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**Advances in Repetitive Transcranial Magnetic Stimulation
for Posttraumatic Stress Disorder: A Systematic Review**

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Author Contributions

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Advances in Repetitive Transcranial Magnetic Stimulation for Posttraumatic Stress Disorder: A Systematic Review

An estimated 70% of the population experiences a traumatic event during their lifetime (Benjet et al., 2016), with between four and nine percent estimated to develop posttraumatic stress disorder (PTSD; Goldstein et al., 2016; Koenen et al., 2017). Several effective psychological and pharmacological PTSD treatment options have been developed, disseminated and implemented over the past two decades. However, despite these treatment advances, a substantial proportion of patients receiving frontline treatments for PTSD will either not complete enough treatment to receive an adequate dose for response or experience inadequate recovery (Kehle-Forbes et al., 2016; Resick et al., 2017; Sripada et al., 2019; Steenkamp et al., 2015).

Neuromodulation strategies that target underlying neurobiological pathology are being investigated as potential treatment options for PTSD. Non-invasive brain stimulation (NIBS) therapies for psychiatric conditions have been in use since the 1930s when electroconvulsive therapy was first described as a treatment for psychosis. Repetitive transcranial magnetic stimulation (rTMS) is one of the most researched NIBS for PTSD and other psychiatric conditions. Originally described by Barker et al. (1985), rTMS uses an electromagnetic field (rather than direct electrical currents) that permits the use of high frequency energy that can be transmitted across the scalp and skull with minimal discomfort to the patient (Koek et al., 2019). Evidence of the effects of rTMS was first demonstrated in humans when stimulations directed toward the motor cortex generated contralateral movements of the associated body parts (Pascual-Leone et al., 1993). These effects could be modified by stimulation repetition, brain region targeted, and the intensity and frequency of stimulations (Pascual-Leone et al., 1994;

Speer et al., 2003). Low frequency (LF) rTMS produced inhibitory changes in the motor cortex (Chen et al., 1997; Wasserman et al., 1996), whereas high frequency (HF) stimulations increased motor excitability (Pascual-Leone et al., 1994). These effects persisted after the termination of stimulations (Fox et al., 1997; Hoogendam et al., 2010) and influenced distal brain regions (Fox et al., 1997; Paus et al., 1997). This phenomenon was later demonstrated on the prefrontal and parietal cortices (Cho & Strafella, 2009; Loo et al., 2003; Speer et al., 2000; Strafella et al., 2001), providing preliminary mechanistic support for the use of this procedure for psychiatric conditions.

Numerous studies have now evaluated the effects of rTMS for a range of psychiatric conditions. Although the biological mechanisms through which rTMS exerts clinical effects are not well understood (Cirillo et al., 2017), proposed theories suggest that neuromodulation of the cortex modulates changes in targeted brain regions and neural systems associated with mood and anxiety (Cho & Strafella, 2009; Keck et al., 2002; Strafella et al., 2001). For instance, rTMS of the dorsolateral prefrontal cortex (DLPFC) has been shown to induce effects on cerebral blood flow and the subcortical production of endogenous dopamine (Tremblay et al., 2020). rTMS treatment protocols have generally relied on parameter adjustments to tailor treatment to the targeted psychiatric conditions based on neurobiological models to inform: left versus right cortex placement (e.g., Berkowitz et al., 2007), and LF versus HF stimulations (Rubens & Zanto, 2012). The DLPFC has been the targeted region in numerous trials, given its central involvement in emotion regulation and its accessibility to the TMS energy currents (Wasserman & Lisansby, 2001).

Traditional prefrontal-limbic models propose that PTSD is characterized by hypo-activity in prefrontal cortical regions that impairs top-down fear regulation, amygdala hyperactivity that underlies exaggerated fear sensitivity and response, and deficient hippocampus functioning that may contribute to the over-generalization of fear cues (Acheson et al., 2012; Rauch et al., 2006). Of particular relevance are two prefrontal cortex regions: the ventral medial prefrontal cortex (vmPFC), and the DLPFC. The vmPFC plays a significant role in fear extinction, integrating sensory-emotional input and projecting down to the amygdala and hypothalamus to modulate fear responsivity (Milad & Quirk, 2012; Rauch et al., 2006). Decreased vmPFC activity coupled with increased amygdala activity is associated with greater PTSD severity (Francati et al., 2007; Hayes et al., 2012; Shin et al., 2005; Sripada et al., 2012). The DLPFC is involved in executive functions and emotional regulation and is thought to influence activity between the vmPFC and amygdala (Delgado et al., 2008; Lyoo et al., 2011).

