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Transcranial Magnetic Stimulation for the Treatment of Concussion: A Systematic Review

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ABSTRACT

Background: Post-concussive symptoms (PCSs) are common, disabling, and challenging to manage. Evolving models of concussion pathophysiology suggest evidence of brain network dysfunction that may be amenable to neuromodulation. Repetitive transcranial magnetic stimulation (rTMS) has emerged as a potential novel treatment option for PCSs.

Objectives: To systematically review rTMS trials for the treatment of symptoms following concussion/mild traumatic brain injury (mTBI).

Materials and Methods: We conducted a systematic review of Pubmed/Medline, Embase, and PsychINFO databases were searched up to May 19, 2020. Studies were included if they were prospective rTMS treatment studies of patients with mTBI/concussion. Variables including patient demographics, study design, rTMS protocol parameters, primary outcome measures, and efficacy data were extracted and qualitatively synthesized. rTMS methodology and study quality were also evaluated.

Results: Of the 342 studies identified, 11 met eligibility criteria and were included for synthesis. Forty-one percent of patients were female and age ranged from 18 to 65 (average age = 38.5 years). Post-concussive depression (seven studies) and headache (four studies) were the most commonly investigated symptoms. The majority of trials were sham-controlled with randomized control trial (RCT) designs, but all were small pilot samples ($n < 30$). Methodological heterogeneity and a low number of identified trials precluded quantitative meta-analysis. Regarding rTMS for post-concussive depression, positive results were found in two out of four studies with depression as a primary outcome, and all three studies that assessed depression as a secondary outcome. All four rTMS studies for post-concussive headache reported positive results.

Conclusions: rTMS for the treatment of concussion/mTBI shows promising preliminary results for post-concussive depression and headache, symptoms that otherwise have limited effective treatment options. More studies with larger sample sizes are needed to further establish potential efficacy.

Keywords: Concussion, depression, headache, mild traumatic brain injury, post-concussive syndrome, transcranial magnetic stimulation

Conflict of Interest: All authors have nothing to disclose.

INTRODUCTION

Traumatic brain injury (TBI) is one of the most common, disabling and costly medical conditions worldwide (1). There are an estimated 69 million new cases worldwide each year (2), and approximately 75–85% of TBIs are concussion/mild traumatic brain injury (mTBI) (3). Common causes of TBI include falls, motor vehicle accidents, assaults, and sports related injuries (3). Concussion has been increasingly recognized as a public health crisis and its incidence is on the rise (4). Approximately 10–30% of patients suffering concussion/mTBI report prolonged or persistent post-concussive symptoms (also known as post-concussive syndrome [PCS]), with upwards of 80% reporting at least one ongoing symptom one-year post injury and 20% of patients remaining functionally impaired (5). However, the exact prevalence of PCS is not known due to the high degree of heterogeneity in diagnostic criteria (e.g., different time cut-offs) and differences between patient sub-populations (6). PCS characteristics can vary widely from patient to patient, but the most common symptom domains

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include post-traumatic headaches, cognitive impairment, and mood dysregulation. In addition, there appears to be a negative effect of depression on the recovery process, with TBI symptoms being more persistent when accompanied by depression (7). Overall, these symptoms have also been linked with significant disability in this population (8,9).

At present, there are limited effective treatment options for PCSs. Management is particularly challenging due to the wide range of overlapping neurologic and psychiatric symptoms, high inter-individual heterogeneity, and high levels of functional impairment (10,11). Current guidelines outline the complexity of treating PCSs and highlight the lack of evidence-base to guide decision-making (12,13). Consequently, there has been great interest in developing new treatment approaches to improve outcomes following concussion/mTBI.

With accumulating neuroimaging research demonstrating evidence of brain network dysfunction in concussion/mTBI patients (14), neuromodulation targeted to specific brain regions and networks could offer an optimal new treatment strategy. Based on this rationale, noninvasive brain stimulation has emerged as a promising new treatment option and repetitive transcranial magnetic stimulation (rTMS) epitomizes this.

rTMS is a safe and well-tolerated treatment modality that has been approved by the U.S. Food and Drug Administration (FDA) for the management of treatment-resistant depression (15), migraine with aura (16), and obsessive–compulsive disorder (17). Over the past five years, there has been a surge in the number of studies investigating the use of rTMS as a treatment for one or more PCSs, including depression, headache, and cognitive impairment. However, there have been mixed results between studies and thus the efficacy of rTMS for this clinical population remains unclear. The objective of our study was to systematically review the methodological protocols and efficacy of rTMS for treatment of concussion/mTBI and grade the quality of included studies.

MATERIALS AND METHODS

A systematic review was performed following PRISMA guidelines. We conducted a literature search using MEDLINE, PubMed, Embase, and PsychINFO until May 19, 2020 with the following search terms: "(TMS OR rTMS OR transcranial magnetic stimulation) AND (concussion OR traumatic brain injury OR TBI OR mTBI OR mild traumatic brain injury)." Studies were included if they were prospective treatment studies of TMS for concussion/mTBI. Studies were excluded if they were case reports or small series ($n < 3$), conference abstracts, not original research (i.e., reviews, opinion articles), nontreatment studies (neurophysiological use of TMS, safety of rTMS), did not involve concussion/mTBI patient populations, or were exclusively animal studies. In trials with mixed TBI severity, the study was only included if the majority of patients had concussion/mTBI.

