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Repetitive transcranial magnetic stimulation for post-traumatic stress disorder in adults (Review)

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[Intervention Review]

Repetitive transcranial magnetic stimulation for post-traumatic stress disorder in adults

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ABSTRACT

Background

The estimated lifetime prevalence of post-traumatic stress disorder (PTSD) in adults worldwide has been estimated at 3.9%. PTSD appears to contribute to alterations in neuronal network connectivity patterns. Current pharmacological and psychotherapeutic treatments for PTSD are associated with inadequate symptom improvement and high dropout rates. Repetitive transcranial magnetic stimulation (rTMS), a non-invasive therapy involving induction of electrical currents in cortical brain tissue, may be an important treatment option for PTSD to improve remission rates and for people who cannot tolerate existing treatments.

Objectives

To assess the effects of repetitive transcranial magnetic stimulation (rTMS) on post-traumatic stress disorder (PTSD) in adults.

Search methods

We searched the Cochrane Common Mental Disorders Controlled Trials Register, CENTRAL, MEDLINE, Embase, three other databases, and two clinical trials registers. We checked reference lists of relevant articles. The most recent search was January 2023.

Selection criteria

We included randomized controlled trials (RCTs) assessing the efficacy and safety of rTMS versus sham rTMS for PTSD in adults from any treatment setting, including veterans. Eligible trials employed at least five rTMS treatment sessions with both active and sham conditions. We included trials with combination interventions, where a pharmacological agent or psychotherapy was combined with rTMS for both intervention and control groups. We included studies meeting the above criteria regardless of whether they reported any of our outcomes of interest.

Data collection and analysis

Two review authors independently extracted data and assessed the risk of bias in accordance with Cochrane standards. Primary outcomes were PTSD severity immediately after treatment and serious adverse events during active treatment. Secondary outcomes were PTSD remission, PTSD response, PTSD severity at two follow-up time points after treatment, dropouts, and depression and anxiety severity immediately after treatment.

Main results

We included 13 RCTs in the review (12 published; 1 unpublished dissertation), with 577 participants. Eight studies included stand-alone rTMS treatment, four combined rTMS with an evidence-based psychotherapeutic treatment, and one investigated rTMS as an adjunctive to treatment-as-usual. Five studies were conducted in the USA, and some predominantly included white, male veterans.

Active rTMS probably makes little to no difference to PTSD severity immediately following treatment (standardized mean difference (SMD) -0.14, 95% confidence interval (CI) -0.54 to 0.27; 3 studies, 99 participants; moderate-certainty evidence). We downgraded the certainty of evidence by one level for imprecision (sample size insufficient to detect a difference of medium effect size). We deemed one study as having a low risk of bias and the remaining two as having 'some concerns' for risk of bias. A sensitivity analysis of change-from-baseline scores enabled inclusion of a greater number of studies (6 studies, 252 participants). This analysis yielded a similar outcome to our main analysis but also indicated significant heterogeneity in efficacy across studies, including two studies with a high risk of bias.

Reported rates of serious adverse events were low, with seven reported (active rTMS: 6; sham rTMS: 1). The evidence is very uncertain about the effect of active rTMS on serious adverse events (odds ratio (OR) 5.26, 95% CI 0.26 to 107.81; 5 studies, 251 participants; very low-certainty evidence [Active rTMS: 23/1000, sham rTMS: 4/1000]). We downgraded the evidence by one level for risk of bias and two levels for imprecision. We rated four of five studies as having a high risk of bias, and the fifth as 'some concerns' for bias.

We were unable to assess PTSD remission immediately after treatment as none of the included studies reported this outcome.

Authors' conclusions

Based on moderate-certainty evidence, our review suggests that active rTMS probably makes little to no difference to PTSD severity immediately following treatment compared to sham stimulation. However, significant heterogeneity in efficacy was detected when we included a larger number of studies in sensitivity analysis. We observed considerable variety in participant and protocol characteristics across studies included in this review. For example, studies tended to be weighted towards inclusion of either male veterans or female civilians. Studies varied greatly in terms of the proportion of the sample with comorbid depression. Study protocols differed in treatment design and stimulation parameters (e.g. session number/duration, treatment course length, stimulation intensity/frequency, location of stimulation). These differences may affect efficacy, particularly when considering interactions with participant factors.

Reported rates of serious adverse events were very low (< 1%) across active and sham conditions. It is uncertain whether rTMS increases the risk of serious adverse event occurrence, as our certainty of evidence was very low. Studies frequently lacked clear definitions for serious adverse events, as well as detail on tracking/assessment of data and information on the safety population. Increased reporting on these elements would likely aid the advancement of both research and clinical recommendations of rTMS for PTSD.

Currently, there is insufficient evidence to meta-analyze PTSD remission, PTSD treatment response, and PTSD severity at different periods post-treatment. Further research into these outcomes could inform the clinical use of rTMS. Additionally, the relatively large contribution of data from trials that focused on white male veterans may limit the generalizability of our conclusions. This could be addressed by prioritizing recruitment of more diverse participant samples.

PLAIN LANGUAGE SUMMARY

Is repetitive transcranial magnetic stimulation (rTMS) an effective and safe treatment for adults with post-traumatic stress disorder (PTSD)?

Key messages

• rTMS probably does not reduce the severity of PTSD symptoms by the end of treatment compared with placebo rTMS (sham stimulation) in adults. These findings, however, were limited by wide variations in how the treatment was delivered and the small number of participants.

• Occurrences of serious unwanted effects in studies of rTMS for PTSD have been rare.

• We need more studies investigating rTMS for PTSD in adults. It would be helpful if future studies reported on unwanted effects in greater detail, and followed participants for longer after treatment to assess PTSD severity.

What is post-traumatic stress disorder?

Post-traumatic stress disorder (PTSD) is a mental health condition characterized by distressing and impairing symptoms that develop in some individuals after exposure to a traumatic event. When left untreated, many individuals with PTSD suffer for years.

How is PTSD treated?

Several treatments exist for PTSD, including medication and psychotherapy. However, existing treatments are associated with high dropout rates, which suggests people may have problems with tolerating treatment and may continue to experience symptoms. More effective treatments for PTSD are needed. Repetitive transcranial magnetic stimulation (rTMS) may be a promising treatment for PTSD.

What is rTMS?

rTMS is a non-invasive treatment that involves inducing an electrical field in brain tissue by placing a coil against the scalp that releases magnetic pulses. The biological pathways by which rTMS produces changes in mental health symptoms remain unclear and are an active area of research. rTMS has proven effective in treating people with major depressive disorder and obsessive-compulsive disorder – two mental health conditions that share important characteristics with PTSD.

What did we want to find out?

We wanted to find out if rTMS is better than placebo treatment (sham stimulation) for reducing the severity of PTSD immediately after treatment, and if it is associated with any serious unwanted effects during treatment. We were interested in the persistence of treatment effects, and so aimed to explore the impact of rTMS on PTSD severity at 1 to 4 weeks and 1 to 3 months after treatment. To investigate how well people tolerate rTMS, we compared the number of participants who dropped out of treatment early in active versus sham rTMS groups. Finally, we wanted to examine the impact of rTMS treatment on anxiety and depression immediately after treatment.

What did we do?

We searched for studies that examined rTMS compared with sham rTMS in adults with PTSD. We compared and summarized the results of the studies and rated our confidence in the evidence, based on factors such as study methods and number of participants.

What did we find?

We included data from 577 people who participated in 13 studies. The studies were conducted in countries around the world, with 5 carried out in the USA. Three studies with 99 participants contributed to our main analysis examining the effect of rTMS on PTSD severity immediately after treatment. Five studies with 251 participants contributed to our main estimate of rTMS safety (occurrence of serious unwanted events).

Main results

• rTMS probably makes little to no difference in PTSD symptoms immediately after treatment compared to sham treatment. However, only 3 studies contributed data to this primary analysis. When we analyzed the results from 6 studies, the effectiveness of rTMS compared to sham treatment varied across the studies. We did not have enough information from the studies included in this review to explore reasons for this variation. Other reviews of rTMS for PTSD suggest some ways of delivering rTMS may be more effective than others.

• Serious unwanted effects from rTMS treatment are rare. It is unclear whether rTMS is associated with increased chances of experiencing a serious unwanted effect.

• We do not know if rTMS has an effect on PTSD severity several weeks or months after treatment as there was insufficient information to explore this question.

• rTMS may make little to no difference in the rate of dropout from treatment or in depression and anxiety symptoms immediately after treatment.

What are the limitations of the evidence?

We are moderately confident in our finding that rTMS probably makes little to no difference in PTSD severity immediately after treatment. This means there is a fair chance that our conclusion may change as new evidence emerges. We are not confident in the evidence about serious unwanted events due to limited descriptions of unwanted effects and how they were measured in the included studies. In general, rates of serious unwanted effects are difficult to estimate, given the rarity of such events. This problem was exacerbated in the current review by the small number of study participants able to be included in this analysis.

How current is the evidence?

The evidence is current to January 2023.

SUMMARY OF FINDINGS

Summary of findings 1. Active rTMS compared to sham rTMS for adults with PTSD

Active rTMS compared to sham rTMS for adults with PTSD

Patient or population: adults with post-traumatic stress disorder (PTSD)
Setting: any (medical centers, health clinics, mental health clinics)
Intervention: active repetitive transcranial magnetic stimulation (rTMS)
Comparison: sham rTMS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sham rTMS	Risk with active rTMS				
PTSD severity (immediately after treatment) assessed with: SMD (CAPS-5 and CAPS-IV)	-	SMD **0.14 lower** (0.54 lower to 0.27 higher)	-	99 (3 RCTs)	⊕⊕⊕⊖ Moderate[a]	Active rTMS probably results in little to no difference in PTSD severity (immediately after treatment). MID for CAPS-IV has been estimated at 10 points. SMD transformed to CAPS-IV (using combined immediate-post SD from active treatment groups of Leong 2020 and Watts 2012): MD -4.08, 95% CI -15.74 to 7.88.
Serious adverse events (active study period) assessed with: count	4 per 1000	**23 per 1000** (1 to 326)	**OR 5.26** (0.26 to 107.81)	251 (5 RCTs)	⊕⊖⊖⊖ Very low[b,c]	Estimate of baseline (sham rTMS) risk of SAEs based upon 11 studies reporting SAE information (1 event per 224 participants). OR estimate is based upon 5 studies (n = 115 sham, n = 136 active), as we excluded studies with zero SAEs across all treatment arms from meta-analysis.
PTSD remission (immediately after treatment) - not reported	-	-	-	-	-	No studies reported this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CAPS-5: Clinician-Administered PTSD Scale for DSM-5; **CAPS-IV:** Clinician-Administered PTSD Scale for DSM-IV; **CI:** confidence interval; **MD:** mean difference; **MID:** minimal important difference; **OR:** odds ratio; **RCT:** randomized controlled trial; **SAE:** serious adverse events; **SMD:** standardized mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_443950817099890476.

[a]Downgraded once for imprecision due to low participant numbers.
[b]Downgraded once for study limitations due to high risk of bias.
[c]Downgraded twice for imprecision due to low participant numbers and large margin of error.

BACKGROUND

Description of the condition

Post-traumatic stress disorder (PTSD) describes a set of persistent and distressing symptoms occurring after exposure to a traumatic event (APA 2013; WHO 1993). For an adult to be diagnosed with PTSD, they must exhibit symptoms for at least a month across four domains: 1) intrusions, including memories or physical sensations that recur long after the stressful event; 2) avoidance of reminders of the event; 3) negative changes in thoughts or mood; and 4) changes in psychological and physiological reactivity. Research on trauma disorders suggests important differences exist in how these disorders manifest in children and adolescents relative to adults (Brewin 2017; Scheeringa 2011).

Lifetime prevalence of PTSD in adults in the USA is estimated at 6% to 7% (Goldstein 2016; Koenen 2017), and 12-month prevalence is estimated at 3.2% for men and 6.1% for women (Goldstein 2016). Additionally, an estimated 23% of veterans who fought in Iraq and Afghanistan meet the criteria for PTSD (Fulton 2015). Koenen and colleagues conducted a large-scale synthesis of survey data from adults in 26 countries between 2001 and 2012 and estimated the average lifetime prevalence of PTSD at 3.9% (Koenen 2017). Rates of PTSD varied across countries, and factors associated with increased risk for PTSD included younger age, female sex, less education, and lower income (Koenen 2017).

Research spanning animal models, experimental studies of healthy people, and clinical studies of individuals diagnosed with PTSD suggest that PTSD is associated with alterations in neural networks underlying fear, including learning and responding to signals of danger (Quirk 2006; VanElzakker 2014). Leading models describe two core alterations in the fear system: 1) overactive threat detection, including increased attention and hypersensitivity to potential threats; and 2) reduced fear extinction, indicated by difficulty learning that former signals of danger are no longer threatening (Quirk 2006; VanElzakker 2014). Overactive response to threat has been associated with hyperactivity of brain regions, including the amygdala and right prefrontal cortex, and reduced fear extinction has been associated with hypoactivity of other brain regions, including the hippocampus and ventromedial prefrontal cortex (Adenauer 2010; Badura-Brack 2018; Hughes 2011; Milad 2009; Rauch 2000; VanElzakker 2014).

PTSD appears to predispose individuals to experience reduced satisfaction in relationships, including intimate partnerships, friendships, and parenting, as well as difficulties with academic pursuits, employment, and maintaining stable housing (Rodriguez 2012; Vogt 2017). Several psychotherapies and medications have demonstrated efficacy in reducing PTSD symptoms, but high levels of residual symptoms often remain. A meta-analysis of trauma-focused psychotherapies for PTSD found these therapies to be associated with symptom improvement with large effect sizes (Steenkamp 2015). Nonetheless, more than half of the participants remained at or above clinical criteria for PTSD after treatment, and dropout rates were high (Steenkamp 2015). Additionally, a chart review of nearly 3000 veterans who received treatment for PTSD found that fewer than 20% achieved remission (i.e. no longer met the criteria for a PTSD diagnosis) following a course of medication (Shiner 2018). New and updated treatments are needed to help those with PTSD achieve symptom relief and remission.

Description of the intervention

Transcranial magnetic stimulation (TMS) is a non-invasive tool used to alter the activity of neurons. This tool involves applying a pulsed magnetic field to the surface of the brain, which induces an electrical field in the underlying brain tissue (George 2002). Over the past two decades, there has been a proliferation of research on TMS and how various parameters, such as pulse frequency, sequence and intensity, may impact brain activity differently (Pell 2011). There are different forms of TMS, with two common types being single-pulse TMS and repetitive TMS, which involve, respectively, a single pulse versus repeated pulses of magnetic field. Only repetitive TMS appears capable of inducing effects that last beyond the period of stimulation, making this the preferred form of TMS for potential clinical application (Rossi 2004). In contrast, single-pulse TMS has primarily been used to explore mechanisms of action (Rossi 2004). Accordingly, this review will focus on repetitive TMS (rTMS).

Some of the most common variations of rTMS used in clinical studies include high- and low-frequency rTMS (> 5 Hz and ≤ 1 Hz, respectively), and continuous or intermittent theta-burst stimulation (TBS). High-frequency rTMS and intermittent TBS appear to induce lingering excitatory effects, while low-frequency rTMS and continuous TBS appear to reduce neural activity (Chen 1997; Fitzgerald 2006; Huang 2005; Pascual-Leone 1994; Speer 2000). These effects are also likely related to changes in excitatory and inhibitory neurotransmitters with neuromodulation (Concerto 2022). Excitation or inhibition of neural activity induced by rTMS is theorized to disrupt maladaptive patterns of neural activity, such as those associated with an overactive threat response, and to potentiate network activity associated with normal functioning (Clark 2015; Koek 2019).

The variations in treatment protocols (including treatment target, intensity of treatment, frequency of stimulation, number of sessions) and patient characteristics (such as comorbid disorders) raise questions about mechanisms of action and thus, optimization of treatment efficacy (Concerto 2022). For example, stimulation of the dorsolateral prefrontal cortex can be delivered to one or both hemispheres at various intensities (% MT); the stimulation can be high or low frequency; or the number of sessions (and therefore total number of pulses) can vary. Treatment may also affect symptoms of comorbid disorders such as depression, which can also influence severity of associated PTSD symptoms (Concerto 2022).