Consistent with the prefrontal-limbic models of PTSD, successful trauma-focused psychotherapy (TFP) is associated with increased DLPFC and decreased amygdala activity (Malejko et al., 2017; Peres et al., 2007). Higher pre-treatment amygdala activity is associated with treatment failure, while higher DLPFC activity is associated with better treatment outcomes (Malejko et al., 2017). HF rTMS is proposed to increase cortical excitability of the DLPFC so as to promote amygdala inhibition. LF rTMS is generally effective for depression and some anxiety disorders (Berlim et al., 2013; Brunelin et al., 2014; Diefenbach et al., 2016; Mantovani et al., 2013), potentially by decreasing cortical activation and disrupting dysfunctional thinking patterns. These effects may generalize to the intrusive symptoms and trauma-related cognitions in PTSD. Thus, both LF and HF might reduce PTSD by differentially impacting PTSD symptom clusters (Kan et al., 2020; Yan et al., 2017).

Several controlled trials have now been conducted on rTMS for PTSD. Most trials have targeted the right DLPFC, applying both inhibitory and excitatory protocols, based on research indicating preferential right hemispheric involvement in PTSD and anxiety disorders (Freeman et al., 1998; Schutter et al., 2001). Although the vmPFC appears to play a central role in PTSD, the conventional rTMS electrical current can only travel a proximal distance (2-3 cm; Koek et al., 2019), limiting the choice of cortical targets. As an exception, deep TMS (dTMS) targeting the vmPFC has been investigated in one trial (Isserles et al., 2013). Trials have demonstrated that both HF and LF rTMS results in improved PTSD outcomes, with discrepant conclusions about which protocol is superior (Cohen et al. 2004; Kozel et al., 2019; Leong et al., 2020). These inconsistent findings challenge the conventional models of PTSD circuitry and/or how rTMS exerts effects on brain activity. Recent systematic reviews have speculated that HF versus LF rTMS may differentially affect the different neural networks and PTSD symptom clusters that underlie PTSD (Berlim & Van Den Eynde, 2014; Kan et al., 2020). Synthesis of newer evidence as proposed in the current review may help shed light on these differential effects.

Notably, newer forms of TMS protocols have been developed and tested with the goal of improving treatment efficacy while reducing patient burden. While standard rTMS uses a figure-8 coil, dTMS uses different coil shapes that can transmit deeper electromagnetic pulses into the cortex, but at the expense of precision (Deng et al., 2013; Guadagnin et al., 2016). Two other novel rTMS approaches include theta-burst stimulation (TBS) and synchronized TMS (sTMS). TBS generates patterned pulses, delivering short bursts of high frequency stimulations that more rapidly deliver a large number of magnetic stimulations compared to conventional rTMS. TBS can be intermittent (iTBS) to induce excitatory effects or continuous (cTBS) to promote inhibitory effects (Di Lazzaro et al., 2005; Huang et al., 2005; Philip et al., 2019b). sTMS is

another form of patterned rTMS that involves three rotating magnets that deliver very low energy that is synchronized to the individuals' brain wave rhythms (Philip et al., 2019a). The sTMS device is more portable and convenient than those used for other rTMS (Philip et al., 2019a).

Current Review

Current treatment guidelines indicate that there is insufficient evidence to recommend for or against rTMS for PTSD (International Society of Traumatic Stress [ISTSS], 2019; Department of Veterans Affairs, Department of Defense [VA/DoD], 2017), although the ISTSS guidelines noted some emerging evidence of rTMS efficacy. This is largely based on the limited number of studies evaluating the efficacy of rTMS for PTSD at the time of the guideline development, and due to inconsistent findings on whether HF or LF rTMS is superior (ISTSS, 2019; Lefaucheur et al., 2020; VA/DoD, 2017). New research has emerged, however, since the publication of these guidelines that can potentially advance the body of evidence on the overall efficacy of rTMS for PTSD. The aims of the present systematic review were to (a) synthesize existing literature on the efficacy of rTMS for PTSD and secondary outcomes; (b) apply recognized standards to evaluate the quality of the evidence; and (c) investigate whether HF or LF rTMS is more efficacious. In the past, limitations in the body of evidence precluded definitive recommendations for rTMS for PTSD in authoritative treatment guidelines. New studies have now emerged that might advance that body of evidence.

Method

Procedure

A systematic review was conducted following standards from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019). Results of that review are reported here in accordance with the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) reporting guidelines (Moher et al., 2009). Our protocol was registered in the international database of prospectively registered systematic reviews in health and social care (PROSPERO; registration CRD42020165825).

Sample

Potential studies were identified through searches of electronic databases, including Ovid MEDLINE, EMBASE, PsycINFO, PTSDpubs, and Cochrane CENTRAL. Relevant grey literature (ongoing or unpublished trials) was identified from searches of clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform. Reference sections of published systematic reviews of rTMS for PTSD were hand searched. Searches were last updated on September 23, 2020, with no restriction on date or language, and included a combination of key words and controlled vocabulary for the concepts of PTSD and rTMS. Search terms within a concept were combined with the Boolean Operator “OR” and concepts were linked with the Boolean Operator “AND” (see Appendix A for full search syntax).