Articles identified through the above databases were reviewed by two independent researchers (M.B. and F.S.). Records were screened and excluded based on the eligibility criteria provided above. Any discrepancies were reviewed and when a consensus was not achieved, a third independent reviewer was called upon to resolve conflicts (P.G.). Study data were extracted by A.M. and included the following variables: participant demographics, duration of treatment, neuroanatomical targets, rTMS protocol parameters, primary outcome measures, results, and follow-up data.

Assessment of study design quality was conducted by A.M. based on a commonly used quality assessment score developed by Walburn et al. (18) The score aims to evaluate variables most important for critical appraisal, although not all variables were relevant to all study designs. These include statement of explicit a priori aims, definition or description of the size of the population under investigation, sample size calculation, justification that the sample is representative of the population, inclusion, and exclusion criteria stated, demographic details of participants, the research undertaken is independent of routine care or practice, justification of the reliability and/or the validity of outcome measures, specification of the response/dropout rate, justification of the response/dropout rate, discussion of generalisability of results and statement of source funding. In addition, each selected study was assigned a "TMS methods score" based on a tool developed by Pollak et al. (19). This scale reflects the amount of detail, and thus the reproducibility, of the rTMS protocol in each selected study. Checklist of rTMS parameters (reproducibility score, maximum score = 8) include coil type, frequency, intensity of stimulation, target area, localisation method, number of stimuli/pulses, number of sessions, and duration of treatment.

RESULTS

Included Studies

A total of 342 studies were identified, and after duplicates were removed 187 abstracts were screened. Of those, 174 articles were excluded (Fig. 1). The most common reasons for exclusion were studies not using TMS, not recruiting concussion/mTBI, or non-interventional. Ultimately, 13 full-text articles were assessed for eligibility, of which two were further excluded because they were identified a case series ($n < 3$) or were not a treatment study. The remaining 11 articles were included in the qualitative synthesis.

Study Characteristics

A total of 11 rTMS treatment studies were included in the descriptive synthesis ($n = 197$ patients). Of those, four studies investigated a primary outcome of depressive symptoms (20–23), four for post-traumatic headache (24–27), two for global PCSs (28,29), one for cognition (23), and one study investigated chronic central pain (30). Secondary outcome measures included; headache (21), depression (24,26,27,29), cognition (20–22,24,26–28), and overall PCSs (20,27). Additional secondary outcome measures evaluating post-traumatic stress symptoms, sleep quality, or quality of life were not synthesized in this review. A summary of methodological parameters and efficacy data are outlined below.

Study Protocols

Nine studies were randomized sham-controlled trials. The remaining two studies included an open-label feasibility study (28) and a large case series (25). Study duration ranged from one week to two months, and treatment duration varied from one week to four weeks, with two to four weeks being the most common. The most frequent follow-up duration was one month, with few studies collecting data beyond three months. There was substantial heterogeneity in the rTMS stimulation protocols across studies. Protocol parameters are described in Table 1 and further details are provided in symptom-specific subsections below. All TMS treatment studies used rTMS as the stimulation protocol (no TMS treatment protocols using single pulse, paired pulse or