Reviews and meta-analyses thus far indicate that treatment with rTMS is safe and well-tolerated in general, and specifically among people with PTSD (Belsher 2021; Cirillo 2019; Rossi 2009; Rossi 2021). Seizure is the only severe adverse effect that has been consistently associated with rTMS (Rossi 2009; Rossi 2021). Importantly, seizure induction by rTMS has been exceedingly rare since the establishment of safety standards for treatment parameters in 1998 (Rossi 2009; Rossi 2021; Wassermann 1998). rTMS treatment has also been associated with temporary headache and pain at the stimulation site (Rossi 2009). Low dropout rates across sham and active arms of randomized controlled trials for rTMS suggest that these side effects are tolerable and do not significantly contribute to treatment discontinuation (Belsher 2021; Cirillo 2019).

How the intervention might work

There is evidence that high-frequency stimulation primes neural excitation and may be applied to increase neural activity in underactive brain regions, such as the medial prefrontal cortex, in PTSD (Shin 2006; Speer 2000). Similarly, low-frequency stimulation may reduce activity in overactive regions such as the right prefrontal cortex (Adenauer 2010; Speer 2000). The high frequency/excitatory and low frequency/inhibitory theory, however, may be overly simplistic, as it assumes stable, coherent activity of the targeted brain regions, and ignores the ways in which stimulation frequency interacts with a host of other rTMS parameters (Huerta 2009; Koek 2019; Ziemann 2008). Current leading theories suggest the neurobiological basis of PTSD and other psychiatric conditions are circuit dysfunctions, with patterns of activity across networks of distributed brain regions holding greater importance than activity levels within particular regions (Akiki 2017; Buckholtz 2012; Koek 2019; Ressler 2007; Williams 2017). For example, a recent study found an association between the magnitude of decrease in PTSD symptoms and change in coherence of neural activity between the subgenual anterior cingulate cortex and the dorsolateral prefrontal cortex and between the hippocampus and salience network (Philip 2018). Patient characteristics may also influence the effects of neuromodulation. The presence of co-occurring biological processes related to age, sex, or physical or psychiatric disorders, for example, may influence treatment response (Nicoletti 2023). The most effective rTMS treatment may require potentiating or inhibiting a highly specific circuit of nodes identified using individualized brain morphology and activity patterns (Cocchi 2018; Fox 2012). It is also possible that any disruption of maladaptive feedback patterns may create the conditions necessary for normal, pre-disorder activity patterns to return. If this is the case, a variety of stimulation locations and frequencies may produce similar effects as long as they induce plasticity somewhere within the disrupted neural circuit (Huerta 2009; Koek 2019).

Although the mechanisms of action remain largely unknown, it is promising that rTMS has been effective in treating two psychiatric conditions with which PTSD shares key symptoms (Solomon 1991). Specifically, the US Food and Drug Administration (FDA) has approved rTMS for treatment-resistant major depressive disorder and obsessive compulsive disorder in adults (Voelker 2018).

We do not explore the impact of rTMS on PTSD in children and adolescents in this review due to evidence of differences in the manifestation of PTSD symptoms in children and adolescents, as well as the absence of FDA approval for and relative dearth of studies of rTMS safety and efficacy in this population (Allen 2017; Brewin 2017; Memon 2021; Scheeringa 2011).

Why it is important to do this review

PTSD is a debilitating condition with significant prevalence in the general population and even higher rates among veterans. Current pharmacological and psychotherapeutic treatments for PTSD demonstrate efficacy in reducing but not eliminating symptoms, and are plagued by high dropout rates. rTMS may be an important treatment option for improving remission rates and for people who cannot tolerate medication or psychotherapy. Several thoughtful and methodologically rigorous systematic reviews on this topic have been conducted in recent years (Belsher 2021; Cirillo 2019; Kan 2020). All three reviews supported rTMS as an effective treatment for PTSD, yet Belsher and colleagues and Cirillo and colleagues all expressed reservations about the quality of evidence. Our review adds to this literature by providing: an up-to-date synthesis of available data; a detailed exploration of the risk of bias using the Cochrane Collaboration's revised standards (the risk of bias 2 tool; Sterne 2019); and outcomes displayed in both tables and graphs that are easily comprehensible to a clinical audience. Provision of clear and reliable estimates for the efficacy and risk profile of rTMS may aid clinicians' decision-making about allocation of resources and treatment selection for PTSD in adults, as well as raise awareness of treatment options for patients.

OBJECTIVES

To assess the effects of repetitive transcranial magnetic stimulation (rTMS) on post-traumatic stress disorder (PTSD) in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) assessing the therapeutic efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) for post-traumatic stress disorder (PTSD). We included all eligible trials, irrespective of language and publication status. We intended to include cross-over trials (trials in which participants undergo multiple interventions sequentially) if we could obtain data after phase 1 (ultimately, no cross-over trials met eligibility criteria). We excluded quasi-randomized trials (trials using a method of intervention assignment that was not truly random, such as allocation by date of birth or order of recruitment).

Types of participants

We included trials in adults (aged 18 years or older) who met the criteria for PTSD, according to the Diagnostic and Statistical Manual of Mental Disorders: DSM-IV or subsequent revisions (DSM-IV-Text Revised [TR], DSM-5), or the International Classification of Diseases – 10th Revision (ICD-10), as determined by structured clinical interview or clinician diagnosis (APA 1994; APA 2000; APA 2013; WHO 1993). Participants were included irrespective of gender, nationality, ethnicity, veteran status, and treatment setting. If studies included a subset of participants who met the above criteria, we included the relevant subset of data, or we contacted the study authors to request these data if not reported separately.

Types of interventions

Interventions

We included trials in which rTMS was applied for a minimum of five sessions. We chose a five-session minimum to distinguish treatment trials from studies using single-pulse or very brief TMS to investigate mechanisms of action rather than effect a treatment response. Additionally, research indicates multiple sessions are required to induce long-term potentiation, defined as protracted increase in neurotransmission across synapses and corresponding increased neural connectivity (Cirillo 2019; Racine 1995; Rossi 2004). We included studies of any duration, dose, and stimulation intensity.

Comparators

For inclusion in this review, we required trials to have a sham stimulation (non-active rTMS) condition applied for a minimum of five sessions. Sham stimulation involves placebo interventions designed to mimic rTMS without delivering the active treatment ingredient (induced electrical field in brain tissue under the site of stimulation).

Combination interventions

We included trials employing combination interventions, where a pharmacological agent or psychotherapy was combined with rTMS treatment. We only included such trials if the intervention and control groups received the same pharmacological or psychological therapy.

Types of outcome measures

We included any studies that met the above criteria, irrespective of whether they reported any of our outcomes of interest.

Primary outcomes

- PTSD severity immediately after treatment: score on any validated PTSD scale such as Clinician-Administered PTSD Scale (CAPS; Blake 1995; Weathers 1999), Comprehensive International Diagnostic Interview (CIDI; WHO 1997), or PTSD Checklist for DSM-5 (PCL-5; Weathers 2013). We gave preference to clinician-reported scales over self-reported scales in studies which reported both. The time window for eligible outcomes included scores taken immediately post-intervention or the earliest available follow-up, not extending beyond one week post-intervention.
- Serious adverse events: number of participants reporting one or more serious adverse events occurring during the period of active or sham treatment. We defined 'serious adverse events' according to the guidelines set forth by the FDA, as potentially life-threatening events or events requiring medical intervention; for example, seizure or manic episode (FDA 2009).

Secondary outcomes

- PTSD remission: number of participants who no longer met criteria for a diagnosis of PTSD immediately post-treatment or the earliest available follow-up (not extending beyond one week post-intervention), as diagnosed by the DSM-IV, DSM-IV-TR, DSM-5, or ICD-10 (APA 1994; APA 2000; APA 2013; WHO 1993).
- PTSD response: number of participants who exhibited at least a 30% decrease in severity between baseline and immediate post-intervention assessment, or the earliest available follow-up (not extending beyond one week post-intervention). There is no standard definition for treatment response, but a 30% decrease in symptom severity is the most commonly-used response metric according to a recent meta-analysis (Varker 2020). We planned to base response versus non-response status on reported response results (using the aforementioned definition) from any validated PTSD scale, such as the Clinician-Administered PTSD Scale (CAPS; Blake 1995; Weathers 1999), Comprehensive International Diagnostic Interview (CIDI; WHO 1997), or PTSD Checklist for DSM-5 (PCL-5; Weathers 2013). We planned to give preference to clinician-administered scales over self-reported scales in studies which reported both.
- PTSD severity (delayed follow-up): score on any validated PTSD scale such as the Clinician-Administered PTSD Scale (CAPS; Blake 1995; Weathers 1999), Comprehensive International Diagnostic Interview (CIDI; WHO 1997), or PTSD Checklist for DSM-5 (PCL-5; Weathers 2013). We gave preference to clinician-administered scales over self-reported scales in studies which reported both. We planned to compare assessments within two follow-up time frames: between one and four weeks after treatment, and between four and 12 weeks after treatment. If a study reported multiple follow-up assessments within one of these follow-up windows, we used data from the follow-up closest to the end of treatment.
- Dropout: number of participants who withdrew from the trial before the end of treatment. We discuss the reasons for dropout (e.g. side effects) in a narrative review (see Effects of interventions).
- Depression severity: score immediately post-intervention or the earliest available follow-up (not extending beyond one week post-intervention), as measured by a validated scale, such as the Hamilton Depression Rating Scale (Hamilton 1960), Montgomery-Åsberg Depression Rating Scale (Montgomery 1979), or Beck Depression Inventory-II (Beck 1961).
- Anxiety severity: score immediately post-intervention or the earliest available follow-up (not extending beyond one week post-intervention), as measured by a validated scale, such as the Beck Anxiety Inventory (Beck 1988), or Spielberger State-Trait Anxiety Inventory (Spielberger 1983).

Search methods for identification of studies

Electronic searches

We searched the following databases and trial registries to identify randomized controlled trials of repetitive transcranial magnetic stimulation (rTMS) for post-traumatic stress disorder (PTSD). We used relevant subject headings (controlled vocabulary) and search syntax appropriate to each resource. Dates listed below are the dates of the most recent search, as the original search was conducted in February 2022 and the searches were updated in January 2023.

- Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR) (all available years to June 2016, search date 4 February 2022).
- The Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, search date 11 January 2023).
- Ovid MEDLINE (1946 to 10 January 2023) (Appendix 1).
- Ovid Embase (1974 to 10 January 2023).
- Ovid PsycINFO (1806 to January Week 2 2023).
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1900 to 11 January 2023).
- ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (1990 to 11 January 2023).
- ProQuest PTSDpubs (inception to 13 January 2023)
- ProQuest Dissertations & Theses A&I (inception to 13 January 2023)
- ClinicalTrials.gov (search date: 13 January 2023) (www.clinicaltrials.gov).
- World Health Organization International Clinical Trials Registry Platform (search date: 13 January 2023) (apps.who.int/trialsearch/).

We did not apply any restrictions on date, language, or publication status to the searches.

Searching other resources

We checked the reference lists of all included trials and relevant systematic reviews to identify additional trials missed from the original electronic searches (e.g. ongoing studies).

Data collection and analysis

Selection of studies

Two review authors (RB and KC) independently screened titles and abstracts of all identified records. We used Covidence systematic review screening software to screen titles and abstracts, and to document eligibility, exclusion, and reasons for exclusion (Covidence). After any discrepancies were resolved through discussion, we retrieved all potentially relevant articles. Two review authors (RB and KC) then independently assessed retrieved articles for inclusion and resolved discrepancies through discussion.

Data extraction and management

Two review authors (RB and KC or KJ) independently extracted data from the included studies. We conducted data extraction using a form that had been piloted on at least one study, as recommended by Li 2021. Discrepancies were resolved through discussion between the review authors. We present the details of the studies included in the Characteristics of included studies table. Data extracted from eligible trials includes the following.

- General descriptors: first author, year of publication, journal, source of funding, notable conflicts of interest, trial location(s), stated aims, start and end dates.
- Sample characteristics: study setting, mean or median age, sex composition, diagnoses, PTSD severity, inclusion and exclusion criteria.
- Interventions: number of sessions, target, localization method, frequency, intensity, total pulses, type of coil, equipment manufacturer and model, concomitant treatments permitted, description of sham treatment.
- Design methodology: study design, unit of allocation, follow-up time points, risk of bias domains.
- Outcome measures: time point of outcome assessment, instrument used for assessment, designation of outcomes as primary and secondary, number of dropouts.
- Statistical methodology: statistical models used, handling of missing data.

We made note of trials where we identified a potential risk of selective non-reporting of results (e.g. study authors stated the intention to assess certain outcomes, but the outcomes were not reported, or only summary statistics for the full sample combined across treatment arms were provided). In studies for which pre-registered study plans (e.g. published protocols, trial registries) were available, we identified discrepancies in outcomes reported in the study plan versus published results. We contacted study authors to attempt to clarify discrepancies. One review author (RB) transferred extracted data into Review Manager (RevMan 2024), and a second review author (KC or KJ) checked the data.

Assessment of risk of bias in included studies

Two review authors (RB and KC or KJ) independently assessed the risk of bias using the Cochrane risk of bias tool version 2.0 (RoB 2) for the following outcome measures: PTSD severity immediately post-intervention and serious adverse events (SAEs; Sterne 2019). We resolved any discrepancies through discussion. Our protocol stated our intention to conduct RoB 2 assessment for our secondary outcomes of PTSD remission and dropout (Brown 2022). However, we did not carry out these assessments as planned because none of the included studies reported on PTSD remission, and we decided that dropout was not an appropriate outcome for a valid RoB 2 assessment (see Risk of bias in included studies for details). We assessed the risk of bias in these domains: randomization process; deviations from intended interventions; missing outcome data; measurement of the outcome; and selection of reported results. Our risk of bias assessment focused on the effect of assignment to intervention (intention-to-treat [ITT] outcomes) for PTSD severity immediately post-intervention, and on the effect of adherence to intervention (using safety population) for SAEs. We rated the risk of bias for each domain and overall risk of bias as 'high', 'some concerns', or 'low', using the signaling questions and algorithms provided by the RoB 2 tool. We used the RoB 2 Excel tool to implement RoB 2 (available on the riskofbiasinfo.org website). The RoB 2 data are available in an external repository (https://osf.io/nmpk4/?view_only=3bf530fec7024a48ad0866c52c7a15f0). Cross-over trials are associated with some unique risk of bias concerns not addressed by the standard RoB 2 tool for parallel trials; however, no cross-over trials met our inclusion criteria.

Measures of treatment effect

The effect of assignment to intervention (the 'intention-to-treat' effect [ITT]) is the effect of interest in this review for efficacy. As such, our meta-analyses of PTSD severity, depression severity, and anxiety severity were limited to ITT outcomes. We explored adherence outcomes (i.e. the 'per-protocol' effect) for our primary efficacy outcome measure using sensitivity analysis. The effect of exposure to treatment is the effect of interest in this review for safety; accordingly, our meta-analysis of SAEs used the safety population.

Continuous outcomes

Continuous outcomes were PTSD severity, anxiety severity, and depression severity. We calculated mean differences (MDs) and 95% confidence intervals (CIs) for data that used the same scale. If studies used different scales, but the outcomes were conceptually consistent, we used standardized mean differences (SMDs). SMDs equivalent to or higher than 0.2, 0.5, and 0.8 were interpreted statistically as small, moderate, and large effect sizes, respectively (Cohen 1988). We gave preference to endpoint measures. To increase our sample size, we converted change scores to endpoint data and vice versa, using formulae provided in the *Cochrane Handbook for Systematic Reviews of Interventions* for sensitivity analyses (Higgins 2021b, hereafter referred to as the *Cochrane Handbook*).

Dichotomous outcomes

Dichotomous outcomes were serious adverse events, PTSD remission, PTSD response, and dropout. We calculated odds ratio (OR) estimates and their 95% CI.

Hierarchy of outcomes

For trials reporting more than one measure for the same outcome, we included data using the following rules (in order of priority): 1) we prioritized data from observer-rated scales over self-report questionnaires; and 2) we prioritized outcome measures used more frequently across the included studies.

Unit of analysis issues

For trials that included multiple treatment groups, we combined data from intervention arms that were sufficiently similar, using methods recommended in the *Cochrane Handbook* (Higgins 2021a; Higgins 2021b). We did not have any cross-over trials and did not expect any other non-standard design features among eligible RCTs (e.g. cluster-randomized controlled trials). If such trials had been included, we planned to provide a narrative summary.