Studies were included if they met the following criteria: (a) record was in English, including published and unpublished studies; (b) study design was a randomized controlled trial, including crossover trials; (c) at least 80% of the sample was aged 18 years or older; (d) at least 70% of the sample was diagnosed with PTSD according to DSM or ICD criteria by means of a structured clinical interview or clinician diagnosis; (e) TMS intervention was compared to sham TMS, waitlist, treatment as usual, psychological treatment, or other TMS intervention.

A total of 896 records were identified through database searches, and 63 additional records were identified through grey literature searches and hand searching. After deduplication, 551 unique titles and abstracts were screened. Records were screened independently at both the title/abstract and full-text stage, with conflicts resolved through discussion or consultation with a

third reviewer, if necessary. At the title/abstract screening stage, 497 records did not meet inclusion criteria and were excluded. Five records identified via clinicaltrials.gov represented ongoing studies, and two represented completed studies where no results or additional information could be obtained. Forty-six full-text records were screened for eligibility, and ten were excluded (see Appendix B for a flow diagram with an accounting of exclusion reasons). Eighteen studies reported across 36 records met inclusion criteria. No results could be obtained for five of those studies. Team members attempted to contact study investigators up to three times to obtain information. References for all included records, ongoing studies, and records awaiting full-text assessment are presented in Appendix C.

Data Extraction

Study characteristics and data were dually extracted according to the protocol, and included authorship, publication date, study design, demographics, sample size, method of PTSD diagnosis, TMS parameters, characteristics of control condition, number and reasons for dropout, number and descriptions of adverse events, data for pre-specified outcomes of interest, and period of follow-up. A participant was considered a dropout if they did not attend all of the primary treatment sessions. The primary outcomes were clinician-reported PTSD symptoms, patient-reported PTSD symptoms, and remission rates (loss of diagnosis). Secondary outcomes included patient-reported depression symptoms, functioning/quality of life and adverse events. Webplotdigitizer 4.0 (<https://apps.automeris.io/wpd/>), a semi-automatic software tool that can extract data that is reported in graphs, was used for data not reported numerically. For crossover trials, data was extracted for the first phase only. Two team members independently assessed risk of bias using the Cochrane Risk of Bias Tool, the standard approach to assessing risk of bias in

randomized controlled trials that included the following categories: selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases (Higgins et al., 2011).

Data Analysis and Synthesis

Multivariate meta-analytic models were used to estimate quantitative summaries of change in PTSD and depression, adverse event proportions, and dropout proportions, by assigned treatment group (White, 2011). For both PTSD and depression, standardized differences in the form of Hedge's g (Hedges & Olkin, 1985) were used to accommodate different primary PTSD outcome measures used in each study to estimate treatment differences expressed in standard deviation units. Calculation of the standardized effect size followed Feingold's (2009) recommendation to use the baseline standard deviation of the measure for a longitudinal analysis. Results indicated the mean differences between treatments. In a secondary model, the selected subset of studies that administered the same PTSD outcome measure to estimate unstandardized differences of changes in scores from baseline to post-treatment to improve inference related to the magnitude of any observed summary effects. Five studies used the PTSD Checklist (PCL) at post-treatment, as compared to just three studies that used the Clinician-Administered PTSD Scale (CAPS) at post-treatment. Given the greater number of studies this allowed us to pool, and the relatively convergent psychometric properties between the PCL-IV and CAPS-IV (Monson et al., 2008), we decided to use the PCL-IV for the unstandardized meta-analysis. We used a double-arcsine transformation of the proportions of participants who experienced adverse events or who dropped out of the study prior to inclusion. The double-arcsine transformation precludes inadmissible confidence interval range estimates and the generation of inverse variance weights that are biased by very low or high prevalence estimates (Barendregt et al., 2013).

For each model, the within-studies correlations were set to zero on account of the randomized design, and the between-studies correlations were constrained to 0.50 given the small number of studies for estimation. We used linear combinations of the regression coefficients to compare each active treatment to sham treatment and to compare the active treatments. We report the summary estimates and associated 95% confidence intervals for each treatment group and for the between-group comparisons. We also report the I^2 as a quantitative indicator of statistical heterogeneity. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to assess the quality of the evidence for the primary outcome using the following five domains to assess the strength of evidence: risk of bias, imprecision, inconsistency, indirectness, and publication bias (Guyatt et al., 2008).