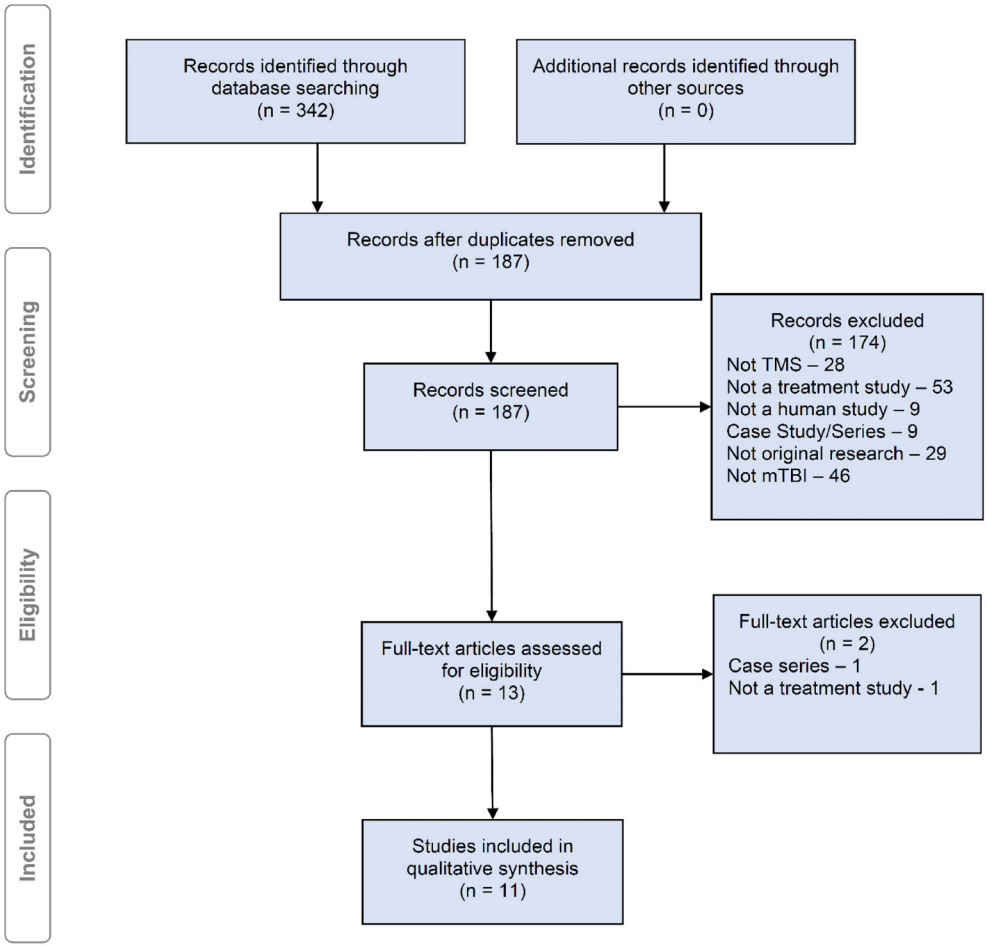

Figure 1. PRISMA flow diagram for selection of rTMS concussion/mTBI treatment studies. TMS, transcranial magnetic stimulation; mTBI, mild traumatic brain injury. [Color figure can be viewed at wileyonlinelibrary.com]

other methods were identified). Neuronavigation methods were incorporated in seven of 11 included studies (21,22,24–27,29), and the remaining four studies employed conventional localization methods (i.e., 5 cm anterior to the primary motor cortex). Only two studies (20,21) combined rTMS with pre/post neuroimaging or neurophysiological data. Siddiqi et al. (21) used fMRI and reported increased connectivity between subgenual cingulate (sgACC) and default mode network (DMN), as well as increased sgACC anti-correlation with the left- and right-sided stimulation sites. Rao et al. (20) reported increased fractional anisotropy on diffusion tensor imaging (DTI) in the right fusiform gyrus, right middle temporal gyrus, left fusiform gyrus, and left para-hippocampal gyrus, suggesting increased white matter integrity in these regions following active rTMS treatment.

Demographics

Most participants in the included studies exclusively recruited patients with concussion/mTBI. However, Siddiqi et al. (21) and Rao et al. (20) included two patients with moderate TBI, Hoy et al. (22) included eight patients with moderate–severe TBI and Lee and Kim (23) reported an average Glasgow Coma Scale (GCS) score of 13.7 (mTBI 13–15). The number of participants in each study varied from 6 to 30 with 18 as the median number across all studies. Females represented 41% of the participants and the age range was 18–65 with an average age of 38.5 ($\pm$11) years. We did not exclude any trials based on age and no pediatric studies of rTMS for mTBI were identified.

Study Quality

Nine studies met all eight of the quality review criteria for rTMS methodology (see Methods section). Koski et al. (28) did not report the number of pulses and Moussavi et al. (29) did not report their localization methods.

Study design quality measure scores ranged from 60% to 100%. The majority of lost points were from lack of sample calculations, no justification that sample is representative of the population, no reporting of reliability or validity of chosen outcome measures, no justification for dropout or response rate, and no mention of funding source. There did not appear to be a qualitative association between higher quality studies and positive or negative results. There were three negative studies (20,22,29) with varying quality scores (92%, 70%, and 66%, respectively).

Follow-up

Seven of 11 studies (20,24,26–30) conducted follow-ups with varying lengths and frequency of longitudinal assessment. Three studies conducted follow-up one-month post-treatment for

Table 1. Overview of Published Studies of rTMS for the Treatment of Concussion/Mild TBI.