Dealing with missing data

For most comparisons, we conducted meta-analyses of continuous and dichotomous outcomes using data from intention-to-treat (ITT) analyses. Specifically, our meta-analyses included outcomes for which data from all randomized participants were included according to randomized treatment assignment (i.e. regardless of non-compliance or dropout). The exception was serious adverse events, for which we used the safety population rather than ITT sample for meta-analysis, in accordance with standard practices for analyzing safety-related outcomes (National Research Council 2010.) We narratively reviewed trials with more than 40% attrition, rather than include these trials in meta-analytic synthesis, as ITT analysis is expected to have limited validity beyond this level of attrition (Armijo-Olivo 2009; Jakobsen 2017). For trials with less than 40% missing data, we accounted for missing data by using outcomes from appropriate imputation methods, including last observation carried forward, imputation of the mean of the other group, multiple imputation, and repeated measures mixed-effects models (Armijo-Olivo 2009). We gave preference to results from multiple imputation or mixed-effects models for trials reporting multiple methods to account for missing data. For studies not reporting ITT analyses, we attempted to contact study authors to obtain ITT outcomes. If the data were not available, we did not attempt our own data imputation as the methods require individual participant data. We described in narrative form the outcomes of such cases, rather than including them in meta-analysis. We examined results from per-protocol analyses in the sensitivity analyses. If a study reported relevant outcome measures without a usable measure of variability, we contacted the study authors in an effort to obtain the missing data. If we were unable to obtain the data, we reported the outcomes narratively.

Assessment of heterogeneity

We assessed heterogeneity by: 1) visually inspecting the forest plot, with heterogeneity indicated by non-overlapping 95% confidence intervals; and 2) calculating the I^2 statistic, with values of 0% to 40%, 30% to 60%, 50% to 90%, and 75% to 100% suggesting, respectively, minimal, moderate, substantial, and considerable inconsistency of results across studies (Deeks 2021). The I^2 statistic is intended to estimate the percentage of heterogeneity not due to sampling error. If high levels of heterogeneity were indicated by visual inspection of the forest plots or an I^2 statistic of75% or higher, we planned to explore this through prespecified subgroup analyses and sensitivity analyses. Subgroup analysis involves performing a test of heterogeneity across subgroups rather than all individual studies; this enables estimation of differences in treatment effect attributable to genuine group differences rather than sampling error (Deeks 2021). Similarly, heterogeneity estimates from sensitivity analyses can provide quantitative support for the presence of influential (outlier) studies that may be exerting undue influence on the meta-analytic estimate.

Assessment of reporting biases

For the primary outcome measures of PTSD severity immediately post-intervention and serious adverse events, if there were at least 10 included studies, we planned to examine potential reporting biases and interpret these using the recommendations of Sterne 2011. Specifically, we planned to create funnel plots and visually inspect them for asymmetry. We also planned to use statistical tests for small study effects as follows: 1) for continuous outcomes, Egger's test (Egger 1997); and 2) for dichotomous outcomes, tests proposed by Harbord 2006 (if the estimated heterogeneity variance of log odds ratio was less than or equal to 0.1). If the estimated heterogeneity variance of log odds ratio was greater than 0.1, then we planned to use the arcsine test including random effects proposed by Rücker 2008. Bias due to selective non-reporting of outcome domains can be difficult to detect (Page 2021). We evaluated trial results for this possibility as outlined in our data extraction plan. For trials with suspected selective non-reporting of outcomes, we evaluated the trial using the standards outlined in the *Cochrane Handbook* (Page 2021), including comparing published results against pre-publication study plans where available. We described the suspected risk of bias and its implications in narrative form.

Data synthesis

Continuous outcomes

For outcomes measured using the same scale, we used mean differences (MDs) and 95% CIs to summarize the data. For outcomes measured with differing yet conceptually analogous scales, we used standardized mean difference (SMD) with 95% CIs to summarize the data.

Dichotomous outcomes

We summarized dichotomous outcomes using the odds ratio (OR) and the accompanying 95% CI.

If we judged participants, interventions, and comparators to be sufficiently similar to ensure clinically meaningful statistical synthesis, then for all primary and secondary outcome measures, we conducted pairwise meta-analyses with random effects for intervention versus comparator. We selected a random-effects rather than a fixed-effect model for use due to predicted clinical heterogeneity from differing rTMS protocols and participant populations (Deeks 2021). We conducted quantitative synthesis using all eligible studies (unrestricted by level of bias rating). We narratively described results that were not appropriate for meta-analysis. We conducted meta-analyses for continuous data using the inverse-variance method in Review Manager (RevMan 2024). We used mixed-effects logistic regression to synthesize dichotomous data. Recent meta-analyses and simulation studies recommend mixed-effects logistic regression over conventional procedures, such as the Mantel-Haenszel method, as the former generates more precise and accurate estimates (Chang 2017; Deeks 2021;

Kuss 2015). We conducted analyses of dichotomous data using R software (R 2021; Viechtbauer 2010) and checked them using SAS (SAS 2013).

Subgroup analysis and investigation of heterogeneity

rTMS for psychiatric conditions is a relatively novel and rapidly developing area of study, resulting in many treatment parameters being non-standardized and not subjected to rigorous evaluation. However, recent reviews have focused on treatment dose (total pulses delivered) as well as the following set of parameters: stimulation location, frequency, pattern (inter-train intervals and spacing of treatments), and intensity (Kan 2020; Klomjai 2015; Rossi 2009). There is also interest in possible synergistic effects from combining rTMS with psychotherapy (Sathappan 2019). Additionally, traumatic brain injury (TBI), comorbid depressive disorders, comorbid anxiety disorders, and comorbid substance-use disorders have been identified as contributing to increased risk, complexity, and persistence of PTSD symptoms and therefore may impact the efficacy of rTMS treatment (Keane 2007; Sareen 2014). We planned to assess the following effect modifiers for impact on primary outcomes by comparisons of mean differences in PTSD severity immediately post-intervention and odds ratios for serious adverse events:

- rTMS dose (total pulses);
- rTMS protocol type;
- combination treatment status;
- comorbid psychiatric diagnosis;
- presence of TBI.

We planned to assess the effect of the total rTMS dose on the primary outcome measures outlined above using meta-regression. We planned to use subgroup analysis to examine the effect of protocol type, combination treatment status, comorbid psychiatric diagnosis, and presence of TBI on PTSD severity immediately post-intervention and on serious adverse events. In order to examine the effect of rTMS protocol type, we grouped trials by use of similar stimulation location, frequency, pattern, and intensity to form protocol types. We examined the effect of combination treatment status using the following comparison: active/sham rTMS versus active/sham rTMS in the context of a course of psychotherapy. We planned to examine the effect of comorbid psychiatric diagnosis by grouping trials according to the following conditions: comorbid depressive disorder, comorbid anxiety disorder, substance-use disorder, other DSM condition, or no comorbid diagnosis identified (classifications made according to DSM-5 categories or corresponding ICD or earlier DSM classification). Finally, we planned to examine the effect of the presence of TBI using the following comparison: with diagnosed TBI versus without diagnosed TBI. We conducted subgroup analyses using the formal test for subgroup differences in Review Manager (RevMan 2024).

Sensitivity analysis

We explored the robustness of our findings using sensitivity analysis. Specifically, we assessed the impact of risk of bias (by excluding studies at high risk of bias), attrition (by analyzing completer outcomes rather than the ITT data used for primary analysis), data synthesis method (by analyzing change scores instead of endpoint scores), and substantial heterogeneity (by excluding trials identified as significant contributors to heterogeneity).

Summary of findings and assessment of the certainty of the evidence

Using GRADEpro GDT software (GRADEpro GDT), we created a summary of findings table to present the following outcomes: PTSD severity immediately post-intervention, serious adverse events, and PTSD remission (Summary of findings 1). Outcome comparisons are included regardless of the risk of bias rating. For dichotomous outcomes, in addition to the odds ratio and corresponding 95% CI, we provided an estimate of assumed (sham) intervention risk per 1000 and corresponding (active treatment) intervention risk per 1000 (and 95% CI). We based the risk estimate for the sham group on the pooled estimate from the control groups of all included studies. We calculated the risk estimate for the treatment group using the formulae provided in the *Cochrane Handbook* on the basis of assumed risk in the control group and the relative risk estimate (Schünemann 2021). We assessed the certainty of the evidence using the methods and recommendations outlined by Schünemann 2021. These methods included assessing evidence across five GRADE domains for risk of bias, inconsistency, indirectness, imprecision, and publication bias. Two review authors (RB and KC) independently graded the evidence. We resolved any disagreement through discussion. We provided the reasons for downgrading and upgrading evidence in the footnotes of the summary of findings table. Using the standards recommended in the *Cochrane Handbook* (Schünemann 2021), we categorized the certainty of the evidence as high, moderate, low, or very low.

RESULTS

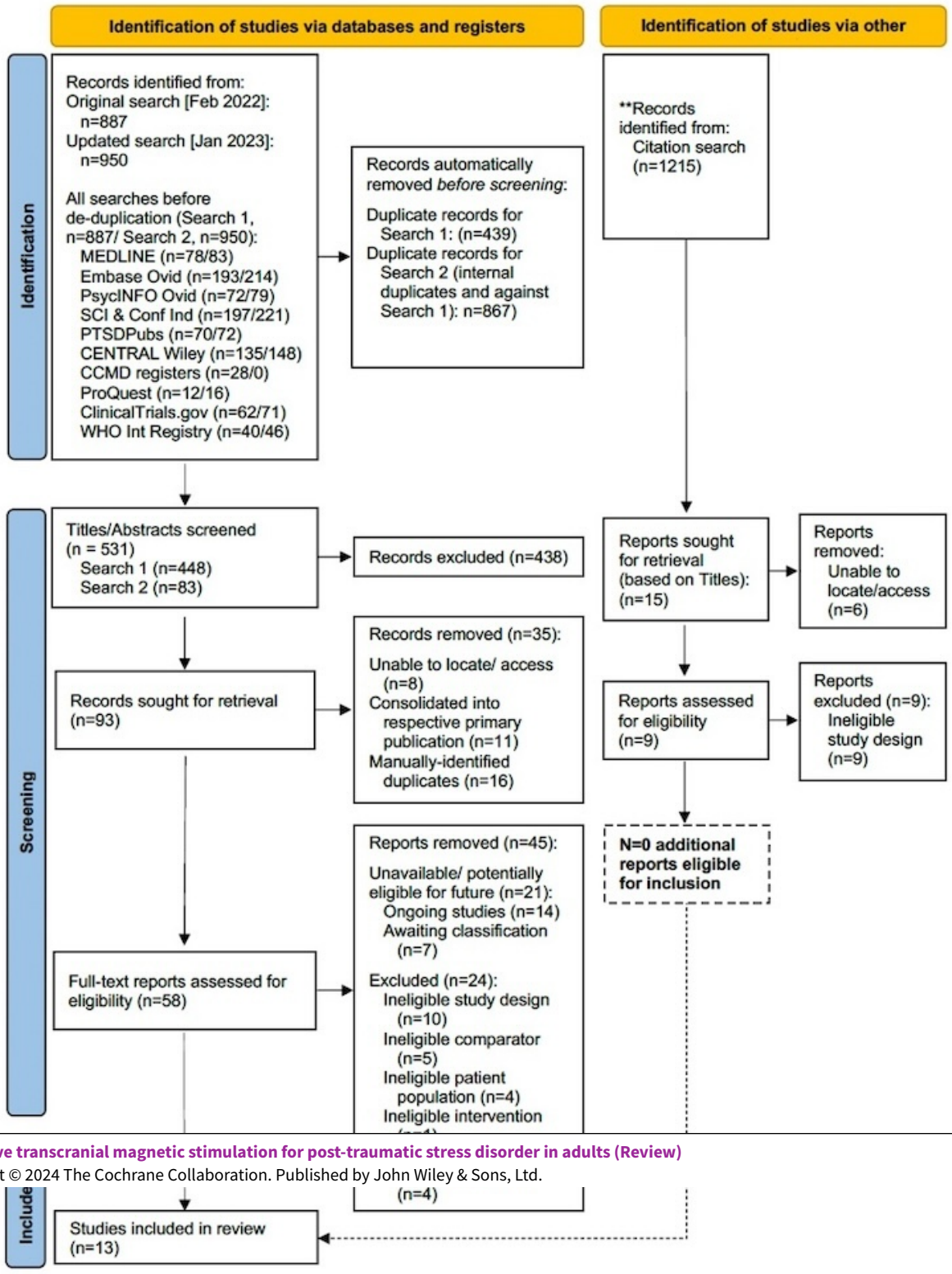
Description of studies

Results of the search

Figure 1 presents a full description of our study screening and selection process. In February 2022, the initial database search yielded 887 records. From these, 439 duplicate records were removed by automated processes in Covidence, resulting in 448 records for title/abstract screening. An updated database search conducted in January 2023 yielded 950 records; a total of 867 duplicates were removed (duplicates from within the updated search as well as duplicates of records identified from the original search), resulting in 83 new records for title/abstract screening. Thus, across both searches, 531 records were available for title/abstract screening. Of these, we excluded 438 records, leaving 93 records for which we sought to obtain a corresponding full-text publication. We then removed a total of 24 records (unable to locate/access full-text publication corresponding to record title for eight records; 16 manually-identified duplicates), resulting in 69 reports for full-text review. Of these 69 records, we identified 11 as non-full-text references corresponding to a primary report (e.g. abstracts, registrations), leaving 58 independent reports. Of the 58 full-text reports (69 references) reviewed, we excluded a total of 45 reports (46 references). We identified 14 ongoing studies (14 references; Characteristics of ongoing studies) and listed seven studies (8 references) as awaiting classification (see Characteristics of studies awaiting classification). We excluded 24 reports (24 references) that did not meet our review inclusion criteria (ineligible study design, n = 10; ineligible comparator, n = 5; ineligible participant population, n = 4; ineligible intervention, n = 1; recruitment terminated/study abandoned, n = 4). Working

independently, two review authors (RB and KC) completed all screening steps outlined above in Covidence, and resolved any discrepancies through discussion. Thirteen studies (with a total of 23 references) met the review's eligibility criteria (see Characteristics of included studies).

Figure 1. PRISMA flow diagram including records identified from original search (February 2022) and search update (January 2023). **Total for records identified by handsearching citations includes duplicates across studies as well as shared with database search; handsearch encompassed all 13 studies included in this review as well as the following recent meta-analyses: Belsher 2021; Cirillo 2019; Harris 2021; Kan 2020; Yan 2017. Abbreviations: CENTRAL: Cochrane Central Register of Controlled Trials; CCMDCTR: Cochrane Common Mental Disorders Controlled Trials Register; ISI Web of Sci: ISI Web of Science Science Citation Index Expanded (SCI-EXPANDED) & Conference Proceedings Citation Index-Science (CPCI-S); ProQuest D&I: ProQuest Dissertations & Theses A&I; ProQuest PTSD: ProQuest PTSDPubs; WHO Int Registry: WHO International Clinical Trials Registry Platform. Figure template adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.



One review author (RB) conducted a handsearch of references from the 13 studies identified by the above processes, as well as five recent meta-analyses (Belsher 2021; Cirillo 2019; Harris 2021; Kan 2020; Yan 2017), yielding a total of 1215 titles. Of these, we sought the full texts of 15 titles. Six reports could not be located/accessed (all from previous meta-analysis Yan 2017; see Appendix 2 for references for these studies). We reviewed nine full-text reports for eligibility; none met the eligibility criteria due to ineligible study design. Thus, a total of 33 studies are listed in Characteristics of excluded studies: this encompasses the 24 studies excluded from the database review, as well as the nine studies excluded from the handsearch process.

Across the database searches and handsearch, a total of 13 studies (12 published; 1 unpublished dissertation) met eligibility criteria and were included in this review (see Characteristics of included studies). Our decision to exclude two studies may be contentious. We chose to exclude the cross-over trial conducted by Osuch 2009 because available information suggested participants underwent quasi-randomized rather than randomized assignment. We based this assessment on the absence of descriptors such as “random assignment” or “randomized” in the publication, as well as the statement that participants “alternately” started with sham or active treatment (Osuch 2009, p. 55). We also excluded a trial using synchronized transcranial magnetic stimulation (Philip 2019b). We believe the use of very low frequency stimulation matched to each participant's endogenous alpha rhythms makes this protocol significantly distinct from other protocols under the umbrella of rTMS. In contrast, we included trials using deep TMS (dTMS), as dTMS has been described as a subset of rTMS (Levkovitz 2015), and employs comparable frequency as standard rTMS protocols.