Results

Study Characteristics

Interrater reliability of included titles/abstracts was high (Cohen's Kappa = 0.86 [BB, EB]; 0.80 [EB, MR]). Study characteristics are displayed in Table 1 for the 13 studies for which data were available. The largest percentage of trials was conducted in the United States ($k = 7$; 53.85%). Ten studies evaluated rTMS, one study evaluated dTMS, one study iTBS, and one study sTMS. All of the rTMS studies included at least one arm in which rTMS was applied to the right DLPFC. Four studies included a specific treatment augmentation with rTMS. All rTMS studies included a sham comparator, except for one study that compared HF to LF rTMS (Kozel et al., 2018). Among the eight studies that did not include rTMS as a treatment augmentation strategy, rTMS treatment generally ranged from two to four weeks with one exception (Kozel et al., 2019). Appendix D lists the risk of bias ratings across the included studies. Given the heterogeneity of treatments, the pooled analyses focused exclusively on rTMS-only protocols.

Results from rTMS-augmentation treatments and rTMS variants (iTBS; sTMS) are narratively reported.

Primary Outcomes

We identified seven RCTs (N=223) that compared rTMS to sham comparisons for patients with PTSD. Treatment-group-specific standardized differences are shown in Table 2. A reduction in symptoms occurred in all treatment groups. Statistical heterogeneity was high for all treatment groups. Active treatment was associated with a greater symptom decrease than sham treatment (SMD = -1.13, 95% CI: -2.10, -0.15). The quality of this evidence was rated as *very low* based on risk of bias in several trials, treatment heterogeneity, statistical heterogeneity, and imprecise confidence intervals (see Appendix E). To get a better sense of the magnitude of this effect difference, summary unstandardized differences across the five studies that used the PCL-IV were calculated. Results indicated that active treatment was associated with a PCL score decrease of 12.14 (95% CI: -15.18, -9.11) compared to sham. Statistical heterogeneity was substantially lower compared to the standardized analysis.

Both HF (SMD = -1.22, 95% CI: -2.36, -0.09) and LF (SMD = -1.03, 95% CI: -2.18, 0.12) treatment was associated with a greater symptom decreases than sham treatment. There was a small difference favoring HF treatment to LF treatment in PTSD symptom reduction, albeit with imprecise confidence intervals that included no effect differences (SMD = -0.19, 95% CI: -1.39, 1.00). In evaluating the mean differences among the five studies that used the PCL, HF rTMS was associated with a PCL score decrease of 16.67 points (95% CI: -20.26, -13.08) relative to sham treatment, and a decrease of 9.04 points (95% CI: -14.07, -4.02) relative to LF rTMS. LF rTMS had a superior symptom reduction relative to sham treatment of 7.62 points (95% CI: -11.88, -3.37).

Secondary Outcomes

PTSD Symptom Clusters

Out of the seven studies that compared rTMS to sham, all studies except for Kozel et al. (2019) relied on the DSM-IV definition of PTSD that is based on the three cluster model (re-experiencing, avoidance/numbing, hyperarousal). Only one trial (Cohen et al., 2004) reported adequate statistical data on changes in PTSD symptom clusters, with the other studies only displaying outcomes in their figures or narratively reporting these results with reference to significance levels. Cohen et al. (2004) found that HF rTMS resulted in meaningful declines in all three PTSD symptom clusters, whereas LF rTMS did not demonstrate any improvements across clusters at post-treatment. Nam et al. (2013) demonstrated that LF rTMS resulted in comparable reductions to sham across the avoidance/numbing and hyperarousal clusters, but a greater decrease on the re-experiencing cluster. In comparing left and right HF rTMS, Boggio et al. (2010) found that right rTMS was more effective in reducing avoidance and hyperarousal symptoms, but not re-experiencing symptoms. Watts et al. (2012) found no significant improvement differences between LF rTMS and a sham comparison on all three PTSD symptom clusters.

Depression

The effect of different rTMS frequency parameters on post-treatment depression severity was evaluated. Five studies, all using different measures, reported depression symptom change. Study-specific and summary SMDs are displayed in Table 2 by treatment type. As with PTSD symptoms, there was evidence of a depression symptom reduction for all three treatment arms. Statistical heterogeneity was low to moderate. rTMS treatment was associated with greater decreases in depression symptoms compared to sham treatment (SMD = -0.83, 95% CI: -1.30, -

0.36). HF rTMS was associated with greater symptom reductions than either LF rTMS (SMD = -1.09, 95% CI: -1.65, -0.52) or sham (SMD = -0.52, 95% CI: -1.08, 0.04). LF rTMS was also associated with greater symptom decrease than sham (SMD = -0.57, 95% CI: -1.09, -0.05).

Drop-out Rates

Study-specific and summary estimates of drop-out proportions of the seven studies are shown in Table 2. Statistical heterogeneity was low for each treatment group. While HF rTMS and sham had the highest point estimates at 0.15 and 0.17 respectively, the 95% CIs were wide for all three treatment types with substantial overlap.