Study	Design	Blinding	Patients	Treatment duration	Target	Treatment protocol	Sham protocol	Quality scores
Depression								
Rao et al. (20)	RCT	Methods not specified. Blinding effectiveness assessed.	Active, *n* = 13 Sham, *n* = 17 Age = 40 ± 14 47% Female	Four weeks	Right DLPFC	• 1 Hz (1200 pulses) • 110% RMT • One session/day (20 total)	Sham coil	Overall: 11/12 TMS: 8/8
Siddiqi et al. (21)	RCT	Double-blind. Blinding effectiveness assessed.	Active, *n* = 9 Sham, *n* = 6 Age = 45 ± 15 26% Female*	Five weeks	Bilateral DLPFC	• L = 10 Hz (4000 pulses), R = 1 Hz (1000 pulses) • 120% RMT • One session/day (20 total)	Sham coil	Overall: 12/12 TMS: 8/8
Hoy et al. (22)	RCT	Double-blind. Blinding effectiveness not assessed.	Active, *n* = 11 Sham, *n* = 10 Age = 46 ± 11 52% Female	Four weeks	Bilateral DLPFC	• L = 10 Hz (1500 pulses), R = 1 Hz (900 pulses) • 110% RMT • One session/day (20 total)	Treatment coil angled 45° off head	Overall: 7/10 TMS: 8/8
Lee and Kim (23)	RCT	Single-blind. Blinding effectiveness not assessed.	Active, *n* = 7 Sham, *n* = 6 Age = 42 ± 11 30% Female	Two weeks	Right DLPFC	• 1 Hz (2000 pulses) • 100% RMT • One session/day (10 total)	Sham coil	Overall: 10/10 TMS: 8/8
Headache/Pain								
Stilling et al. (27)	RCT	Double-blind. Blinding effectiveness assessed.	Active, *n* = 10 Sham, *n* = 10 Age = 36 ± 11 90% Female	Two weeks	Left DLPFC	• 10 Hz (600 pulses) • 70% RMT • One session/day (10 total)	Sham coil	Overall: 10/12 TMS: 8/8
Leung et al. (24)	RCT	Single-blind. Blinding effectiveness assessed.	Active, n = 14 Sham, n = 15 Age = 34 ± 8 21% Female	One week	Left DLPFC	• 10 Hz (2000 pulses) • 80% RMT • Four sessions total	Sham coil	Overall: 8/12 TMS: 8/8
Leung et al. (25)	Case series	N/A	Active, *n* = 6 No sham group Age = 50 ± 10 0% Female	Two months	Left DLPFC and Left PMC	• 10 Hz (2000 pulses) • 80% RMT • Four sessions total	No sham condition	Overall: 6/10 TMS: 8/8
Leung et al. (26)	RCT	Single-blind. Blinding effectiveness assessed.	Active, *n* = 12 Sham, *n* = 12 Age = 41 ± 14 12.5% Female	One week	Left PMC	• 10 Hz (2000 pulses) • 80% RMT • Three sessions total	Sham coil	Overall: 10/12 TMS: 8/8
Choi et al. (30)	RCT	Double-blind. Blinding effectiveness not assessed.	Active, *n* = 6 Sham, *n* = 6 Age = 42 ± 9 50% Female	Two weeks	PMC*	• 10 Hz (1000 pulses) • 90% RMT • One session/day (ten total)	Treatment coil angled 90° to skull	Overall: 7/10 TMS: 8/8
Global Post-Concussive Symptoms								
Moussavi et al. (29)	RCT	Double-blind. Blinding effectiveness not assessed.	Active, *n* = 9 Sham, *n* = 9 Age = 48 ± 12 50% Female	Three weeks	Left DLPFC	• 20 Hz (750 pulses) • 100% RMT • One session/day (13 total)	Custom-made sham coil	Overall: 8/12 TMS: 7/8
Koski et al. (28)	PC	N/A	Active, *n* = 15 No control Age = 34 ± 11 40% Female	Four weeks	Left DLPFC	• 10 Hz (pulses not reported) • 110% RMT • One session/day (20 total)	No sham condition	Overall: 10/12 TMS: 7/8

DLPFC = dorsolateral prefrontal cortex; N/A = not applicable; PMC = primary motor cortex; PC = prospective cohort; RCT = randomized control trial; RMT = resting motor threshold; TMS = transcranial magnetic stimulation.
*Affected hemisphere of PMC stimulated.

headache (24,25) or central pain (30) with positive results mostly sustained (Leung et al. (24) trended positively but significance was not sustained). Moussavi et al. (29) followed up with patients at one- and two-months post-treatment and found the significant effects of rTMS for overall PCSs were only maintained for those with more recent injuries (<12 months) who received active stimulation. Koski et al. (28) followed up with patients three-months post-treatment and found initial positive effects of rTMS on overall PCS were not maintained. Rao et al. (20) followed patients at 4, 8, 12, and 16 weeks (four months) post-treatment and found certain weeks to favor sham group over the active stimulation group, but this was not a consistent result. Lastly, Stilling et al. (27) followed patients for up to six months, the longest of any study included in this review, and found initial treatment effects were not maintained for any of their outcomes; headache severity and frequency (primary outcomes), or depression (secondary outcome).

rTMS for Post-Concussive Depressive Symptoms

Four studies (20–23) measured the effects of rTMS on depressive symptoms following concussion/mTBI. Time-since-injury varied greatly between studies with Lee and Kim (23) (n = 13) recruiting patient with more acute injuries (<6 months) and Hoy et al. (22) (n = 21) recruiting patients who had chronic symptoms. Site of stimulation included right dorsolateral prefrontal cortex (DLPFC) (20,23) and bilateral DLPFC (21,22). For all studies, stimulation targeting the left DLPFC was excitatory (≥10 Hz) and the right DLPFC was inhibitory (≤1 Hz). Other specific protocol parameters varied widely across trials (Table 1). For the two studies that stimulated right DLPFC, Rao et al. (20) (n = 30) was a negative study, while Lee and Kim (23) reported positive results, and both were similar quality studies. For the two studies with bilateral DLPFC stimulation, Hoy et al. (22) found improved depressive symptoms in both groups but no significant differences between active treatment and placebo, while Siddiqi et al. (21) reported significant improvement over placebo. Siddiqi et al. (21) was the higher quality study.

