5 (13.5)	24.6 (15.2)
SHAM	28.5 (11.9)	27.2 (14.2)	26.0 (14.6)	25.2 (14.6)	23.7 (16.0)	23.9 (15.9)

Figure 3. Headache frequency distributions. A) Headache frequency was documented as a headache being present in the morning, afternoon, or evening each day. Summing these frequencies accounted for a maximum possible total of forty-two headaches/two-weeks. Frequency was modeled as descriptive data due to non-parametric results. B,C) Mean changes of headache frequency from baseline, during, post-treatment (day 14), 1 month, 3 months, and 6 months post-treatment. Between baseline and 1-month assessment, the average frequency of the REAL group changed from 35.4 (SD=8.4) to 30.2 (SD=12.6), while the average frequency of SHAM group decreased from 28.5 (SD=11.9) to 25.2 (SD=14.6); small effect size: Hedges' g = -0.267, 95% CI [-1.16, 0.606]. Abbreviations: NPRS=numeric pain rating scale; Post-Tr=post-treatment.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.



Treatment Mean (SD)	Time	MoCA	RPSQ-3	RPSQ-13	BCPSI	HIT6	PHQ9	GAD7	PCL5	QOLIBRI
REAL	Baseline	27.2 (1.54)	7.2 (2.09)	34.1 (11.27)	33.3 (11.91)	65.9 (7.93)	11.8 (6.88)	10.3 (6.28)	21.6 (17.78)	48.6 (21.69)
	1- Month	27.1 (2.34)	5.2 (1.94)	27.0 (11.87)	25.3 (12.67)	60.3 (7.35)	7.5 (5.26)	6.0 (5.31)	14.8 (11.38)	54.2 (24.11)
SHAM	Baseline	27.7 (1.42)	7.4 (2.15)	31.6 (7.55)	34.1 (7.34)	67.7 (2.83)	12.0 (6.59)	8.2 (5.10)	24.6 (15.41)	45.2 (15.35)
	1-Month	27.6 (2.01)	6.2 (2.36)	28.2 (7.65)	28.4 (7.80)	64.0 (3.03)	11.3 (4.43)	6.5 (4.34)	20.0 (11.38)	47.1 (17.31)
Effect Size	Hedges' g	0.00	-0.46	-0.48	-0.19	-0.44	-0.82	-0.55	-0.21	0.31
	95% CI	[-0.88, 0.88]	[-1.36, 0.42]	[-1.38, 0.40]	[-1.07, 0.69]	[-1.34, 0.44]	[-1.77, 0.07]	[-1.47, 0.32]	[-1.10, 0.66]	[-0.57, 1.20]

Figure 4: Secondary outcome measures. A) *: Statistically significant difference between baseline and 1 month for the RPSQ-3, HIT-6, and PHQ-9 for the REAL group and the HIT-6 for the SHAM group at $p<0.05$, Bonferroni adjustment**.** Small to medium effect sizes are observed for post-concussion symptoms, functional impact, quality of life based on Hedges' g effect analysis. A large effect between REAL and SHAM for depression was demonstrated (Hedges' g, -0.82 [95% CI -1.77, 0.07]. **B)** There was a REAL>SHAM decrease in post-concussion symptoms measured by the Rivermead Post Concussion Symptom Questionnaire (RPSQ-3, RPSQ-13) and the British Columbia Post Concussion Symptoms Questionnaire (BC-PSI). Functional impairment (HIT-6), depression (PHQ-9), anxiety (GAD-7), post-traumatic stress (PCL-5), and quality of life (QOLIBRI) all improved following rTMS in both groups, with changes persisting up to 6 months following treatment. Changes were greater in the REAL group when compared to the SHAM, however this was not statistically significant.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3-4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5-7
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9-11

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

			42
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	12
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	10
	11b	If relevant, description of the similarity of	N/A

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

		interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8 (Figure 1)
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	8
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9,13 (Table 1)
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	13
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	13-15 (Figures 2-4)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A

Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	16
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	23
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	22-23
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	18-24
Other information			
Registration	23	Registration number and name of trial registry	4, 8
Protocol	24	Where the full trial protocol can be accessed, if available	Contact author.
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	25

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Journal of Neurotrauma
Treatment of persistent post-traumatic headache and post-concussion symptoms using rTMS: a pilot, double-blind, randomized controlled trial. (DOI: 10.1089/neu.2019.6692)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.