Adverse Events

The three most common adverse events reported across studies was headaches (k = 6), discomfort (k = 4), and physical symptoms such as neck pain, nausea, and dizziness (k = 4). Study-specific and summary proportion estimates for the occurrence of adverse events are presented in Table 2. Probability estimates of adverse events were similar for all three treatment types and the 95% CIs were wide with considerable overlap between groups. Statistical heterogeneity was high for all three treatment types.

Other TMS protocols

Two other modalities of rTMS treatments were identified - rTMS augmentation of a specific treatment, and newer variants of rTMS (i.e., dTMS, sTMS and iTBS) - but were not analytically pooled because of treatment heterogeneity. In general, several pilot studies demonstrated the safety and feasibility of augmenting trauma therapy with rTMS (Fryml et al., 2019; Osuch et al., 2009). Kozel et al. (2018) evaluated an LF rTMS augmentation to standard cognitive processing therapy (CPT) compared to CPT plus rTMS sham (N = 103). CPT + rTMS was associated with significantly greater PTSD reductions relative to CPT alone at post-

treatment and 6-months follow-up, demonstrating clinically meaningful differences between groups on the PCL (but not CAPS).

Three other trials evaluated variant forms of TMS. Isserles et al. (2013) conducted a 3-arm trial, evaluating dTMS (targeting the vmPFC) plus an exposure paradigm (N=30). Results indicated that dTMS was generally safe and tolerable to patients, and that dTMS plus exposure may be a promising treatment worthy of future research. Two variant forms of rTMS were evaluated in two other studies: sTMS and iTBS. In a pilot trial, sTMS was well tolerated and resulted in lower self-reported PTSD and depression scores compared to the sham arm (Philips et al., 2019a). In the other trial, iTBS was also well-tolerated and results, which included longer-term data from the unblinded phase, demonstrated that iTBS resulted in superior PTSD and depression outcomes compared to a sham (Philips et al., 2019b).

Discussion

Our review identified 13 eligible RCTs that evaluated rTMS, or rTMS variants, for the treatment of PTSD. Pooled results from seven studies that implemented rTMS without a specific treatment augmentation indicated that rTMS for PTSD was associated with improved PTSD and depression outcomes compared to sham. The quality of this evidence, however, was rated as *very low* due to small samples sizes, treatment heterogeneity, inconsistent results, and an imprecise pooled effect that included wide 95% confidence intervals. Thus, our primary results suggest that rTMS is more effective than sham, but that the magnitude of this effect is still relatively uncertain. To get a better sense of the magnitude of the effect difference, we then evaluated just those studies that used the PCL. rTMS was associated with a 12-point decrease on the PCL-IV (95% CI: -15.18, -9.11) relative to sham. In comparing HF and LF rTMS, results suggest that HF rTMS may be slightly more effective than LF rTMS on post-treatment PTSD and depression

severity, however with a very imprecise estimate that also indicates the possibility of no differences between treatments. Relying on mean differences of studies that used the PCL-IV, HF rTMS was associated with a 9-point greater decrease (95% CI: -14.07, -4.02) than LF rTMS.

As described previously, effective PTSD treatment most likely involves engaging brain plasticity to correct previous PTSD-related learning patterns contributing to sensitivity of the fear response system and overgeneralization of trauma related fear learning. Since TMS has been found to impact brain plasticity (Freitas et al., 2013), many have begun to explore whether it can speed response or augment learning based PTSD interventions. Several studies were identified that evaluated the use of rTMS as an augmentation to exposure therapy (Fryml et al., 2019; Kozel et al., 2018; Osuch et al., 2009), or which tested variant forms of TMS (Isserles et al., 2013; Philip et al., 2019a; Philip et al., 2019b). Studies of rTMS augmentation tended to include only a small number of subjects, and generally indicated that rTMS augmentation was safe and acceptable. As an exception, Kozel et al. (2018) conducted a larger trial in which CPT augmented with LF rTMS demonstrated superior short-term and longer-term PTSD reductions than CPT alone. Given our findings that suggest that HF rTMS may be slightly more effective than LF, future trials should consider augmenting evidence-based PTSD treatments with HF rTMS.

In regard to the variant forms of rTMS, dTMS targeting the vmPFC demonstrated promising findings when paired with a brief exposure paradigm. In the first sham-controlled trial of iTBS for PTSD, Philip et al. (2019b) demonstrated the safety, feasibility, and preliminary effectiveness (further substantiated via neuroimaging) of iTBS. In a separate pilot trial, Philip et al. (2019a) also demonstrated encouraging results on the use of sTMS for PTSD. These newer forms of rTMS are intriguing as iTBS can deliver comparable effects of HF rTMS but in a

fraction of the time, while sTMS has the potential to be a portable treatment. More research is needed to substantiate the treatment efficacy of these approaches and compare their efficacy with conventional rTMS.