Finally, Leung et al. (24,26), Moussavi et al. (29), and Stilling et al. (27) reported depression efficacy data as secondary outcomes in their studies focused on other PCSs. All three studies reported significant improvements on depression scores after rTMS treatment but Leung et al. (24) found these effects were not sustained at one-month follow-up. Leung et al. (26) did not find significant changes to HRSD scores following three sessions of left primary motor cortex (PMC) stimulation.

rTMS for Post-Traumatic Headache and Pain

Four studies (24–27) investigated rTMS and headache following mTBI. Studies varied with regard to time-since-injury, ranging from 3 months to >150 months. All four studies used the same outcome measures to evaluate headache intensity (numeric pain scale [NPS]) and frequency (diary). All rTMS protocols used "excitatory" high-frequency (≥10 Hz) stimulation and targeting the left DLPFC. However, other parameters such as total number of pulses, % resting motor threshold (RMT), number of sessions and frequency of sessions varied widely (Table 1). All four studies reported improvements in NPS scores and reduced headache frequency. Stilling et al. (27) (n = 20) found significant reductions in NPS (p = 0.03) but not for headache frequency. Only one study (26) (n = 24) found sustained improvements at one-month follow-up post-treatment. Stilling et al. (27) also measured function via percentage of participants who returned to work, with 60% in the active group returning as compared to 10% in the sham group (Table 2).

Siddiqi et al. (21) was the only study to evaluate headache as a secondary outcome and did not find any significant changes following 20 sessions of bilateral DLPFC stimulation.

Choi et al. (30) (n = 12) investigated the effects of rTMS on TBI-related chronic central pain and found significant improvements on NPS scores following stimulation with 1000 pulses at 10 Hz of the PMC of the affected hemisphere compared with sham stimulation. The effects were maintained at one-month follow-up.

rTMS for Treatment of Post-Concussive Cognitive Impairment

Lee and Kim (23) (n = 13) were the only study specifically focused on post-concussive cognition as a primary outcome (alongside depression). Compared with a sham stimulation group, ten sessions of 2000 pulses at 1 Hz over the right DLPFC was associated with significant improvements in working memory and executive function. They did not conduct any follow-up.

Seven studies assessed cognition as a secondary outcome following rTMS for mTBI patients (20–22,24,26–28). Stilling et al. (27) did not find any significant changes in Montreal Cognitive Assessment (MoCA) scores in either the active or sham stimulation group. Siddiqi et al. (21) also did not find any significant changes in NIH Toolbox Cognitive Battery scores following 20 sessions of bilateral DLPFC stimulation. Leung et al. (24,26) did not find any significant changes in tests of attention, working memory, verbal memory, or executive function following four session of left DLPFC stimulation (24) or three sessions of left PMC stimulation (26). Rao et al. (20) (n = 30) found mixed results with improved immediate recall, verbal memory, and working memory (small effect sizes, Hedges' g ranging between 0.02 and 0.39) in the active stimulation group, while the sham group demonstrated improvements in processing speed, mental flexibility, and delayed recall (small effect sizes, Hedges' g ranging between −0.02 and −0.28). Hoy et al. (22) found positive trends on tests of working memory (Digit Span Backwards, Arithmetic, and Trail Making Test B) after 20 sessions of bilateral DLPFC stimulation in the active treatment group. Lastly, Koski et al. (28) reported significantly improved measures of executive function (Stroop task) and verbal fluency (Animal Naming task) and found increased fMRI task-related activation peaks in the left DLPFC after 20 sessions of rTMS to the left DLPFC.

rTMS for Treatment of Global PCSs

Two studies assessed global PCSs as a primary outcome following rTMS in mTBI (28,29). Koski et al. (28) (n = 15) involved a prospective cohort study design without a sham stimulation group and reported significantly improved overall PCSs scale scores following 20 sessions of left DLPFC rTMS. Moussavi et al. (29) (n = 18) did not find significant differences between active and placebo groups after 13 sessions of left DLPFC stimulation by their primary treatment endpoint. However, they observed symptomatic improvements in both the active and sham groups and continued significant improvements in the active stimulation group of mTBI patients with more recent injuries (<12 months) by two-months follow-up.

Global PCSs were assessed as a secondary outcome in two studies (20,27). Rao et al. (20) (n = 30) found that Rivermead Post

Table 2. Overview of Outcome Data of rTMS for the Treatment of Concussion/Mild TBI.