Of the 13 studies included in our review, three contributed to meta-analysis for the primary outcome PTSD severity immediately after treatment (Leong 2020; Philip 2019a; Watts 2012). Eleven studies contributed to meta-analysis for the primary safety outcome, occurrence of serious adverse events during the active study period (Boggio 2010; Cohen 2004; Fryml 2019; George 2014; Isserles 2013; Isserles 2021; Kozel 2018; Leong 2020; Levasseur-Moreau 2018; Nam 2013; Philip 2019a). Regarding secondary outcomes, we did not perform meta-analysis for the following outcomes, as no studies provided these outcomes in a format eligible for our analysis: PTSD severity at one to four weeks after treatment, PTSD remission immediately after treatment, and PTSD response immediately after treatment. Only one study provided PTSD severity scores for the ITT sample at four to 12 weeks after treatment (Isserles 2021). All 13 studies contributed to meta-analysis for treatment dropout. Three and two studies, respectively, contributed to meta-analysis for depression severity immediately after treatment (Leong 2020; Philip 2019a; Watts 2012), and anxiety severity immediately after treatment (Leong 2020; Watts 2012).

Included studies

We included 13 studies in this review. Twelve studies are published reports and one is an unpublished dissertation. The studies included a total of 577 participants, with a range of eight to 125 participants and a median of 31. Some studies included groups not relevant to this review; in such cases, participants in these groups were excluded from sample size totals reported above and throughout this review. For further details, see Characteristics of included studies. All studies reported results in English, with one study reporting results in both English and French (Levasseur-Moreau 2018).

Studies were conducted in Brazil (one study: Boggio 2010), Canada (two studies: Leong 2020; Levasseur-Moreau 2018), Iran (one study: Ahmadizadeh 2018), Israel (two studies: Cohen 2004; Isserles 2013), South Korea (one study: Nam 2013), USA (five studies: Fryml 2019; George 2014; Kozel 2018; Philip 2019a; Watts 2012), and one multicenter study (Isserles 2021). Most studies were conducted in medical centers, with the remaining settings comprising health centers or research institutes. One study reported involvement of hospitalized participants (George 2014).

Study designs

All 13 studies included in this review were parallel-group, double-blind, randomized controlled trials (RCTs). Two studies, Philip 2019a and Isserles 2013, offered participants open-label treatment following completion of the RCT portion, thus limiting the relevant follow-up period to immediate post-treatment. Eight studies investigated rTMS as a stand-alone treatment (except for some forms of stable pharmacological and/or psychological treatment; Ahmadizadeh 2018; Boggio 2010; Cohen 2004; Leong 2020; Levasseur-Moreau 2018; Nam 2013; Philip 2019a; Watts 2012), four investigated rTMS combined with some form of exposure or evidence-based psychotherapy treatment for PTSD (Fryml 2019; Isserles 2013; Isserles 2021; Kozel 2018), and one investigated rTMS as a brief adjunctive treatment alongside treatment as usual (George 2014). Eight studies included two treatment arms (active versus sham; Fryml 2019; George 2014; Isserles 2021; Kozel 2018; Levasseur-Moreau 2018; Nam 2013; Philip 2019a; Watts 2012), four included three arms (two active arms in addition to sham; Ahmadizadeh 2018; Boggio 2010; Cohen 2004; Leong 2020), and one study involved three treatment arms, but only two were relevant to this review (Isserles 2013). All the included studies appear to have taken place within the past three decades. Reported start dates ranged from 2005 to 2016. Three studies did not report a start date, including what was likely the earliest study, based on its publication date of 2004 (Cohen 2004).

Study aims

Most studies' reported aim was to assess rTMS for treating PTSD. The singular exception was George 2014, which was designed to assess the efficacy of brief rTMS as an adjunct to treatment as usual for acute suicidality. This study was nonetheless eligible for inclusion in this review, as it involved nine rTMS treatments and, for funding reasons, almost all participants (97.5%) had a diagnosis of PTSD. Of the remaining 12 studies, 10 aimed to assess the efficacy of rTMS or rTMS combined with other treatments for the treatment of PTSD (Ahmadizadeh 2018; Boggio 2010; Cohen 2004; Isserles 2013; Isserles 2021; Kozel 2018; Leong 2020; Levasseur-Moreau 2018; Nam 2013; Watts 2012); one aimed to assess the tolerability and efficacy of rTMS for PTSD (Philip 2019a), and one aimed to assess the feasibility of combining rTMS with prolonged exposure therapy (Fryml 2019).

Participants

A summary of several of the main characteristics of study samples is provided in Table 1. Many studies did not detail the recruitment process. Ten studies indicated recruitment from healthcare or mental healthcare settings (Ahmadizadeh 2018; Cohen 2004;

George 2014; Isserles 2013; Kozel 2018; Leong 2020; Levasseur-Moreau 2018; Nam 2013; Philip 2019a; Watts 2012), four studies specifically reported referral by physicians (Boggio 2010; George 2014; Isserles 2013; Isserles 2021), and three studies reported public advertisements as a form of recruitment (Boggio 2010; Isserles 2013; Isserles 2021). One study did not provide any information regarding recruitment sources (Fryml 2019). As outlined in our protocol, all studies included in this review focused on adults. The literature search did not identify any rTMS RCTs focused on children or adolescents. Three studies did not specify age-related inclusion criteria (Cohen 2004; Isserles 2013; Nam 2013). Of the studies reporting age-related inclusion criteria, requirements for minimum age ranged from 18 to 42 years old, with a median of 18.5. Maximum age requirements ranged from 50 to 70 years old, with a median of 68.5. All 13 studies provided an average age for their study sample, albeit for six of the studies, the provided average was for a subset of the ITT sample (treatment-criterion or per-protocol sample; Ahmadizadeh 2018; Cohen 2004; Isserles 2013; Leong 2020; Levasseur-Moreau 2018; Nam 2013). The average age of participants across studies was 42.7 years. Most studies did not report any data regarding the race or ethnicity of participants. Five studies had a majority (70% to 100%) of white participants (George 2014; Isserles 2021; Kozel 2018; Philip 2019a; Watts 2012). In terms of sex breakdown, five studies only provided statistics for a subset of the ITT sample (Cohen 2004; Isserles 2013; Leong 2020; Levasseur-Moreau 2018; Nam 2013); this reduces the total sample size from 577 to 557. Of the 557 participants for which sex statistics were provided, 386 were male and 171 were female. No studies reported inclusion of trans, intersex, non-binary, or other gender-diverse participants. Samples for many studies were heavily weighted towards either male or female participants; specifically, more than 80% of the sample for Ahmadizadeh 2018, Fryml 2019, George 2014, Isserles 2013, Kozel 2018, Levasseur-Moreau 2018, Philip 2019a, and Watts 2012 was male while more than 80% of the sample for Leong 2020 was female.

The imbalanced sex ratio observed can likely be attributed, at least in part, to veteran versus civilian recruitment populations. All studies with more than 80% male participants involved defined or presumed veteran populations, whereas for the study with more than 80% female participants, Leong 2020 reported recruiting exclusively from a civilian population. Overall, veteran status was clearly delineated as an inclusion criterion for five studies (Ahmadizadeh 2018; Fryml 2019; Kozel 2018; Levasseur-Moreau 2018; Philip 2019a). Four additional studies did not specify veteran status in the study inclusion criteria, but nonetheless involved presumed veteran populations based on the following evidence: comments made in the discussion section (Watts 2012); study location in Israel where military participation is mandatory (Cohen 2004; Isserles 2013); and study setting at Veterans' Affairs (VA) medical centers and funding by the Department of Defense (George 2014). One study specifically indicated a civilian population (Leong 2020); another study involved a presumed civilian population based on the description of the traumatizing incidents and the study setting of a university hospital (Nam 2013). The remaining two studies did not provide information regarding the civilian or veteran status of the participants (Boggio 2010; Isserles 2021). Most included studies did not indicate whether recruitment was restricted to inpatients or outpatients. Three studies specified recruitment from outpatient pools (Ahmadizadeh 2018; Isserles 2021; Leong 2020), and one study restricted recruitment to inpatients (George 2014).

A diagnosis of PTSD was required for inclusion in 12 out of 13 studies. The exception, George 2014, required either a diagnosis of PTSD or mild traumatic brain injury (mTBI) for inclusion; nonetheless, in this study all but one participant had a diagnosis of PTSD. Three studies required the source of PTSD to be a combat-related incident (Kozel 2018; Levasseur-Moreau 2018; Watts 2012), while one required PTSD be non-combat-related (Leong 2020). Two studies only recruited participants with treatment refractory PTSD (Isserles 2013; Levasseur-Moreau 2018), and two studies described recruiting participants with “chronic” PTSD (Philip 2019a; Watts 2012). The remaining nine studies did not report recruitment on the basis of PTSD treatment refractoriness or chronicity.

There was substantial variety in the presence of comorbid psychological conditions across study samples. The most common comorbid psychological diagnosis was depression. For four studies, most participants had unipolar or bipolar depression (89% to 100% of the study sample; George 2014; Leong 2020; Levasseur-Moreau 2018; Philip 2019a). Approximately one-third of the study sample for Kozel 2018 had a diagnosis of depression. Ahmadizadeh 2018 presumably had no participants with depression, as any axis I disorders other than PTSD were an exclusion criterion. Isserles 2021 likely had relatively few participants with depression, as the average Hamilton Depression Rating Scale (HDRS) score at baseline was 15.8 (indicative of mild depression; Zimmerman 2013). The remaining six studies did not report the presence or absence of depression among participants (Boggio 2010; Cohen 2004; Fryml 2019; Isserles 2013; Nam 2013; Watts 2012). Eligibility restrictions around problematic substance use were common. Six studies either specifically designated substance-use disorder as an exclusion criterion or provided a general statement about excluding non-PTSD axis I disorders (Ahmadizadeh 2018; Boggio 2010; Cohen 2004; Isserles 2013; Kozel 2018; Levasseur-Moreau 2018). Additionally, four studies imposed eligibility restrictions around recent substance use (George 2014; Isserles 2021; Leong 2020; Watts 2012), ranging from a requirement for no substance-use disorder within the past six months (Isserles 2021), to no substance dependence within the six days preceding study entry (George 2014). In Philip 2019a, approximately half of the study sample (54%) were diagnosed with a mild substance-use disorder. Five studies either indicated psychotic disorders were an exclusion criterion or provided diagnostic statistics indicating the absence of psychotic disorders among participants (Fryml 2019; George 2014; Isserles 2021; Kozel 2018; Philip 2019a); the remaining studies did not provide information regarding psychotic disorders among study participants. Most studies also did not provide information regarding the diagnosis of bipolar disorder among study participants. Of the five studies that did, one excluded all bipolar disorders (Isserles 2021), three excluded bipolar I disorder but permitted participants with a diagnosis of bipolar II disorder (George 2014; Leong 2020; Philip 2019a), and the fifth study reported 1.9% of the study sample had a diagnosis of bipolar disorder (type I or II not specified; Kozel 2018).

There was also a range of medical conditions present across study samples, but most studies appeared to be fairly restrictive in terms of permitted medical comorbidity. Six studies did not describe inclusion or exclusion criteria regarding TBI. Three studies excluded “brain trauma” or “head trauma” (Boggio 2010; Cohen 2004; Fryml 2019). Four studies excluded potential participants with moderate or severe TBI (Ahmadizadeh 2018; George 2014; Kozel 2018; Philip 2019a), and Isserles 2021 excluded “significant” TBI. Only two

studies described the composition of the sample with TBI: 24% of the sample for Philip 2019a had mTBI and 58% of the sample for George 2014 had mTBI. Kozel 2018 did not report TBI statistics, but did report composition of the sample in terms of concussion grades; 30%, 13%, 11%, and 47% of the sample was diagnosed with a grade 0, grade 1, grade 2, and grade 3 concussion, respectively. Aside from George 2014, which required either PTSD or mTBI (or these conditions combined), no other studies specified inclusion criteria of medical conditions. In terms of medical exclusions, six studies excluded participants with a history of seizure (Fryml 2019; George 2014; Kozel 2018; Leong 2020; Philip 2019a; Watts 2012), five studies excluded acute or unstable medical conditions (Fryml 2019; George 2014; Leong 2020; Philip 2019a; Watts 2012), two studies excluded chronic medical conditions (Boggio 2010; Cohen 2004), and seven studies excluded participants with neurological or significant brain disorder (Ahmadizadeh 2018; Isserles 2021; Kozel 2018; Leong 2020; Levasseur-Moreau 2018; Nam 2013; Philip 2019a).

Next, we summarize the composition of our review regarding concomitant pharmacological and psychological treatments permitted. Three studies specifically reported the exclusion of participants taking medications known to decrease the seizure threshold (Fryml 2019; George 2014; Watts 2012). There is some evidence from studies of rTMS for depression that benzodiazepines may interfere with rTMS treatment (Hunter 2019; Kaster 2019; for opposing evidence, see Fitzgerald 2020). Four studies did not describe benzodiazepine-use status among participants (Ahmadizadeh 2018; Kozel 2018; Nam 2013; Watts 2012), and one study required that participants not use benzodiazepines in order to participate (Fryml 2019). The eight remaining studies permitted the use of benzodiazepines, but only six reported statistics on use among participants. The number of participants taking benzodiazepines varied considerably across studies: for Isserles 2013, Isserles 2021, Leong 2020, and George 2014, less than half of the participants were taking benzodiazepines (21% to 37%), whereas for Levasseur-Moreau 2018 and Cohen 2004, most participants were taking benzodiazepines (68% and 79%, respectively). With regard to antipsychotics, eight studies did not report any information regarding antipsychotic use among participants. Five studies included statistics on antipsychotic use: the percentage of the study sample using antipsychotics ranged from 11% to 34% (Cohen 2004; George 2014; Isserles 2013; Leong 2020; Levasseur-Moreau 2018). Most studies set restrictions to preserve stability of pharmacological treatment for a period of time preceding study entry. Requirements for the period of time on stable pharmacological medication preceding study entry were two months for two studies (Ahmadizadeh 2018; Watts 2012), six weeks for one study (Philip 2019a), four weeks for three studies (Isserles 2013; Isserles 2021; Leong 2020), and three weeks for three studies (Boggio 2010; Cohen 2004; Levasseur-Moreau 2018). Fryml 2019 and Nam 2013 required stable pharmacological treatment only during trial participation. Two studies did not restrict pharmacological treatment during the trial (George 2014; Kozel 2018). George 2014 permitted treatment as usual, including any medication modifications. Kozel 2018 encouraged stable medication use, but changes were made to the medication regimen for approximately 25% of participants in both active and sham treatment groups. Fewer studies provided information regarding psychotherapy treatment allowed during the trial. Six studies required no changes in psychotherapy treatment for three to eight weeks preceding study entry (Ahmadizadeh 2018; Boggio 2010; Isserles 2021; Levasseur-Moreau 2018; Philip 2019a; Watts 2012). Nam 2013 required no changes in psychotherapy treatment during the active study period. We assume that three studies forbid changes in psychotherapeutic treatment during the active study period (Fryml 2019; Isserles 2013; Kozel 2018), given that these studies involved concurrent therapy in the trial, and it is standard practice in psychotherapy to discourage concurrent psychotherapy treatment with different practitioners.

rTMS protocols

Studies included in this review employed a wide variety of rTMS protocols (see Table 2). Most studies targeted stimulation of the right dorsolateral prefrontal cortex (rDLPFC; Cohen 2004; Kozel 2018; Leong 2020; Levasseur-Moreau 2018; Philip 2019a; Watts 2012), or the right prefrontal cortex (rPFC; Nam 2013). Two studies included a treatment arm targeting the rDLPFC (Ahmadizadeh 2018; Boggio 2010). Fryml 2019 split the active treatment sample between rDLPFC and left dorsolateral prefrontal cortex (lDLPFC) stimulation, but did not present separate outcomes for each group. One study exclusively targeted stimulation to the lDLPFC (George 2014), and Boggio 2010 included a treatment arm targeting the lDLPFC. Isserles 2013 and Isserles 2021 targeted the medial PFC (mPFC) using deep brain stimulation, and Ahmadizadeh 2018 included a treatment arm with bilateral stimulation of the DLPFC. Five studies either used low-frequency stimulation (Kozel 2018; Nam 2013; Watts 2012), or included a treatment arm using low-frequency stimulation (Cohen 2004; Leong 2020). In all cases, low-frequency stimulation used a frequency of 1 Hz. Ten studies either used high-frequency stimulation (Ahmadizadeh 2018; Boggio 2010; Fryml 2019; George 2014; Isserles 2013; Isserles 2021; Levasseur-Moreau 2018; Philip 2019a), or included a treatment arm with high-frequency stimulation (Cohen 2004; Leong 2020). Frequencies used for high-frequency stimulation varied from 10 Hz to 50 Hz. Five studies applied stimulation at intensities below the motor threshold (80% to 90% MT; Boggio 2010; Cohen 2004; Levasseur-Moreau 2018; Philip 2019a; Watts 2012), three studies applied stimulation at the motor threshold (100% MT; Ahmadizadeh 2018; Isserles 2021; Nam 2013), and the remaining five studies applied stimulation at intensities exceeding the motor threshold (110% to 120% MT; Fryml 2019; George 2014; Isserles 2013; Kozel 2018; Leong 2020). For all studies with multiple active treatment arms, consistent stimulation intensity was maintained across the treatment groups (i.e. there was no within-study exploration of the impact of stimulation intensity on outcomes). There was considerable variation in duration and pattern of stimulation applied. Most studies had a treatment session length of 20 to 30 minutes (Ahmadizadeh 2018; Boggio 2010; Cohen 2004; Fryml 2019; George 2014; Isserles 2021; Kozel 2018; Nam 2013; Watts 2012). The shortest session length was 3.2 minutes (Levasseur-Moreau 2018), and the longest session length was 37.5 minutes (Leong 2020). Four studies used relatively newly developed forms of rTMS: specifically, Philip 2019a and Levasseur-Moreau 2018 used intermittent theta-burst stimulation (TBS), a form of high-frequency rTMS designed to mimic natural rhythms of the mammalian hippocampus (Suppa 2016). Isserles 2013 and Isserles 2021 used deep TMS, which uses a specialized coil to stimulate brain tissue several centimeters deeper than standard coils (Zangen 2005).