Our results are generally consistent with the previous systematic reviews that showed that rTMS of the right DLPFC yielded promising results when compared to a sham (Berlim & Van Den Eynde, 2014; Kan et al., 2020). Similar to previous systematic reviews, we also demonstrated that LF and HF rTMS result in decreased PTSD severity. However, our results further indicate that HF rTMS may result in slightly improved effects on PTSD and depression severity compared to LF rTMS (although these findings are very imprecise). While this finding is consistent with the neurobiological models of PTSD, it does not explain why LF rTMS would also exert therapeutic effects for PTSD. One potential explanation is that LF rTMS demonstrated some potential efficacy on the re-experiencing cluster (Nam et al., 2013), whereas HF rTMS appeared to be effective in reducing avoiding/numbing and hyper-arousal clusters. However, this observation was not consistent across trials (Cohen et al., 2004). Unfortunately, only one trial (Cohen et al., 2004) reported adequate statistical data on cluster score changes and demonstrated that HF rTMS was associated with decreased scores on all clusters relative to LF rTMS.

Although several systematic reviews have been conducted on this topic, there are several points worth noting. Our review methodology was comprehensive, including risk of bias assessment, quantitative analysis, and assessment of the certainty of the evidence across outcomes using GRADE. GRADE is now used in several major guidelines and is increasingly considered a gold standard technique to provide a transparent and reliable estimate on the quality of the evidence (Guyatt et al., 2008). Our review included systematic searches of several databases, as well as grey literature searches of clinical trial databases to identify unpublished

and/or ongoing studies. As a result, we identified several unpublished studies for which data was unavailable. It is important to acknowledge the potential role of publication bias in systematic reviews of rTMS for PTSD. Further, unlike other recent reviews, we included depression as an outcome and demonstrated that rTMS is also effective in reducing depression symptoms among patients with PTSD. Because PTSD is often comorbid with depression, this finding has important implications for treating individuals with comorbid PTSD and depression. Finally, to get a better sense of the magnitude of change between treatments, we also calculated unstandardized PTSD differences which can provide more meaningful symptom change data than effect sizes alone. Thus, we were able to detect that HF rTMS was associated with PCL scores that were 16.67 points (95% CI: -20.26, -13.08) lower compared to sham, and 9.04 points lower (95% CI: -14.07, -4.02) relative to LF rTMS.

Given the complex symptom constellation underlying PTSD and its often comorbid presentation, more refined methods to evaluate the effect of high versus low frequency rTMS are needed. Notably, recent research has documented that HF and LF stimulation both result in increased cortical activity proximal to the coil placement (Tremblay et al., 2020) raising questions about the proposed inhibitory/excitatory effects of frequency intensity. Given the heterogeneous presentations of PTSD, there may also be variability in the match between rTMS protocol and PTSD subtype. For instance, evaluating functional connectivity patterns, Zhang et al. (2020) identified two clinically relevant subtypes of PTSD with one subtype that was less responsive to psychotherapy for PTSD. In a depression study, Speer et al. (2000) found that changes in mood following different rTMS frequencies were inversely related such that individuals who improved with one frequency worsened with the other. Future research is warranted to evaluate whether different rTMS protocols are more efficacious for different PTSD

subtypes, potentially beyond just cluster score differences. Thus, current findings that HF and LF rTMS were both efficacious may reflect imprecise neurobiological models of PTSD, an incomplete understanding of the effects of rTMS on neural networks, and/or measurement limitations.

Across the small number of included trials there was wide heterogeneity in the rTMS protocols. Given the small body of research, we were unable to conduct analyses to adequately assess whether many of these factors accounted for some or all of the observed heterogeneity beyond frequency level. Before rTMS can be recommended in future CPGs and standardly applied in practice, greater standardization of treatment protocols is needed. There was also wide heterogeneity in the research samples recruited across these studies. rTMS clinical studies tended to be limited to patients with refractory PTSD who are concurrently receiving another treatment. If rTMS is proposed to be a front-line monotherapy for PTSD, then future trials will need to carefully consider patient selection. If rTMS is proposed to be an augmentation therapy for refractory PTSD (as it has been established for depression), then future trials will need to continue to recruit accordingly and CPG developers should take this into account.

Several limitations to the current review are important to note. First, we only included peer-reviewed literature that was published in English and so we may have omitted relevant non-English publications. Second, the body of research on rTMS for PTSD is still relatively small which limits our confidence in our pooled results. Furthermore, we were unable to systematically analyze the effects of rTMS on the PTSD symptom clusters given the lack of reported data. The trials that did report on symptom clusters also tended to report on the 3-cluster model, as opposed to the 4-cluster model that is currently used. Although there were a few studies that used rTMS as an augmentation strategy for specific TFPs, there were not enough of those studies to

analytically pool together. Given the proposed mechanisms of rTMS, TFP augmentation with rTMS is a promising avenue for future research.