Study	Outcome (Measure)	Active TMS Prescore	Active TMS Postscore	Sham TMS Prescore	Sham TMS Postscore	Results	Follow-up
Depression							
Rao et al. (20)	Depression (HRSD)	12.73 ± 2.15	10.42 ± 2.02	9.38 ± 3.22	7.24 ± 3.17	No significant differences between groups with small effect size (g = 0.14)	Follow-up at 4, 8, 12, and 16 weeks. High degree of variability in results between follow-up periods (sham favored in some weeks).
Siddiqi et al. (21)	Depression (MADRS)	N/A	56% ± 14%	N/A	27% ± 25%	Improved overall with large effect size (d = 1.43) Lassitude (d = 2.0) and suicidal thoughts (d = 1.75)	No follow-up conducted. Study was discontinued early due to logistical issues.
Hoy et al. (22)	Depression (MADRS)	33.64 ± 9.36	27.10 ± 3.40	34.40 ± 6.22	24.13 ± 3.65	No significant differences between groups but overall improved symptoms ($p = 0.002$)	No follow-up conducted
Lee and Kim (23)	Depression (MADRS)	23.43 ± 5.06	16.57 ± 5.47	24.17 ± 3.13	23.83 ± 4.54	Improved overall ($p < 0.01$) with large effect size d = 1.44)	No follow-up conducted
	Cognition (TMT, seconds) (Stroop, seconds)	96.39 ± 3.36 158.03 ± 17.37	90.36 ± 3.17 138.03 ± 13.79	98.65 ± 5.38 160.49 ± 12.65	97.45 ± 5.93 157.49 ± 13.94	Improved overall ($p < 0.01$) with large effect sizes for working memory (d = 1.24), and executive function (d = 1.49)	
Headache							
Stilling et al. (27)	HA severity (NPS)	4.42 ± 1.20	4.21 ± 1.64	5.09 ± 0.62	4.68 ± 1.17	Improved ($p = 0.03$) with small effect size (g = 0.182)	Follow up at one, three, and six months. Effects not sustained at six months, but 60% of rTMS group returned to work (vs 10% of placebo group).
	HA frequency (diary)	35.4 ± 8.4%	30.2 ± 12.6%	28.5 ± 11.9%	25.2 ± 14.6%	No significant differences between groups with small effect size (g = −0.267)	
Leung et al. (24)	HA severity (NPS)	N/A	Reduced by 25.3 ± 16.8%	N/A	Reduced by <1 ± 11.7%	Improved ($p < .0001$)	Effects continued to trend positively but were not significant at one-month post treatment
	HA frequency (diary)	N/A	50% no longer had persistent HA	N/A	7% no longer had persistent HA	Improved ($p < 0.01$)	
Leung et al. (25)	HA severity (NPS)	5.5 ± 1.4	2.6 ± 1.8	N/A	N/A	Improved ($p < 0.01$)	No follow-up conducted
	HA frequency (diary)	N/A	Reduced by 53.05 ± 19.90%	N/A	N/A	Improved, average of 78% HA reduction ($p < 0.05$)	
Leung et al. (26)	HA severity (NPS)	5.7 ± 1.9	2.2 ± 2.7	4.6 ± 1.3	3.5 ± 2.0	Improved ($p = 0.04$)	Effects sustained at one-month
	HA frequency (diary)	N/A	Reduced by 56.3 ± 48.2%	N/A	Reduced by 15.4 ± 43.6%	Improved, 58% in active group had 50% reduced HA ($p = 0.035$)	
Choi et al. (30)	Chronic central pain (NPS)	5.8 ± 0.8	Numeric value not reported	5.8 ± 0.8	Numeric value not reported	Improved pain scores ($p < 0.001$) in active treatment group	Effects sustained at one-month
Global Post-Concussive Symptoms and Other Symptoms							
Moussavi et al. (29)	Global PCS (RPQ3) (RPQ13)	7.7 ± 3.0 32.1 ± 10.7	6.7 ± 2.9 28.1 ± 9.6	7.6 ± 3.6 31.2 ± 10.2	6.1 ± 3.1 29.6 ± 10.9	No significant differences between groups but overall improved symptoms	Follow-up at one and two months. Continued improvements in active group only for those with more recent injuries (<12 months) ($p = 0.005$).
Koski et al. (28)	Global PCS (PCS scale)	45.8 ± 17.2	14.6 ± 16.1	N/A	N/A	Improved PCS symptom scale scores ($p = 0.009$, d = 0.91) Better response in older participants ($p < 0.05$)	Effects not sustained on PCS symptom scale at three-months

All outcome values are mean ± standard deviation (SD). g = Hedge's g; d = Cohen's d; HA = Headache, HRSD = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale (MADRS) score, N/A = not applicable, NS = not significant, NPS = numeric pain scale, PCS = Post Concussive Symptoms, RPQ = Rivermead Post-Concussion Symptoms Questionnaire, TMS = transcranial magnetic stimulation, TMT = Trail making test.

Concussion Symptom Questionnaire (RPSQ) scores preferentially improved in the sham treatment group (small effect size, Hedges' g = −0.53), whereas Stilling et al. (27) (n = 20) found significant improvements in RPSQ scores in the active stimulation group with a small-moderate effect size one-month post-treatment with rTMS over the left DLPFC.

DISCUSSION

This is the first systematic review to specifically assess TMS for the treatment of PCSs. Our review suggests that rTMS could potentially be effective for the treatment of this complex and challenging to manage patient population. This includes mixed but largely positive results for post-concussive depression, the most commonly investigated symptom, and limited but promising data for post-traumatic headache and cognitive impairment. Individual study design and TMS methodology quality was reasonably strong. However, there was large heterogeneity in study protocols and all included trials had small sample sizes (n < 30). Thus, caution is needed in the interpretation of these synthesized results.

rTMS for Post-Concussive Depression

Overall, four out of the seven TMS studies measuring depression outcomes reported significant clinical improvement. These results are in line with the previously demonstrated efficacy of rTMS for non-TBI treatment-resistant depression (15). All seven of these studies targeted the DLPFC, a well-recognized target from large trials of non-TBI depression. This literature proposes therapeutic mechanism(s) based on the DLPFC's anti-correlation to the subgenual cingulate (sgACC) and modulation of relevant default mode and central executive network dynamics (31). Of note, only two studies (Siddiqi et al. and Hoy et al.) used navigation to optimally target such regions of anti-correlation. The DLPFC may have also been selected in some of our reviewed trials for practical purposes as there are established methods for stimulating this region without the need of MRI guidance (e.g., 5–6 cm anterior to the motor hot spot) (32).