Eleven studies either included data on total pulses and treatment duration or included sufficient information for these to be estimated. We were unable to include Fryml 2019 and Kozel 2018 in estimates for total pulses and treatment duration. Kozel

2018 administered treatments that ranged from 12 to15 weeks, depending on whether additional sessions of psychotherapy (paired with rTMS) were deemed necessary. We were unable to ascertain whether five or eight rTMS sessions were completed in Fryml 2019. For the remaining 11 studies, total pulses ranged from 1000 pulses to 54,000 pulses, with a median of 18,000 pulses. Additionally, for these 11 studies, the number of treatment sessions ranged from five to 15, with a median (and mode) of 10. Length of treatment varied, from three days (George 2014), one week (Levasseur-Moreau 2018), two weeks (Boggio 2010; Cohen 2004; Leong 2020; Philip 2019a; Watts 2012), three weeks (Nam 2013), to four weeks (Ahmadizadeh 2018; Isserles 2013; Isserles 2021). The frequency of treatment sessions generally ranged from one to five treatments per week. The exception was George 2014, which was the only study to employ multiple treatments per day, spacing same-day sessions by a minimum of one hour. Seven studies administered daily treatment (on weekdays) for the duration of the treatment period (Boggio 2010; Cohen 2004; Leong 2020; Levasseur-Moreau 2018; Nam 2013; Philip 2019a; Watts 2012). Alternative treatment schedules used by studies included three treatments per week (Isserles 2013; Isserles 2021), one treatment per week (Fryml 2019; Kozel 2018), and a tapering schedule of treatments (three treatments per week to two treatments per week; Ahmadizadeh 2018).

Studies employed various methods of sham stimulation that likely varied in effective mimicry of active stimulation. We could not find any information regarding the characteristics of sham stimulation used by Philip 2019a. For the remaining 12 studies, nine either reported using sham coils with a similar appearance to the active coil or used the same coil for sham and active stimulation, thus ensuring an identical appearance (Ahmadizadeh 2018; Boggio 2010; Cohen 2004; Fryml 2019; George 2014; Kozel 2018; Leong 2020; Nam 2013; Watts 2012). Ten studies reported that their sham stimulation method produced similar sounds as active stimulation (Ahmadizadeh 2018; Cohen 2004; George 2014; Isserles 2013; Isserles 2021; Kozel 2018; Leong 2020; Levasseur-Moreau 2018; Nam 2013; Watts 2012). George 2014 reported that, as for the active coil, the sham coil warmed during stimulation; no other studies described temperature change or lack thereof for the sham coil. Five studies reported that the sham coil employed some form of stimulation of the skull to mimic sensations from active stimulation. Specifically, Boggio 2010 and George 2014 described using a transcutaneous electrical nerve stimulator and a small electrical stimulator, respectively, to produce these sensations. Isserles 2013, Isserles 2021, and Leong 2020 did not specify how the sham coil produced scalp sensations, but reported that such sensations were produced. Additionally, we presume the method of sham stimulation used by Cohen 2004 may have produced some minimal scalp sensations based on authors' description of using an active coil rotated to 90 degrees (Lisanby 2001). Four studies employed an advanced method of double-blinding through use of the same coil for active and sham stimulation with the type of stimulation determined by a pre-programmed electronic system or magnetic card (Fryml 2019; George 2014; Isserles 2013; Isserles 2021).

Outcomes

Primary outcomes

For our primary efficacy outcome, three studies met eligibility criteria for inclusion in meta-analytic synthesis (Leong 2020; Philip 2019a; Watts 2012). These studies provided PTSD severity scores immediately after treatment (up to one week post-treatment) for the ITT sample, including a mean and identifiable error term. We privileged clinician-rated outcomes over self-reports, resulting in synthesis of scores from the CAPS-5 (Philip 2019a) and CAPS-IV (Leong 2020; Watts 2012). Three additional studies provided change scores of the ITT sample for PTSD severity from baseline to immediate post-treatment and were eligible for inclusion in sensitivity analysis (Fryml 2019; Isserles 2013; Isserles 2021; albeit, for Fryml 2019, we assumed variance was standard deviation [SD], but this was not clearly stated). Therefore, sensitivity analyses for this outcome included synthesis of data from a maximum of six studies. Six additional studies provided sufficient information for narrative review (Ahmadizadeh 2018; Boggio 2010; Cohen 2004; George 2014; Kozel 2018; Levasseur-Moreau 2018). Reasons for exclusion from meta-analytic synthesis included absence of quantitative outcomes for the ITT sample, and inability to ascertain error statistics. We did not include Nam 2013 in either meta-analytic synthesis or narrative review. Nam 2013 described assessing PTSD severity at “baseline and weeks 2, 4, and 8” (p. 98). Based on the figure labels and description in the text, we were unable to ascertain whether these assessments took place at weeks two, four, and eight post-baseline, or at two, four, and eight weeks after treatment. Due to this ambiguity regarding which outcomes corresponded to immediate post-treatment, we did not include them. Additionally, Nam 2013 only provided outcomes for the per-protocol sample and did not specify the type of variance presented in the figures.

Eleven of the 13 studies included in our review provided sufficient information regarding serious adverse events (SAEs) occurring during the active study period to be assessed for this outcome. For our main analysis of SAEs, we used a form of mixed-effects logistic regression that required each study to have at least one event across treatment arms for inclusion. This model restriction excluded six studies, resulting in synthesis of outcomes from a total of five studies in our main meta-analytic estimate (Cohen 2004; Isserles 2013; Isserles 2021; Leong 2020; Philip 2019a). We also calculated a meta-analytic estimate that included the six double-zero studies, using code developed by Xiao 2021, for sensitivity analysis. The reason for the exclusion of two studies from all quantitative synthesis for SAEs was the absence of a clear statement of serious adverse event occurrence (see data extraction forms in external data repository for details (https://osf.io/nmpk4/?view_only=3bf530fec7024a48ad0866c52c7a15f0); Ahmadizadeh 2018; Watts 2012).

Secondary outcomes

No studies provided PTSD remission or PTSD response outcomes, as defined by this review.

No studies provided PTSD severity outcomes for the ITT sample between one and four weeks after treatment that were eligible for meta-analytic synthesis. Cohen 2004 provided outcomes for the per-protocol sample at 14 days post-treatment, and so we provide a narrative review of outcomes for this study. Boggio 2010 also assessed PTSD severity at 14 days post-treatment in figure form; however, we were unable to ascertain the variance statistic presented and thus did not describe this outcome (see data extraction form in external data repository for details; Boggio 2010). As was the case for PTSD severity immediately after treatment, ambiguity in the time points of outcome measurement for Nam 2013 precluded its inclusion in the meta-analysis.

One study provided ITT outcomes for PTSD severity at four to 12 weeks after treatment. Specifically, Isserles 2021 provided the change in PTSD severity (CAPS-5) from baseline to five weeks post-treatment. As no other studies reported eligible outcomes in this time window, we present the change-from-baseline estimate and error for Isserles 2021 (rather than introducing additional error by transforming the estimate to endpoint scores). Three additional studies provided outcomes for PTSD severity at four to 12 weeks after treatment that were eligible for narrative review (Kozel 2018; Levasseur-Moreau 2018; Watts 2012). Reasons for exclusion from meta-analytic synthesis were: absence of outcomes for the ITT sample (Levasseur-Moreau 2018); missing mean and variance for some treatment arms (Watts 2012); and prohibitively high levels of attrition for valid ITT estimation (Kozel 2018). Leong 2020 reported assessing PTSD severity at 12 weeks post-treatment, but these outcomes were not included in the publication due to high attrition in the sham arm of the study. Additionally, PTSD severity outcomes at four to 12 weeks after treatment were assessed by Boggio 2010 and may have been assessed by Nam 2013, but we have not presented them in this review for the same reasons described above (i.e. unable to ascertain the variance statistic presented in Boggio 2010; ambiguity in time points of outcome measurement in Nam 2013).

All thirteen studies provided sufficient information regarding dropout during the active study period to warrant inclusion of outcomes. Two studies did not report any dropouts in either arm and therefore were not included in our main meta-analytic synthesis for this outcome. We included these two studies in a sensitivity analysis using code developed by Xiao 2021 that can accommodate inclusion of double-zero outcomes.

Three studies provided depression severity scores immediately after treatment for the ITT sample and were eligible for inclusion in our meta-analytic synthesis for this outcome (Leong 2020; Philip 2019a; Watts 2012). A fourth study, Isserles 2021, provided the change in depression severity scores for the ITT sample from baseline to immediate post-treatment, and was therefore eligible for inclusion in one of our sensitivity analyses (change from baseline, including imputed data). Six additional studies provided sufficient information for narrative review (Boggio 2010; Cohen 2004; Fryml 2019; George 2014; Isserles 2013; Levasseur-Moreau 2018). Reasons for exclusion from meta-analytic synthesis included absence of quantitative outcomes for the ITT sample and lack of clarity regarding variance statistics.

Two studies provided anxiety severity scores immediately after treatment for the ITT sample and were eligible for inclusion in our meta-analytic synthesis for this outcome (Leong 2020; Watts 2012). Four additional studies provided sufficient information for inclusion in a narrative review (Boggio 2010; Cohen 2004; George 2014; Levasseur-Moreau 2018). George 2014 assessed anxiety using ratings on a single item from a custom-developed visual analogue scale. Given the study-specific nature of this scale, we did not consider it to meet our eligibility criteria for being a psychometrically-validated measure. For the remaining three studies, reasons for exclusion from meta-analytic synthesis included absence of quantitative outcomes for the ITT sample and lack of clarity regarding variance statistics.

Excluded studies

We excluded 24 studies because they did not include randomized treatment assignment (n = 10), did not include a sham comparator arm (n = 5), did not focus on our population of interest (adults with PTSD, n = 4), did not meet rTMS intervention criteria (n = 1), or the study was not completed (n = 4). We excluded nine further studies identified through handsearching, as they did not meet the eligibility criteria due to ineligible study design. See Characteristics of excluded studies for details.

We designated seven studies as 'awaiting classification' (see Studies awaiting classification). We presume these studies have been completed and are relevant to our review topic, but we were unable to acquire the necessary data or methodological detail (or both) to enable their inclusion in the current review. We identified 14 records associated with ongoing studies; these could not be included in the current review but may be eligible for inclusion in future updates (see Ongoing studies).

Risk of bias in included studies

We assessed the risk of bias (using the RoB 2 tool) for the two outcomes presented in our summary of findings table (Summary of findings 1):

- PTSD severity immediately after treatment (ITT outcome; efficacy);
- occurrence of serious adverse events during treatment period (safety).

We included three studies in our main efficacy analysis, effect of rTMS on PTSD severity immediately after treatment. We rated one as low risk of bias and two with some concerns. Domains contributing to the elevated risk of bias were lack of detail regarding the randomization process (Watts 2012), lack of blinding or unclear blinding status for staff administering the rTMS treatments (Leong 2020; Watts 2012), missing data (Leong 2020), and lack of detailed reporting regarding missing data/withdrawals (Watts 2012). Please see Risk of bias table for Analysis 1.1 for details.

Given the small number of studies meeting our criteria for meta-analytic synthesis for our main efficacy outcome, we also conducted a sensitivity analysis using change-from-baseline PTSD severity scores, including imputed data (Analysis 1.3). This synthesis included the three studies for the main efficacy analysis (described above) plus three additional studies. In total, we rated one study at low risk of bias (Philip 2019a), three at some concerns (Isserles 2013; Leong 2020; Watts 2012), and two at high risk of bias (Fryml 2019; Isserles 2021). Ratings in the domain of missingness (domain 3) were responsible for elevating Isserles 2021 to high risk of bias, as this study had a relatively large attrition rate of 27.2%. We judged Fryml 2019 to be at high risk of bias overall due to a rating of 'some concerns' in four of five domains, paired with the very small study sample size (8 participants). Across the six studies included in this sensitivity analysis, domains contributing to increased risk of bias included the randomization process (Fryml 2019; Watts 2012), deviations from intended interventions (Fryml 2019; Isserles 2013; Isserles 2021; Leong 2020; Watts 2012), missing data (Fryml 2019; Isserles 2013; Isserles 2021; Leong 2020; Watts 2012), and selection of the reported results (Fryml 2019). All six studies appeared to employ rigorous methods for measurement of PTSD severity (domain 4).

We included five studies in our main meta-analytic synthesis for serious adverse events during active treatment. For this outcome, we judged four of the five studies as having an overall high risk of bias (Cohen 2004; Isserles 2013; Isserles 2021; Leong 2020), and the remaining study as 'some concerns' (Philip 2019a). The aspects contributing to increased risk of bias included absence of SAE definition used (Cohen 2004; Isserles 2013; Isserles 2021; Leong 2020; Philip 2019a), lack of description for a systematic strategy to identify SAEs (Cohen 2004; Isserles 2013; Leong 2020), ambiguity in the size of the safety population (Isserles 2013; Isserles 2021), ambiguous blinding status or lack of blinding for the staff administering rTMS treatments (Cohen 2004; Leong 2020), ambiguous blinding status or lack of blinding for persons responsible for identifying SAEs (Cohen 2004; Isserles 2013; Leong 2020), and missing data (Cohen 2004; Isserles 2013; Isserles 2021; Leong 2020). Overall, we found the methodological rigor of results presented for this outcome to be low. We also conducted risk of bias assessments for studies providing some information on serious adverse events, but reporting zero SAEs in any treatment arm (these six studies were included in sensitivity analysis for SAEs). These studies all received ratings of high risk of bias for SAEs (Boggio 2010; Fryml 2019; George 2014; Kozel 2018; Levasseur-Moreau 2018; Nam 2013).

Our protocol also outlined our intention to conduct RoB 2 assessment for PTSD remission immediately after treatment and dropout during the treatment period. We did not conduct these assessments for the following reasons: 1) no studies included in our systematic review provided remission outcomes; and 2) we determined dropout not to be an appropriate outcome for valid RoB 2 assessment (e.g. ratings for domain 3 [attrition] is not applicable and dropout is rarely reported as an outcome measure, leading to few details regarding plans for assessment and analysis).

Effects of interventions

See: **Summary of findings 1** Active rTMS compared to sham rTMS for adults with PTSD

Active rTMS compared to sham rTMS

Primary outcomes

Efficacy immediately after treatment (PTSD severity)

Our primary meta-analytic estimate pooled data from studies that published PTSD severity scores assessed immediately after treatment (endpoint scores up to seven days post-treatment for the ITT sample), measured using a validated assessment. As studies used different assessments, we computed this estimate using standardized mean differences (SMD). Our analysis, presented in the summary of findings table, indicated that rTMS probably makes little or no difference to PTSD severity immediately after treatment (SMD -0.14, 95% CI -0.54 to 0.27; 3 studies, 99 participants; moderate-certainty evidence; Analysis 1.1; Summary of findings 1; EPOC 2018). We transformed SMD to MD for CAPS-IV to facilitate interpretability. Although the CAPS-5 is more recent and aligns best with current diagnostic criteria for PTSD (DSM-5), we chose to transform outcomes to the CAPS-IV, as we could only find a minimal important difference (the smallest change in assessment score that patients perceive as important) in the literature for this version of the assessment. The CAPS-IV has a score range of 0 to 136, with higher scores indicating greater severity; the minimal important difference for the CAPS-IV has been estimated as a change of 10 points (Belsher 2019; Schnurr 2001). We transformed SMD to the scale of the CAPS-IV using the combined (weighted average) standard deviation at endpoint from the active treatment groups for Leong 2020 and Watts 2012 (SD 29.14, n = 30). The point estimate favored active treatment but did not reach the magnitude of minimal important difference; the margin of error indicated rTMS may improve, make no difference, or even worsen symptoms of PTSD immediately after treatment (MD -4.08, 95% CI -15.74 to 7.88; Summary of findings 1).