Conclusion

Our results identified some evidence to support the efficacy of rTMS for PTSD across a small subset of trials with an overall quality rating of *very low*. rTMS is more efficacious than sham, but the magnitude of this effect is still imprecise. Future trials need to take into account many of the limitations of the current body of evidence to further advance recommendations on the use of rTMS for PTSD in clinical practice.

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Table 1. Characteristics of included studies

	Country	Group n ¹	PTSD diagnosis	Concurrent Treatment	Target	Intensity	Frequency	# Sessions	Additional Treatment Components	PTSD & depression measures	Longest follow-up
Ahmadizadeh 2018	Iran	B-rTMS = 22 R-rTMS = 21 Sham = 22	SCID	2-months stable meds and psychotherapy prior to trial	DLPFC	100%	20 Hz	10 4 weeks		PCL-M	End of treatment
Boggio 2010	Brazil	R-rTMS = 10 L-rTMS = 10 Sham = 10	SCID	3-weeks stable meds and psychotherapy prior to trial, continued during trial	DLPFC	80%	20 Hz	10 2 weeks		PCL, TOP-8, HDRS	12-weeks post-treatment
Cohen 2004	Israel	1Hz-rTMS = 8 10Hz-rTMS = 10 Sham = 6	SCID	3-weeks stable meds and psychotherapy prior to trial, continued during trial	RDLPF C	80%	1 Hz and 10 Hz	10 2 weeks		PCL, TOP-8, CAPS, HDRS	2-weeks post-treatment
Fryml 2019	US	PE + L-rTMS = 3 PE + L-sham = 2 PE + R-rTMS = 2 PE + R-sham = 1	SCID	Allowed to remain on current meds, kept stable for duration of trial	Right or left DLPFC	120%	10 Hz	8 8 weeks	Prolonged exposure	CAPS, HDRS, PCL	End of treatment
Isserles 2013	Israel	Exposure + DTMS = 10 Sham exposure + DTMS = 10 Exposure + sham DTMS = 10	CAPS	4-weeks stable meds prior to trial, no change during trial	mPFC	120%	20 Hz	12 4 weeks	Brief exposure	CAPS, PSS-SR, HDRS, BDI-II	2-months post-treatment
Kozel 2018	US	CPT + rTMS = 54 CPT + Sham = 49	CAPS	Allowed to remain on current meds, could not start new psychotherapy	Right DLPFC	110%	1 Hz	12 12 weeks	Cognitive processing therapy	CAPS, PCL, QIDS-16	6-months post-treatment
Kozel 2019	US	1 Hz-rTMS = 17 10 Hz-rTMS = 18	CAPS	1-month stable meds maintained during trial, could not be enrolled in PE, CPT, or EMDR	Right DLPFC	110%	1 Hz and 10 Hz	36 9 weeks		CAPS-5, PCL, QIDS-SR, MADRS	3-months post-treatment
Leong 2020	Canada	1 Hz-rTMS = 11 10 Hz-rTMS = 10 Sham = 10	MINI	4-weeks stable meds, no changes in meds or psychotherapy during trial	Right DLPFC	120%	1 Hz and 10 Hz	10 2 weeks		CAPS, PCL, HDRS, QIDS	3-months post-treatment
Nam 2013	South Korea	1 Hz-rTMS = 9 Sham = 9	Clinical interview	Meds and psychotherapy maintained during trial	Right PFC	100%	1 Hz	15 3 weeks		CAPS	5-weeks post-treatment
Osuch 2009 ²	US	Exposure + rTMS = 9 Exposure + Sham = 9	CAPS	3-weeks stable for certain meds, tapered off others	Right DLPFC	100%	1 Hz	20 3-5 per week	Brief exposure	CAPS, HDRS	End of treatment
Philip 2019 iTBS	US	iTBS = 25 Sham = 25	SCID	6-weeks stable meds and psychotherapy, allowed to continue unchanged during trial	Right DLPFC	80%	NA	10 2 weeks		CAPS-5, PCL, IDS-SR	1-month post-treatment

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Philip 2019 sTMS	US	sTMS = 10 Sham = 13	CAPS	6-weeks stable meds and psychotherapy, allowed to continue unchanged during trial	NA	NA	NA	20 4 weeks	PCL, QIDS	End of treatment
Watts 2012	US	rTMS = 10 Sham = 10	SCID	2-months stable meds and psychotherapy prior to trial, no changes during trial	Right DLPFC	90%	1 Hz	10 2 weeks	CAPS, PCL, BDI	2-months post-treatment

Table 2. Multivariate meta-analytic results of changes in PTSD and depression, adverse event proportions, and dropout proportions, by assigned treatment group