The DLPFC could certainly be implicated in concussion pathogenesis (33); however, the lack of mechanism-based rationale for treatment protocols specific to post-concussion/mTBI depression is very apparent. There is also evidence that TBI-related depression may represent a distinct pathophysiology from traditional non-TBI depression (34) and thus neuromodulatory treatment protocols should ideally be tailored to the former. Siddiqi et al. (21) was the only study employing a protocol specific to TBI by using individualized resting-state fMRI mapping of networks implicated in TBI to inform TMS targeting. Furthermore, a recent analysis by Siddiqi et al. (35) suggests that there may be two distinct symptom-specific circuit targets for rTMS in depression; a "dysphoric" target, localized around the DLPFC, and an "anxiosomatic" target, localized around the dorsomedial prefrontal cortex (DMPFC). The DMPFC target has shown mixed results in treatment-resistant depression studies (36–38) but has not yet been explored in concussion/mTBI-related depression. Given the anxiosomatic characteristics frequently seen in patients with persistent PCSs (39), the DMPFC may be a worthwhile target to explore in future TMS RCTs. A large-scale study of rTMS for post-concussive depression is currently being conducted (https://clinicaltrials.gov/ct2/show/NCT03523507).

rTMS for Post-Traumatic Headache

Despite being recognized as a primary predictor of recovery after concussion/mTBI, there has been very limited research on optimizing management for post-traumatic headache (40). These disabling headaches have a complex pathophysiology that includes impaired descending modulation, neurometabolic changes, neuroinflammation and activation of the trigeminal sensory system (41). The four trials included in our review reported consistent benefits from TMS on frequency and severity of post-traumatic headaches. Three studies used high-frequency stimulation targeting the left DLPFC (24,25,27), and two studies targeted the PMC (Leung et al. (26) stimulated the left PMC, while Choi et al. (30) stimulated the PMC of the affected hemisphere). There did not appear to be a mechanistic rationale specific to post-traumatic headache. Post-traumatic headache severity/chronicity can be highly associated with mood and other psychological factors (42), and thus it is possible that the benefits from this rTMS protocol on headache were due to improvement in mood. In line with this reasoning, both Leung et al. (24) and Stilling et al. (27) reported significant reductions in depression ratings alongside reductions in headache severity.

Single pulses and low-frequency "inhibitory" stimulation targeting visual cortex has demonstrated efficacy in migraine abortion and prevention and is FDA-approved for these indications (16,43). Burke et al. recently showed that regions of gray matter volume loss in migraine patients localize to a common brain network defined by connectivity to the visual cortex. In addition, the direction of this connectivity implicated visual cortex hyperactivity and thus these findings may offer a mechanistic rationale for the TMS protocol (44). Despite similarities in clinical phenotypes and potential shared underlying mechanisms of post-traumatic headaches and migraine, no post-traumatic headache rTMS treatment studies have investigated a visual cortex target to date.

rTMS for Post-Concussive Cognitive Impairment and Global Symptoms

The symptoms following concussion/mTBI are tightly interwoven and thus treating single symptom(s) in isolation may offer limited overall benefit. Post-concussive cognitive difficulties such as inattention and short-term memory deficits are very common and epitomize this. These cognitive deficits may transiently be a direct result of the head injury itself but contributing post-concussive factors such as depression, headache/pain, and insomnia often perpetuate these deficits and disentangling etiological origins is challenging (42).

Composite concussion symptom scales and cognitive symptoms scores demonstrated relatively consistent improvement after DLPFC-targeted rTMS. A recent fMRI study by Ansado and colleagues (45) provides support for using unilateral left DLPFC stimulation in this context. They found that such a protocol may engage bilateral working memory networks and may restore interhemispheric network balance in these individuals (45). There is also a controversial set of research demonstrating that DLPFC stimulation may enhance cognition in healthy controls (46). However, cognitive improvement in non-TBI patient populations offer mixed results (32) and a recent sham-controlled RCT of 10 Hz left DLPFC rTMS for moderate–severe TBI was not found to be effective (47).

Placebo Effects and Concussion

Placebo effects can be defined as beneficial therapeutic effects derived from contextual variables surrounding administration of a treatment rather than the treatment itself. A growing body of research has found that placebo effects may meaningfully modulate brain regions/networks and neurotransmitter systems (e.g., opioid, dopaminergic) in similar ways as active treatments (48). Placebo responses reported in clinical trials include placebo effects as well as other factors such as spontaneous improvement and regression to the mean. Multiple studies in our review (20,22,29) reported robust placebo responses in the sham arms of the trials. Indeed, the lack of reported efficacy in these trials was not because patients randomized to active rTMS did not improve PCSs, but rather that both the active and placebo groups showed considerable improvements in symptoms. This is consistent with recent reviews reporting high placebo responsiveness of PCSs (49) and that elaborate therapeutic devices such as rTMS may yield particularly elevated placebo effects (50). Further research is needed to better understand these mechanisms and how they may be harnessed for concussion recovery. For example, three-armed trials with active, sham and no-treatment control groups could delineate between active effects, placebo effects and natural history. It is also critical to ensure sham TMS devices used in the placebo group adequately blind participants. Although a topic of ongoing debate, angled active TMS coils (tilted off the scalp) may be more prone to unblinding than sham TMS coils specifically designed to mimic all aspects of active rTMS except for the induction of electromagnetic fields (51). If a patient thinks that they are not receiving active TMS due to poor blinding, their expectations change, and placebo effects may be diminished. In the reviewed studies, only five studies (20,21,24,26,27) collected data on blinding effectiveness. It is very important for TMS studies to collect this information, which informs investigators of whether or not participants are properly blinded and indeed unaware (no better than chance) of their group assignment.