Our certainty in the evidence, rated using the GRADE criteria, was moderate (Summary of findings 1). We downgraded the evidence by one level for imprecision, as our meta-analytic sample size was not large enough to detect a small or medium effect size using standard power analysis. We observed minimal statistical heterogeneity (I^2 = 0%, P = 0.58) and did not have serious doubts about the indirectness of included participants, interventions, and outcomes. We assessed the overall risk of bias as low for Philip 2019a, with some concerns for Leong 2020 and Watts 2012. We judged the risk of bias for Leong 2020 and Watts 2012 to be elevated due to concerns about missing data (resulting from small study sample sizes, which is addressed in the imprecision domain), as well as the possibility that staff administering rTMS treatment were not blind to the treatment group (allowing the possibility of staff to inadvertently convey treatment expectations to participants). We did not view these risks of bias as sufficiently strong to warrant downgrading a level.

We conducted a sensitivity analysis to evaluate the robustness of our meta-analytic estimate. No studies included in our primary meta-analytic estimate were at high risk of bias nor had attrition rates exceeding 20%. There was also minimal statistical heterogeneity (I^2 = 0%, P = 0.58) across these three studies. Accordingly, we did not conduct planned sensitivity analyses on the basis of risk of bias, attrition, or heterogeneity. None of our sensitivity analyses produced outcomes indicating an important difference in effect between sham and active rTMS. We calculated a pooled estimate of endpoint SMD including imputed data. Imputation involved conversion from the published change from baseline to endpoint scores for Fryml 2019 and Isserles 2021 using methods outlined in the *Cochrane Handbook* (Higgins 2021b). Specifically, we used standard deviations from baseline at endpoint. It should also be noted that Fryml 2019 did not clearly state the variance to be SD; based on the magnitude of the reported values, we assumed this to be the case for the sake of inclusion in sensitivity analysis. The SMD we estimated when including imputed endpoint scores did not meaningfully alter the estimate (SMD 0.08, 95% CI -0.35 to 0.51; 5 studies, 232 participants; Analysis 1.2). We also calculated a pooled estimate including imputed data for change from baseline. Imputation involved converting standard error to standard deviation (Isserles 2013), confidence intervals to standard deviations (Fryml 2019; Isserles 2021), assuming a normal distribution and t-distribution, respectively, and deriving baseline to immediate-post correlations for Philip 2019a, Leong 2020, and Watts 2012 to estimate change-from-baseline SDs. We calculated an average correlation of 0.71 for Philip 2019a. Our calculations for Leong 2020 and Watts 2012 yielded unreliable correlations (average < 0.5) and so we used the conventional correlation of 0.7 to derive SDs for these studies. The meta-analytic estimate based on change from baseline, including imputed data, again suggested rTMS may make little or no difference to PTSD severity immediately after treatment in adults (SMD -0.44, 95% CI -0.98 to 0.10; 6 studies, 252

participants; Analysis 1.3). However, this estimate did indicate the presence of substantial statistical heterogeneity not attributable to sampling error (I^2 = 69%, P = 0.007; Deeks 2021). Finally, we calculated a pooled estimate of endpoint SMD from studies that published PTSD severity scores at the study endpoint for the per-protocol sample. Interpretation of the estimate derived from this analysis was also consistent with that of our primary meta-analytic outcome (i.e. rTMS may make little or no difference to PTSD severity immediately after treatment; SMD -0.26, 95% CI -0.69 to 0.17; 3 studies, 85 participants; Analysis 1.4).

Six studies that were not included in either the main analysis or sensitivity analyses described above reported PTSD severity outcomes immediately after treatment in some form, as follows. George 2014 stated that there was no significant difference in post-treatment CAPS scores across groups. Boggio 2010 only provided error statistics in figure form, and did not specify the type of error, thus preventing valid extraction using PlotDigitizer 2020 (data extraction tool for published figures). Boggio 2010 reported a significant interaction between treatment group and time from baseline to immediately after treatment for the Treatment Outcome PTSD Scale (P < 0.001, 30 participants, ITT sample), with a significant decrease from baseline to immediately after treatment in both active treatment groups, but not in the sham group (note: we use the terminology "significant interaction" to describe outcomes of analyses for which the relationship between an independent variable [time] and a dependent variable [PTSD severity] differed to a degree that reached statistical significance on the basis of a third independent variable [treatment group]). Only per-protocol outcomes for PTSD severity immediately after treatment were provided by Cohen 2004, Kozel 2018, and Levasseur-Moreau 2018. We presumed the outcomes reported in Ahmadizadeh 2018 to be per-protocol outcomes (see data extraction form in external repository for details). Combining across the two active treatment groups, outcomes in Cohen 2004 for the Treatment Outcome PTSD Scale indicated rTMS may make little or no difference to PTSD severity immediately after treatment (MD -2.17, 95% CI -5.75 to 1.41; 24 participants). Kozel 2018 assessed PTSD severity immediately after treatment using the PCL (based on the DSM-IV). Reliable change (i.e. change not attributable to chance) on the PCL has been estimated to range from 5 to 10 points (Weathers 2013). Per-protocol outcomes in Kozel 2018 suggested rTMS made little to no difference in PTSD severity immediately after treatment; the range where the actual effect may be (the margin of error) included both improvement and worsening of PTSD severity for rTMS relative to sham treatment (MD -0.76, 95% CI -6.52 to 5.0; 60 participants). Using the Modified PTSD Symptom Scale, Levasseur-Moreau 2018 did not find a statistically significant difference between active and sham rTMS immediately after treatment (MD -7.29, 95% CI -23.58 to 9.0; 28 participants). Ahmadizadeh 2018 did detect a statistically significant difference between active (collapsed across unilateral and bilateral) and sham stimulation, favoring active treatment (MD -19.27, 95% CI -24.72 to -13.82; 49 participants).

Subgroup analyses

In our protocol, we outlined the intention to conduct meta-regression/subgroup analysis for the primary efficacy outcome on the basis of rTMS dose, rTMS protocol type, combination treatment status, comorbid psychiatric diagnosis status, and presence of traumatic brain injury (TBI). Subgroup analyses are intended to explore potential causes of statistical heterogeneity; in the absence of such heterogeneity, subgroup analyses are not indicated. Additionally, presenting subgroup analyses can be misleading in the absence of sufficient studies (Deeks 2021). The *Cochrane Handbook* suggests a minimum of 10 studies is required for meaningful meta-regression (Deeks 2021). Fu 2011 offers more detailed guidelines, suggesting a minimum of four studies per subgroup in the case of categorical analysis. Our main meta-analytic estimate for PTSD severity immediately after treatment only included three studies and did not detect significant statistical heterogeneity; therefore, we did not conduct these planned subgroup analyses.

We conducted exploratory subgroup analyses of PTSD severity change from baseline to immediate post-treatment outcomes across six studies (including imputed data; Analysis 2.1; Analysis 2.2). We detected substantial statistical heterogeneity across the included studies (I^2 = 69%, Chi^2 = 16.11, P = 0.007). However, the exploratory subgroup analyses we present should be interpreted with caution, as the minimum criteria outlined by Deeks 2021 and Fu 2011 were still not met.

Our first exploratory subgroup analysis involved comparisons distinguished by frequency (i.e. a high frequency [> 5 Hz] versus sham comparison, and a low frequency [≤ 1 Hz] versus sham comparison). Leong 2020 involved two active treatment groups, one receiving 1 Hz stimulation and the other receiving 10 Hz stimulation; we split the control sample in half to accommodate inclusion of this study's outcomes. This approach introduces further validity concerns as interdependence across subgroups from multiple outcomes deriving from the same study is not accounted for statistically. We assessed outcomes using SMD as different scales were used across studies. The low-frequency (LF) comparison included two studies with a 1 Hz treatment arm (Leong 2020; Watts 2012). The high-frequency (HF) comparison included five studies with a 10 Hz to 50 Hz treatment arm (Fryml 2019; Isserles 2013; Isserles 2021; Leong 2020; Philip 2019a). Overall statistical heterogeneity for this set of seven comparisons was substantial (I^2 = 63%, P = .01), and within-group heterogeneity was reduced relative to this combined statistic; LF (two comparisons, I^2 = 0%, P = 0.38), HF (five comparisons, I^2 = 24%, P = 0.26; Analysis 2.1). The test for subgroup differences was significant (Chi^2 = 8.20, degrees of freedom (df) = 1 [P = .004], I^2 = 87.8%). The meta-analytic estimate for the low-frequency subgroup favored active treatment (SMD -1.32, 95% CI -2.11 to -0.53; 2 studies, 35 participants), while the estimate for the high-frequency subgroup did not (SMD -0.06, 95% CI -0.41 to 0.30; 5 studies, 216 participants). The aforementioned concerns as well as the much lower sample size available for the low-frequency subgroup indicate these outcomes should be interpreted with caution. Additionally, it is notable that Cohen 2004 reported outcomes inconsistent with those described above; specifically, Cohen 2004 compared low-frequency (1 Hz), high-frequency (10 Hz), and sham treatment with analysis of variance (ANOVA) for change from baseline to immediately after treatment (per-protocol outcomes for Treatment Outcome PTSD Scale). This study found that the decrease in PTSD severity from baseline to immediately after treatment was significantly greater for the high-frequency treatment group compared to the low-frequency or sham treatment groups. However, these were per-protocol outcomes and therefore not eligible for inclusion in our meta-analytic estimate.

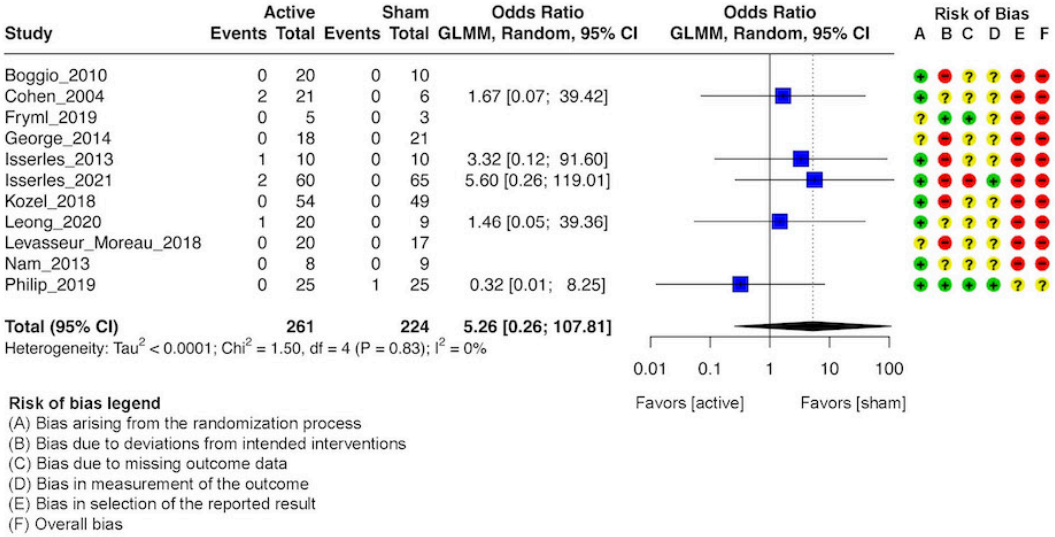
We also conducted an exploratory subgroup analysis of PTSD severity change from baseline to immediately after treatment for combination treatment status: rTMS as a stand-alone treatment (“stand-alone”) versus rTMS combined with exposure/exposure-based psychotherapy ("combination”; Analysis 2.2). We included six studies in this analysis: three studies contributed outcomes for stand-alone rTMS (Leong 2020; Philip 2019a; Watts 2012), and three studies for combination rTMS (Fryml 2019; Isserles 2013; Isserles 2021). There was an overall substantial level of statistical heterogeneity across all six studies (I^2 = 69%, Chi^2 = 16.11, P = 0.007; Analysis 2.2). Within-group heterogeneity was minimally reduced relative to this combined statistic: stand-alone (three comparisons, I^2 = 68%, P = 0.04), combination (three comparisons, I^2 = 55%, P = 0.11). The test for subgroup differences was not significant (Chi^2 = 1.05, df =1 [P = 0.31], I^2 = 4.4%). The meta-analytic estimate for the stand-alone subgroup slightly favored active treatment (SMD -0.71, 95% CI -1.51 to 0.09; 3 studies, 99 participants), as did the estimate for the combination subgroup (SMD -0.15, 95% CI -0.86 to 0.56; 3 studies, 153 participants) although confidence intervals included the possibility of an effect in either direction.

Primary safety/acceptability outcome: serious adverse events (during active treatment)

Given the challenges in deriving a reliable estimate of the occurrence of rare events such as serious adverse events (SAEs), and to give context to the types of adverse events, we provide a narrative review to complement the meta-analytic estimates provided below. Among the 13 studies included in this review, a total of seven SAEs were reported across five studies. Six of these events occurred in the active treatment arm, and one occurred in the sham arm. The single SAE reported among sham participants, an escalation of homicidal ideation, occurred in Philip 2019a. Of the six SAEs reported among participants who received active stimulation, there were three cases of increased suicidality (suicidal ideation warranting hospitalization or a suicide attempt) (Leong 2020; Isserles 2021), two manic episodes (Cohen 2004), and one seizure (Isserles 2013). We defined serious adverse events as events warranting hospitalization, including but not limited to seizure, increased suicidal ideation, mania, and syncope (FDA 2009; Wang 2022). Identification of SAEs was, in some cases, based on our judgment and did not align with the judgments made by study authors in all cases. Specifically, Cohen 2004 reported two manic episodes, but did not consider these to qualify as serious adverse events. Additionally, George 2014 reported the occurrence of a second-degree scalp burn in the active treatment group that led to protocol modifications (i.e. monitoring of coil temperature and insertion of a foam pad between the coil and skin). The study authors did not define this as an SAE given that second-degree burns are routinely treated on an outpatient basis.

Eleven of the 13 studies included in our review provided sufficient information regarding SAEs occurring during the active study period to be assessed for this outcome. However, six of these studies did not report any SAEs in either arm and therefore were not included in our meta-analytic synthesis using mixed-effects logistic regression. To place the magnitude of our point estimate in perspective, Chen 2010 calculated that odds ratios (OR) of 3.47 and 6.71 correspond to a Cohen’s d of 0.5 (medium effect size) and 0.8 (large effect size), respectively, with a 1% baseline disease rate. Corresponding ORs for the 0.4% baseline incidence rate estimated for this review would correspond to slightly larger odds ratios. Our analysis indicates rTMS may lead to increased odds of SAE; however, the 95% CI also included little to no difference and decreased odds of SAE for rTMS relative to sham treatment for adults with PTSD (OR 5.26, 95% CI 0.26 to 107.81; 5 studies, 251 participants; very low-certainty evidence; Figure 2 [Analysis 3.1];Summary of findings 1; EPOC 2018). To further aid interpretation, we converted this estimate of relative effect into estimates of absolute effect; we used SAE occurrence among sham participants across all 11 studies as our estimate of baseline occurrence (1/224). We chose to use this estimate rather than occurrence among the five studies included in our meta-analytic estimate since restricting the sample to studies reporting at least one SAE inflates the occurrence rate. This analysis translated to an estimate of four SAEs per 1000 participants in the sham arm and 23 SAEs per 1000 participants in the active arm (95% CI 1 to 326; Summary of findings 1).

Figure 2. Analysis 3.1, conducted using R software. Forest plot of comparison: Active rTMS versus sham rTMS in adults, Outcome 2: Serious adverse events (count) during active treatment period Figure created using R software (R 2021; Viechtbauer 2010) and RevMan (risk of bias traffic light plot) (RevMan 2024).