Study	High freq. rTMS	Low freq. rTMS	Sham rTMS
PTSD, standardized (g [95% CI])			
Ahmadizadeha (2018)	-2.36 [-3.23, -1.50]		-0.41 [-0.85, 0.03]
Boggio (2010)	-4.05 [-5.92, -2.19]		-0.84 [-1.52, -0.16]
Cohen (2004)	-1.61 [-2.52, -0.70]	-0.57 [-1.26, 0.12]	-0.05 [-0.74, 0.65]
Kozel (2019)	-0.87 [-1.40, -0.35]	-0.74 [-1.26, -0.23]	
Leong (2020)	0.21 [-0.40, 0.81]	-0.58 [-1.18, 0.02]	0.59 [-0.07, 1.24]
Nam (2013)		-4.62 [-6.84, -2.40]	-3.50 [-5.22, -1.78]
Watts (2012)		-2.34 [-3.51, -1.16]	-0.89 [-1.59, -0.20]
Summary	-1.84 [-2.90, -0.79]	-1.65 [-2.71, -0.59]	-0.62 [-1.56, 0.32]
I ² (%)	88.68	88.96	91.23
n	66	55	64
PCL-IV, unstandardized (b [95% CI])			
Ahmadizadeha (2018)	-21.16 [-24.78, -17.54]		-3.62 [-7.90, 0.66]
Boggio (2010)	-20.91 [-25.11, -16.71]		-5.02 [-8.60, -1.44]
Cohen (2004)	-19.70 [-26.58, -12.82]	-6.50 [-11.42, -1.58]	-1.80 [-5.00, 1.40]
Leong (2020)	-11.89 [-24.79, 1.01]	-11.30 [-23.66, 1.06]	-9.48 [-15.48, -3.48]
Watts (2012)		-16.20 [-21.60, -10.80]	-2.50 [-5.28, 0.28]
Summary	-20.39 [-23.43, -17.35]	-11.34 [-15.38, -7.30]	-3.72 [-5.93, -1.51]
I ² (%)	22.22	16.54	38.51
n	48	29	55
Depression, standardized (g [95% CI])			
Boggio (2010)	-1.84 [-2.83, -0.85]		-0.69 [-1.33, -0.04]
Cohen (2004)	-1.17 [-1.93, -0.40]	-0.54 [-1.22, 0.14]	0.29 [-0.42, 1.01]
Kozel (2019)	-1.59 [-2.27, -0.90]	-1.09 [-1.68, -0.51]	
Leong (2020)	-0.66 [-1.33, 0.01]	-0.41 [-0.99, 0.16]	0.00 [-0.60, 0.60]
Watts (2012)		-0.76 [-1.42, -0.10]	-0.13 [-0.70, 0.45]
Summary	-1.26 [-1.71, -0.81]	-0.74 [-1.14, -0.34]	-0.17 [-0.57, 0.23]
I ² (%)	30.11	39.11	38.57
n	47	46	35
Dropout (p [95% CI])			
Ahmadizadeha (2018)	0.19 [0.05, 0.39]		0.27 [0.10, 0.48]
Boggio (2010)	0.10 [0.08, 0.38]		0.20 [0.01, 0.51]
Cohen (2004)	0.09 [0.07, 0.35]	0.20 [0.01, 0.51]	0.25 [0.01, 0.62]
Kozel (2019)	0.28 [0.09, 0.51]	0.18 [0.03, 0.40]	
Leong (2020)	0.10 [0.08, 0.38]	0.00 [0.00, 0.15]	0.10 [0.08, 0.38]
Nam (2013)		0.22 [0.01, 0.56]	0.22 [0.01, 0.56]
Watts (2012)		0.00 [0.00, 0.17]	0.00 [0.00, 0.17]
Summary	0.15 [0.06, 0.28]	0.09 [0.01, 0.21]	0.17 [0.07, 0.29]
I ² (%)	23.47	20.28	20.14
n	70	57	69
Adverse events (p [95% CI])			
Ahmadizadeha (2018)	0.00 [0.00, 0.08]		0.00 [0.00, 0.08]
Kozel (2019)	0.11 [0.00, 0.31]	0.00 [0.00, 0.10]	

Leong (2020)	0.00 [0.00, 0.17]	0.09 [0.07, 0.35]	0.00 [0.00, 0.17]
Nam (2013)		0.44 [0.13, 0.78]	0.44 [0.13, 0.78]
Watts (2012)		0.00 [0.00, 0.17]	0.00 [0.00, 0.17]
Summary	0.04 [0.00, 0.23]	0.06 [0.09, 0.25]	0.04 [0.00, 0.22]
I ² (%)	73.42	66.82	67.53
n	50	47	50

rTMS = repetitive transcranial magnetic stimulation; PTSD = posttraumatic stress disorder; PCL-IV = PTSD checklist for DSM IV; High freq. rTMS > 1 Hz; Low freq. rTMS ≤ 1 Hz; I² = heterogeneity; CI = confidence intervals; g = Hedge's g effect size; b = unstandardized effect size; p = proportion estimates