Limitations

There are many limitations to acknowledge in this systematic review. Most notably, all included studies had small sample sizes (the largest had 30 participants) and there was limited and inconsistent follow-up between studies to evaluate durability of effects (majority of studies had no follow-up beyond one-month post-treatment). There was also variability in outcomes which could be a result of the high heterogeneity of recruited patient populations (chronic vs. more acute, different definitions for concussion/mTBI), variability in rTMS protocol parameters (number of sessions, intensity, frequency, and neuroanatomical targets) and varying sham controls and blinding procedures. The small number of trials and methodological heterogeneity precluded quantitative synthesis (i.e., meta-analysis) and thus conclusions of pooled efficacy cannot be made at this time. Potential for publication bias in the synthesized studies was also not assessed. This is an important issue given our small number of identified published studies with non-positive trials being less likely to be published. A future area of work could be to quantify publication bias by reviewing registry databases such as clinicaltrials.gov to identify registered trials and then a systematic review of MEDLINE to determine what percentage were published. Previous reviews on this topic are limited. One review assessed rTMS for TBI of all severity (mild to severe), did not include measures of study quality, and did not include several concussion/mTBI studies that were published recently (52).

Conclusion

There is promising data from pilot trials investigating rTMS for treatment of PCSs. Given the lack of existing treatment options for concussion/mTBI and the high safety and tolerability profile of rTMS, we strongly encourage further efforts in this field. Looking forward, there is a clear need for one or more large sample-size trials in order to further establish the efficacy of rTMS in this patient population. Longer and more consistent follow-up periods are required to evaluate durability of effects following rTMS and to assess the need for maintenance stimulation, particularly in patients with chronic PCSs. Other important future directions include studies incorporating pre-post functional neuroimaging and/or neurophysiological measures (e.g., fMRI, MEG, and EEG) to better understand relevant neurobiology and mechanisms of therapeutic response. This could inform new rTMS circuit-based targets and protocols specific to concussion/mTBI. As we move toward more network-driven targets for concussion, we would encourage future TMS studies to utilize evolving image-guided neuronavigation methods that may be able to localize targets more accurately than conventional approaches (e.g., 5 cm markings). Additionally, we encourage future studies of rTMS for concussion treatment to explore other stimulation methods (i.e., theta-burst TMS) as all studies included in this review used conventional rTMS stimulation protocols. Finally, a growing number of rTMS studies are combining stimulation with concurrent therapies (e.g., cognitive therapy) with encouraging results (53,54) and this could be considered in future rTMS concussion/mTBI trials.

Authorship Statements

Matthew J. Burke and Adriano Mollica were responsible for the study concept and design. Matthew J. Burke, Adriano Mollica, and Farnaz Safavifar were responsible for data collection and processing. Adriano Mollica, Matthew J. Burke, Michael Fralick, Peter Giacobbe, and Nir Lipsman drafted the manuscript. All authors critically revised and approved the manuscript.

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COMMENTS

This is a thorough review of the literature surrounding TMS for the treatment of post-concussive symptoms. The literature is scarce and this narrative review has been conducted, outlining the many opportunities for future studies in this field.

Joan Stilling
Calgary, AB Canada

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This is a well-designed literature review of rTMS in the treatment of individuals with mild Traumatic Brain Injury/concussion. The authors established clear guidelines for manuscript selection, as well as a clear method for evaluating the quality of the studies extracted from their literature review. The authors also well-described the limitations in their review and in the field in terms of making definitive clinical decisions in using rTMS for individuals with mTBI.

Paul Pasquina, MD
Bethesda, MD USA

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The current paper is an outstanding effort by the authors to summarize and review the scarce literature for a novel treatment modality offered for a difficult-to-treat condition. It points out that more well-designed studies are being performed to add transcranial magnetic stimulation (TMS) to the array of tools available in the field of neuromodulation. I would like to emphasize what the authors pointed out about limitations of sham in TMS and the resulting placebo effect.

Vafi Salmasi, MD
Stanford, CA USA

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This is a valuable systematic review synthesizing complex literature about a heterogeneous condition. The authors adeptly summarize the literature on rTMS for concussive TBI and its various sequelae. Despite the heterogeneity of the literature, the results are presented in a coherent and well-thought-out fashion. This review helps to make the clear case that rTMS holds promise as a treatment for various symptoms associated with concussive TBI, and that better-quality studies are needed in order to clearly demonstrate this.

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