The certainty of evidence, rated using the GRADE criteria, was very low (Summary of findings 1). We downgraded the evidence by one level for risk of bias and two levels for imprecision. Four of the five included studies received an overall rating of high risk of bias and the remaining was rated as some concerns. The main aspects contributing to the increased risk of bias were absence of reporting what definition of SAE was used (Cohen 2004; Isserles 2013; Isserles 2021; Leong 2020; Philip 2019a), lack of description of a systematic strategy to identify SAEs (Cohen 2004; Isserles 2013; Leong 2020), ambiguity in the size of the safety population (Isserles 2013; Isserles 2021), and high attrition (> 20%, Isserles 2021.) We downgraded the evidence by two levels for imprecision as our meta-analytic sample size did not meet the review information threshold for detecting a difference between interventions of small effect size (Cohen's d = 0.2, threshold n = 414; Flight 2016), and the 95% CI was quite large. We observed minimal statistical heterogeneity (I^2 = 0%, P = 0.83) and did not have serious doubts about the indirectness of included participants, interventions, and outcomes.

We conducted a sensitivity analysis to explore the robustness of our estimate. We re-conducted our main analysis using SAS rather than R, and obtained an estimate that was consistent: OR 5.26, 95% CI 0.26 to 107.81. We also derived an estimate of the odds ratio that included studies with double-zeroes using a bivariate generalized linear mixed-effects model using code provided by Xiao 2021 (note: calculation of the estimate yielded a warning message likely related to the relatively small sample size, sparse distribution, or both). This analysis yielded a comparable estimate of relative effect (OR 5.25, 95% CI 0.46 to 60.27; 11 studies, 485 participants). Using a baseline (sham arm) estimate of four SAEs per 1000 participants, this corresponds to an absolute effect estimate of 23 SAEs per 1000 participants receiving active rTMS (95% CI 2 to 213). We also attempted a sensitivity analysis to exclude studies at high risk of bias; this restricted our sample size to a single study, Philip 2019a, and thus is not very informative. Philip 2019a reported only one SAE, occurring in the sham arm.

As for our primary efficacy outcome (PTSD severity immediate after treatment), we considered subgroup analyses were not appropriate as we detected minimal statistical heterogeneity (I^2 = 0%, P = 0.83), and there were only five studies available for inclusion (lower than the recommended minimum of 10 studies or four studies per subgroup [Deeks 2021; Fu 2011]). We attempted exploratory subgroup analysis for combination treatment status and stimulation frequency, but for both analyses, there was insufficient information to produce a reliable estimate for at least one of the subgroups (95% confidence boundary for the estimate extended to infinity).

Secondary outcomes

PTSD remission (immediately after treatment)

None of the included studies provided outcomes for PTSD remission immediately after treatment.

PTSD response (immediately after treatment)

None of the included studies provided outcomes for PTSD response (according to our definition of > 30% change) immediately after treatment.

PTSD severity (delayed follow-up)

PTSD severity between one and four weeks after treatment

No studies provided PTSD severity outcomes between one and four weeks after treatment that were eligible for meta-analytic synthesis.

One study provided some data regarding PTSD severity in this time window (Cohen 2004). Outcomes are presented narratively. Specifically, Cohen 2004 provided per-protocol outcomes for the

CAPS (CAPS-IV) 14 days after treatment. Combining outcomes across the two active treatment arms, outcomes indicated rTMS may make little or no difference to PTSD severity at one to four weeks after treatment (MD -0.18, 95% CI -12.36 to 12.00; 24 participants). However, combining across active treatment groups could have disguised a potential effect, as an ANOVA for change from baseline to day 14 post-treatment was statistically significant (P < 0.001), with post hoc tests indicating significantly greater decrease in the high-frequency arm relative to low-frequency active treatment and sham treatment (P < 0.05).

PTSD severity at four to 12 weeks after treatment

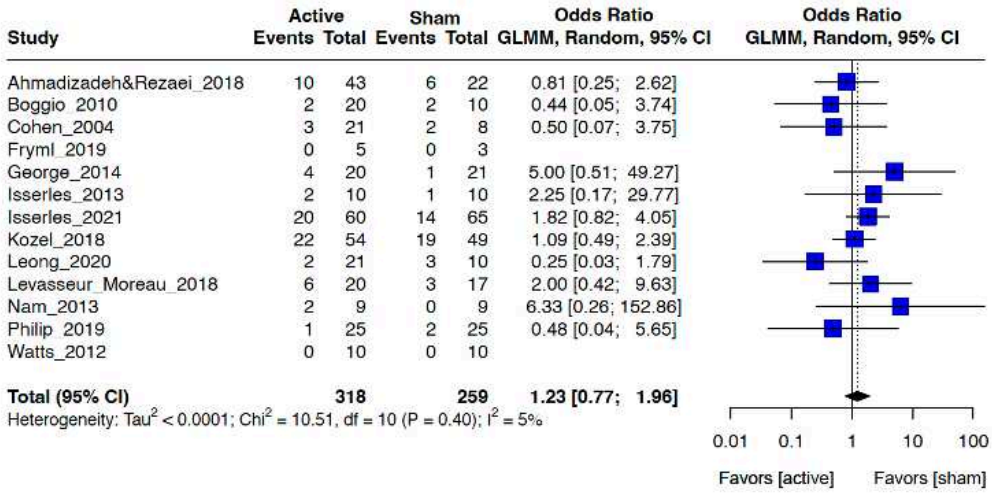
Only one study provided ITT PTSD severity outcomes at four to 12 weeks after treatment, measured using a validated assessment (Isserles 2021). Specifically, this study provided change-from-baseline outcomes assessed using the CAPS-5 five weeks after the end of the active treatment period. We found that among adults with PTSD, the estimate favored sham treatment (MD 5.83, 95% CI 0.49 to 11.17; 125 participants; Analysis 4.1). We could not find a minimal important difference in the literature for the CAPS-5, but Marx 2022 reports reliable change (change beyond what should be attributed to measurement error) for the CAPS-5 to be 12 to 13 points (CAPS-5 total score has a scale of 0 to 80 of increasing severity). Our outcome suggests a difference of small effect size favoring sham treatment for this study. We could not conduct sensitivity analyses given that outcomes were only available from one study.

Three additional studies presented some extractable data for PTSD severity scores at four to 12 weeks after treatment but were not eligible for inclusion in the meta-analysis. We describe these outcomes narratively. Watts 2012 only provided information about CAPS-IV scores in the active treatment group at four weeks after treatment; specifically, they reported an average decrease of 17.7 points from baseline to four weeks after treatment but did not provide an accompanying variance estimate nor information for the sham treatment group. Levasseur-Moreau 2018 only provided per-protocol outcomes for PTSD severity at four weeks after treatment. Using the Modified PTSD Symptom Scale, per-protocol outcomes at four weeks after treatment favored active rTMS but included the possibility of an effect in either direction (MD -16.71, 95% CI -35.04 to 1.62; 28 participants). Kozel 2018 provided both ITT and per-protocol outcomes at four weeks after treatment for the CAPS-IV. Estimates of limits to the level of missingness at which imputation methods can produce valid results vary, but range from a maximum of 20% to 40% missing (Armijo-Olivo 2009; Jakobsen 2017). At four weeks after treatment, attrition for Kozel 2018 was 41%. Therefore, we have chosen to report the per-protocol outcomes. The minimal important difference for the CAPS-IV has been estimated at 10 points (Belsher 2019; Schnurr 2001). Per-protocol outcomes for the CAPS-IV at four weeks after treatment slightly favored active rTMS but included the possibility of an effect in either direction (MD -7.18, 95% CI -18.97 to 4.61; 61 participants). A fourth study, Leong 2020, assessed PTSD severity at 12 weeks after treatment. Authors chose not to present the outcomes of this analysis due to disproportionate attrition in the sham arm, and so we have followed suit.

Dropout

All 13 studies included in our review provided sufficient information regarding dropouts occurring during the active study period to be assessed for this outcome. Across studies, dropout rates ranged from 0% to 40%. The two studies with the highest dropout rates (40% for Kozel 2018, 27% for Isserles 2021) both involved combination treatment with some form of exposure. Two studies did not report any dropouts in either arm and therefore were not included in our meta-analytic synthesis using mixed-effects logistic regression. We found that rTMS may make little to no difference in the odds of dropout during the treatment period (OR 1.23, 95% CI 0.77 to 1.96; 11 studies, 549 participants; Figure 3; [Analysis 5.1]). We observed minimal statistical heterogeneity (I^2 = 5%, P = 0.4).

Figure 3. Analysis 5.1, conducted using R software. Forest plot of comparison: Active rTMS versus sham rTMS in adults, Outcome 6: Dropout (count) during active treatment period Figure created using R software (R 2021; Viechtbauer 2010).



To aid interpretation, we converted this estimate of relative effect into estimates of absolute effect for sham and active rTMS. As an estimate of baseline occurrence, we used dropout occurrence among sham participants across all 13 studies (53/259). We chose to use this rather than occurrence among the 11 studies included in our meta-analytic estimate since restricting the sample to studies reporting at least one dropout inflates the occurrence rate. This translated to an estimate of 204 dropouts per 1000 participants in the sham arm and 240 dropouts per 1000 participants in the active arm (95% CI 165 to 335).

We conducted a sensitivity analysis to explore the robustness of our estimate. We re-conducted our main analysis using SAS rather than R, and obtained an estimate that was similar: OR 1.23, 95% CI 0.77 to 1.97. We derived an estimate of the odds ratio that included studies with double-zeroes using a bivariate generalized linear mixed-effects model using code provided by Xiao 2021. As was the case for SAEs, calculation of the estimate yielded a warning message (likely related to the relatively small sample size, sparse distribution, or both). The estimate of relative effect was comparable to that obtained excluding double-zeros (OR 1.20, 95% CI 0.74 to 1.96; 13 studies, 577 participants). This corresponds to an absolute effect estimate of 236 dropouts per 1000 participants in the active arm (95% CI 160 to 335) compared to the assumed baseline of 204 dropouts per 1000 participants in the sham arm.

Depression severity immediately after treatment

Our meta-analytic estimate pooled data from three studies that published depression severity scores assessed immediately after treatment (endpoint scores up to seven days after treatment), measured using a validated assessment (Leong 2020; Philip 2019a; Watts 2012). As these studies used different assessments, we computed this estimate using standardized mean differences (SMD). We found that among adults with PTSD, the estimate favored rTMS (with a small effect size) but included the possibility of an effect in either direction (SMD -0.27, 95% CI -0.68 to 0.13; 3 studies, 99 participants; Analysis 6.1). Statistical heterogeneity was minimal (I^2 = 0%, P = 0.80). We transformed the SMD to MD for the Hamilton Depression Rating Scale (HDRS) to facilitate interpretability. Moncrieff 2015 reports that a change of seven points on the HDRS-17 corresponds to a clinician rating of minimal improvement. The aforementioned threshold for minimal improvement was derived from the HDRS-17, while our SD estimate used to transform the SMD derives from a study using the HDRS-21 (Leong 2020; SD = 8.03, combined score from active treatment groups immediately after treatment); thus, the estimates should be interpreted with caution. Our SMD estimate transformed to the scale of the HDRS using the immediate post-treatment standard deviation from Leong 2020 (combined across active treatment groups) suggested little to no effect of rTMS on depression severity immediately after treatment, with the margin of error excluding both clinician-rated minimal improvement and worsening from rTMS (MD -2.17, 95% CI -5.46 to 1.04).

We conducted sensitivity analyses to evaluate the robustness of our meta-analytic estimate. No studies included in our primary meta-analysis had attrition exceeding 20% and statistical heterogeneity was minimal (I^2 = 0%, P = 0.80). Thus, we conducted no sensitivity analyses for attrition or heterogeneity. Both of our sensitivity analyses produced outcomes indicating rTMS may make little or no difference to depression severity immediately after treatment. We calculated a pooled estimate of endpoint SMD including imputed data. Imputation involved conversion from the published change-from-baseline to endpoint scores for Isserles 2021; we used standard deviations from baseline at endpoint. The SMD estimate, including imputed endpoint scores, moved the point estimate towards no difference in effect, and did not meaningfully alter the interpretation of the outcome. The estimate included the possibility of an effect in either direction (SMD -0.04, 95% CI -0.40 to 0.32; 4 studies, 224 participants; Analysis 6.2). Heterogeneity was minimal to moderate (I^2 = 32%, P = 0.22). We also calculated a pooled estimate including imputed data for change from baseline. Imputation involved converting the confidence interval to standard deviations for Isserles 2021, assuming a normal distribution. We also derived baseline to immediate-post correlations for Philip 2019a, Leong 2020, and Watts 2012 to estimate change-from-baseline SDs. We calculated an average correlation of 0.66 and 0.79, respectively, for Philip 2019a and Watts 2012. The calculation for Leong 2020 yielded an unreliable correlation (average < 0.5) and so we used the conventional correlation of 0.7 to derive the SDs. The estimate favored rTMS (with small effect size) but included the possibility of an effect in either direction (SMD -0.44, 95% CI -1.05 to 0.17; 4 studies, 224 participants; Analysis 6.3). Statistical heterogeneity was substantial (I^2 = 74%, P = 0.01). While estimates derived from endpoint scores and change-from-baseline scores (including imputed data) both indicated the possibility of an effect in either direction, outcomes derived from the change-from-baseline analysis provided a point estimate favoring active treatment and indicated increased heterogeneity of effect across studies. One element that may have contributed to these differences is that for Watts 2012, Leong 2020, and Philip 2019a, the average depression score at baseline was lower in the sham treatment group than in the active treatment group(s). The difference in baseline scores was not statistically significant, but nonetheless may contribute to the observed differences. We did not calculate a pooled estimate of endpoint SMD for the per-protocol sample, as of the three studies included in the main analysis for depression, Watts 2012 was the only study that provided these data, and the per-protocol and ITT estimates are equivalent as there was no dropout.

Six additional studies presented some information about depression severity scores assessed immediately after treatment but were not eligible for inclusion in the meta-analysis. We describe outcomes from these studies narratively. George 2014 only provided a statement that there were no statistically significant between-group differences in HDRS scores immediately after treatment. We could not extract reliable depression scores presented by Boggio 2010, as they were presented in figure form with an unclear error metric. The authors reported a significant interaction between treatment group and time from baseline to immediately after treatment for the HDRS (P < 0.001, 30 participants, ITT sample), with a post hoc analysis indicating a significant decrease from baseline to immediate post-treatment for left rTMS only (neither right rTMS nor sham showed a significant decrease). Fryml 2019 did not provide outcome estimates, but reported a significant interaction between treatment group and time (P = 0.035), with significantly lower HDRS scores immediately after treatment in the active rTMS compared to sham rTMS group. Isserles 2013 only provided a description of depression outcomes immediately after treatment for a modified ITT sample; repeated measures ANOVA from baseline to immediate post-treatment did not indicate a significant treatment group by time interaction. Finally, Cohen 2004 and Levasseur-Moreau 2018 only provided

per-protocol outcomes for depression severity immediately after treatment. Comparing HDRS outcomes for the sham arm to those from the two active treatment arms combined, the outcomes in Cohen 2004 slightly favored active treatment but included the possibility of an effect in either direction (MD -2.19, 95% CI -10.17 to 5.79; 24 participants). Using the Beck Depression Inventory (BDI) as a measure of depression severity, Levasseur-Moreau 2018 found no evidence of an effect from intermittent theta-burst stimulation (iTBS) on depression severity immediately after treatment; the point estimate was close to zero and the 95% confidence interval of the estimate included the possibility of an effect in either direction (MD 0.43, 95% CI -7.46 to 8.32; 28 participants).

Anxiety severity immediately after treatment

Our meta-analytic estimate pooled data from two studies that published anxiety severity scores assessed immediately after treatment (endpoint scores up to seven days after treatment), measured using a validated assessment (Leong 2020; Watts 2012). As these studies used different assessments, we computed this estimate using standardized mean differences (SMD). We found that among adults with PTSD, the estimate favored rTMS (with a small effect size), but included the possibility of an effect in either direction (SMD -0.34, 95% CI -0.93 to 0.25; 2 studies, 49 participants; Analysis 7.1). Statistical heterogeneity was minimal (I^2 = 0%, P = 0.75). We transformed the SMD to MD for the Beck Anxiety Inventory (BAI) to facilitate interpretability. The minimal important difference for the BAI was estimated at 8.8 in a study conducted among people with Parkinson's disease (Leentjens 2011). Additionally, Westbrook 2005 estimated reliable change on the BAI at 9 to 10 points. Our SMD estimate transformed to the scale of the BAI using baseline standard deviation from Leong 2020 (SD 17.99, combined across active treatment groups) did not indicate a difference between groups beyond that which could be attributable to measurement error or that reached the threshold of minimal important difference (MD -6.12, 95% CI -16.73 to 4.50).

To explore the robustness of our estimate, we re-calculated a pooled estimate using change-from-baseline outcomes. No studies published change-from-baseline data and so this estimate involved converting the endpoint outcomes from Leong 2020 and Watts 2012 to change-from-baseline scores. We derived baseline to immediate-post correlations for Leong 2020 and Watts 2012 to estimate change-from-baseline SDs. Neither calculation yielded a reliable correlation, and so we used the conventional correlation of 0.7 to derive the SDs for both studies. The estimate favored rTMS (with medium effect size) but included the possibility of an effect in either direction (SMD -0.51, 95% CI -1.31 to 0.30; 2 studies, 49 participants; Analysis 7.2). Statistical heterogeneity was moderate (I^2 = 43%, P = 0.19). We did not conduct any additional sensitivity analyses as no data were available for our planned analyses.

Four additional studies presented anxiety severity scores assessed immediately after treatment but were not eligible for inclusion in the meta-analysis. We describe these outcomes narratively. As was the case for PTSD severity immediately after treatment, Boggio 2010 only provided error statistics in figure form and did not specify the type of error statistic presented. Boggio 2010 reported a significant interaction between treatment group and time from baseline to immediately after treatment for the Hamilton Anxiety Rating Scale (HARS; P < 0.001, 30 participants, ITT sample), with a post hoc analysis indicating a significant decrease from baseline to immediately after treatment for right rTMS only (neither left rTMS nor sham showed a significant decrease). George 2014 assessed anxiety using ratings on a single item from a study-specific visual analogue scale. Given the custom nature of this scale, we did not consider it to be a psychometrically-validated measure eligible for inclusion in our meta-analytic estimate. George 2014 reported a statistically significant difference across groups in baseline to immediate post-treatment change scores, with greater reductions in anxiety in the sham treatment group (mITT sample of n = 39). Cohen 2004 and Levasseur-Moreau 2018 provided only per-protocol outcomes for anxiety severity immediately after treatment. Combining across the two active treatment groups, the outcomes in Cohen 2004 for the HARS favored active treatment, but included the possibility of an effect in either direction (MD -3.09, 95% CI -7.71 to 1.53; 24 participants). Using the BAI, the outcomes in Levasseur-Moreau 2018 slightly favored active treatment but included the possibility of an effect in either direction (MD -6.21, 95% CI -14.21 to 1.79; 28 participants). It should also be noted that, for Levasseur-Moreau 2018, the average BAI score at baseline was 12.57 points lower in the active rTMS group than in the sham rTMS group, which may impact the comparison of endpoint scores.

DISCUSSION

Summary of main results

This review included 13 studies and 577 participants in total. Our primary objective was to determine if active repetitive transcranial magnetic stimulation (rTMS) was more effective than sham rTMS in reducing post-traumatic stress disorder (PTSD) severity immediately after treatment, and whether there were any differences in the occurrence of serious adverse events (SAEs) between the two groups.

rTMS probably makes little or no difference to PTSD severity assessed immediately after treatment. Statistical heterogeneity across studies contributing to this assessment was low. Our GRADE assessment of the certainty of the evidence derived from only three studies with outcomes eligible for meta-analytic synthesis (99 participants; all studies using 10 rTMS sessions over two weeks; stimulation frequency varying from 1 Hz to 50 Hz; total pulses varying from 4000 to 30,000 over the full treatment), thus limiting the strength of confidence in this estimate. However, sensitivity analyses including imputed data (imputing endpoint scores from change-from-baseline scores and vice versa) as well as per-protocol data yielded estimates with a consistent overall interpretation of little to no difference in PTSD severity immediately after treatment for active versus sham rTMS. In contrast with the low statistical heterogeneity observed in the main analysis, sensitivity analysis of change scores for PTSD severity from baseline to immediate post-treatment (including imputed data) showed substantial heterogeneity. Subgroup analyses suggested dividing studies by combination treatment status had little impact on heterogeneity, whereas dividing studies by stimulation frequency reduced heterogeneity. The meta-analytic estimate from the low-frequency stimulation subgroup favored active treatment while the high-frequency subgroup suggested little to no impact of rTMS on change in PTSD severity from baseline to immediate post-treatment. However, these subgroup outcomes were exploratory and underpowered according to recommendations for required study numbers for subgroup analysis.

Reported rates of SAEs were low across both sham and active treatment arms of the studies included in this review. Our analysis

indicates rTMS may lead to increased chances of experiencing SAEs during the active treatment period. However, our estimate was based on very low-certainty evidence and the margin of error also included the possibility of no difference in odds of SAEs and even decreased odds of SAEs for active rTMS compared to sham treatment.

We are unable to comment on the impact of rTMS on PTSD remission, PTSD treatment response (> 30% decrease in severity score from baseline), or PTSD severity at longer follow-up times after treatment (one to four weeks post-treatment, four to 12 weeks post-treatment), due to few or no studies providing outcomes eligible for meta-analysis. We hope these outcomes may be explored in future studies and reviews of rTMS for PTSD.

Secondary analysis of the dropout rate during the active treatment period was fairly robust, with 11 out of 13 studies contributing outcomes eligible for meta-analysis. We found little to no difference in the odds of dropout during the treatment period for active versus sham rTMS. Low statistical heterogeneity and a relatively large sample size of 549 participants support the interpretation of little to no difference in effect. While there are some concerns about using dropout as a proxy for treatment tolerability, it is often used as such (Peryer 2023). If we apply this interpretation, our results suggest little difference in the tolerability of active versus sham rTMS among adults with PTSD.

Our secondary analyses of depression and anxiety severity assessed immediately after treatment suggest rTMS makes little or no difference to symptom severity compared to sham stimulation. These analyses were relatively limited in scope, with three studies contributing to the estimate for depression severity (99 participants) and two studies contributing to the estimate for anxiety severity (49 participants).

Overall completeness and applicability of evidence

This systematic review aimed to provide a comprehensive synthesis of RCTs examining the safety and efficacy of rTMS for adults with PTSD. Several recent reviews and meta-analyses have been published in this area; we believe our review adds to this literature by presenting a systematic and meticulous exploration of potential biases and reliability of outcomes. We contacted study authors for clarification and to request unpublished outcomes as needed, and we received responses to a fair number of our queries.

The studies included in this review varied considerably in terms of study characteristics (study location, setting, treatment parameters) and participant characteristics (nationality, gender, veteran status, age, comorbid conditions). This heterogeneity suggests our summary of outcomes should have good external validity. However, synthesis across heterogeneous factors in some domains, such as treatment parameters, may have limited our ability to detect potentially important treatment effects. Veterans and men were over-represented in the sample, with more than half of the sample exhibiting both of these identities. Only five studies provided data on the racial/ethnic identity of participants. Most participants were white, with a sample composition ranging from 71% to 100% white (with four out of five studies reporting at least 80% white participants). Four of these five studies were conducted in the USA. Potential explanations for the discrepancy between national demographics and the composition of samples for these studies include white-predominant local populations surrounding the sites of the clinical trials, recruitment that is biased towards the inclusion of white people, and differing attitudes among white and non-white populations towards rTMS and clinical trial participation. In the USA, lower levels of trust in healthcare institutions has been well-documented among African Americans and Native Americans, and is associated with ongoing discrimination and historical traumas inflicted by the American medical system (Livaudais-Toman 2014; Scanlon 2021).

Our review focused on outcomes assessed immediately after treatment. We chose this focus at the protocol stage, as we anticipated that this would likely be the time point for which there would be the maximum amount of data for synthesis. This prediction was accurate, as no studies reported outcomes assessed at one to four weeks after treatment that were eligible for meta-analysis, and only one study reported outcomes assessed at four to 12 weeks after treatment that were eligible for meta-analysis. However, our emphasis on the immediate post-treatment time period may underestimate the effectiveness of rTMS treatment for PTSD as there is some evidence for a delayed effect of rTMS treatment. For example, per-protocol outcomes from Kozel 2018 and Cohen 2004 suggest decreased PTSD severity scores in the active treatment group at three months compared to scores at one month after treatment and immediately after treatment, respectively. The theory of meta-plasticity proposes that rTMS produces a period of flexibility, enabling shifts in the patterns of neural activity underlying symptoms of mental health disorders, such as depression and PTSD, to occur. This suggests the treatment effects of rTMS may continue after the active treatment period, as learning and behavioral change reinforce new firing patterns of neural circuits (Kozel 2018; Schmidt 2013; Weise 2017). As previously described, a paucity of outcomes available at our prespecified longer follow-up time points prevented us from exploring potential delayed effects. We should also note that the single study, Isserles 2021, that provided outcomes suitable for meta-analysis at a later time point was an outlier, in that it was the only study to report a potential benefit of sham rTMS compared to active rTMS. Our ability to explore changes in PTSD severity at later time points was limited by insufficient reporting in the included studies (e.g. intention-to-treat [ITT] outcomes not assessed or not reported [or both] at later time points; failure to identify variance metric) and study design choices (e.g. no longer-term follow-up assessments; open-label treatment provided directly following the double-blind phase).

Related to the concern of potentially missing delayed effects of rTMS are issues of adequate treatment duration and dose. We were unable to conduct a meta-regression to explore a relationship between dose and treatment effects; this may be informative for future reviews. The importance of attention to dose and duration is exemplified by findings from another domain of brain stimulation, deep brain stimulation (DBS). Early enthusiasm for DBS for treatment-resistant depression after several positive open-label trials was followed by a loss of confidence and reassessment of the technique when the first large-scale RCT failed to indicate a significant difference between the active and sham arms (Holtzheimer 2017). However, follow-up analysis suggested that the selected RCT endpoint was premature, and that significant benefit was observed in participants receiving treatment for one year and longer (Holtzheimer 2017; Kopell 2023). These updated analyses pushed DBS to be designated as a breakthrough treatment for treatment-resistant depression (Holtzheimer 2017; Kopell 2023).

Among the studies included in this review, Levasseur-Moreau 2018 explicitly addressed inadequate dose as a potential limitation of their study design. Additionally, in correspondence during the development of this review, authors of Philip 2019a expressed the perception that other reviews and media commentary on their study have emphasized the lack of observed difference in PTSD severity across the active and sham treatment arms at the end of the double-blind phase of the trial at the expense of outcomes from the dose-finding analysis. The latter indicated that participants receiving twice as much rTMS (active double-blind followed by active open-label) had superior outcomes to participants who only received active stimulation during the open-label phase (sham double-blind followed by active open-label) at one month and one year after treatment (Philip 2019a; Petrosino 2020). These patterns of effect found in related domains of brain stimulation, together with the impressions of researchers conducting studies of rTMS for PTSD, suggest that exploration of larger doses and longer duration of rTMS for PTSD may be warranted.

Restricting our review to RCTs may have introduced some limitations to our examination of serious adverse events. Our primary review objective was to examine the efficacy of rTMS for PTSD in adults. Cochrane's guidelines strongly recommend inclusion of a safety or tolerability measure as well, in order to provide a more holistic picture of intervention effects (Peryer 2023). We selected serious adverse events to present as we judged this to be the most important outcome for patients, stakeholders, and researchers alike. However, as our primary outcome was exploration of intervention efficacy, our study design was oriented towards this outcome. While it is common practice for systematic reviews of intervention efficacy to focus on RCTs to lower potential risk of bias, this is not considered to be optimal for safety and tolerability outcomes. The *Cochrane Handbook* recommends that reviews of adverse events also include case reports/series, open-label studies, clinical study reports, and information from regulatory agency websites (Peryer 2023). Omission of these sources of data may be a limitation in the scope of many systematic reviews, including the current review. However, a review that includes case reports/series could be prone to overestimating the occurrence of serious adverse events, since the nature of case reports involves describing unusual events. Restricting our analysis to RCTs neutralizes this publication bias. However, we found that the certainty of the evidence for serious adverse events was already very low.

Our exploration of treatment tolerability was limited. We analyzed the odds of dropout, but dropout has been shown to be a flawed metric of tolerability (Peryer 2023). There was substantial variation in dropout rates across studies, ranging from 0% (Fryml 2019; Watts 2012) to 40% (Kozel 2018). The three studies with the highest dropout rate were also the studies with the largest sample sizes (Ahmadizadeh 2018; Isserles 2021; Kozel 2018). One explanation is that these studies may have placed less focus on retention, since there was a sufficient sample size to absorb the loss of participants and retain sufficient power for statistical analysis. However, it is possible that the apparent association between sample size and dropout is completely spurious; two of these trials involved a form of exposure or exposure therapy (Isserles 2021; Kozel 2018). Exposure-based therapies for trauma are associated with high dropout rates (Steenkamp 2015). Taken together, the dropout percentage was approximately equivalent across active and sham treatment groups: in Kozel 2018, the percentages were 41% and 39% for active and sham groups, respectively; in Isserles 2021, dropout was slightly higher in the active (33%) compared to the sham group (22%); and in Ahmadizadeh 2018, dropout was slightly higher in the sham group (27%) compared to the active group (23%). This is consistent with outcomes from our analysis of all 13 studies, which indicated little or no difference in odds of dropout for sham versus active rTMS treatment. Even in the absence of an imbalance in dropouts across groups, it is possible that reasons for dropout differed between them. For example, dropout in the active treatment group could be associated with unpleasant side effects, while dropout in the sham arm could be associated with lack of symptom improvement, belief that one has been assigned to the placebo arm, or both. We did not systematically extract and assess the occurrence of non-serious adverse events or side effects in this review. However, available information does not provide compelling evidence that participants in active versus sham stimulation groups dropped out for different reasons. Specifically, of the five studies that systematically collected information about side effects (e.g. headache, pain at stimulation site), all reported no overall difference in total side effects reported across groups (Ahmadizadeh 2018; George 2014; Isserles 2021; Levasseur-Moreau 2018; Philip 2019a). Additionally, of the three studies that reported on the assessment of blinding integrity, all indicated that most participants were unable to guess their group assignment correctly with confidence (George 2014; Isserles 2021; Levasseur-Moreau 2018).

Certainty of the evidence

Using GRADE criteria, we judged the certainty of evidence for our primary efficacy outcome of PTSD severity immediately after treatment as moderate. We downgraded the certainty of evidence by one level for imprecision due to the relatively small sample size available for meta-analysis. Confidence in our estimate was reinforced by low statistical heterogeneity across studies and consistent outcomes from several sensitivity analyses. Of 12 studies that provided some outcome data for PTSD severity immediately after treatment, only three presented data eligible for our main analysis (i.e. provided sample mean and identifiable variance term for ITT sample at endpoint). Thus, our estimate is not as comprehensive as we would have wanted. Our main meta-analytic estimate was also derived from relatively small studies (maximum sample size n = 50). A collection of small studies can be a warning signal for publication bias, as small positive trials are frequently published before larger studies can be funded, and tend to have outcomes of larger effect size (Boutron 2023; Lipsey 1993). We were unable to assess publication bias given the few studies available for meta-analytic synthesis. However, there is no strong indication of publication bias given that our combined estimate suggested little difference in effect between active and sham treatment. There was also little evidence for bias deriving from funding sources. Most studies were funded by research grants, defense department grants, or both. Two studies received funding from BrainsWay (Isserles 2013; Isserles 2021), a well-known manufacturer of rTMS devices. However, the second, larger study reported negative outcomes (favoring sham over active treatment), indicating reporting was likely not impacted by funding source. Sensitivity analysis of change from baseline to immediate post-treatment PTSD severity indicated substantial statistical heterogeneity in outcomes. Subgroup analysis suggested outcomes from studies using low-frequency rTMS favored active treatment while studies using high-frequency rTMS showed little to

no difference across treatment arms. As described elsewhere in this review, there are a number of factors tempering confidence in this outcome, including the exploratory nature of the analysis, small sample size, inclusion of imputed data, and conflicting outcomes from a study not eligible for inclusion in the meta-analysis (Cohen 2004). Therefore, we suggest the main conclusion to draw from this exploratory analysis is that stimulation parameters may impact the effectiveness of rTMS treatment for PTSD. Future studies increasing the power to detect effects, as well as network meta-analysis, may help clarify these effects. This conclusion is consistent with research on rTMS for depression, for which there is growing evidence that certain stimulation parameters increase treatment efficacy and that personalizing treatment to neurobiological markers can have an impact (Cash 2021; Klooster 2022).

Using GRADE criteria, we judged the certainty of evidence for the odds of experiencing a serious adverse event (SAE) during the treatment period as very low. We downgraded evidence certainty by one level for risk of bias and two levels for imprecision. The rarity of SAEs renders accurate estimation of the relative and absolute risk of SAEs difficult. Five studies contributed to our main meta-analytic estimate of the odds of experiencing an SAE during the treatment period. None of these studies provided a statement defining the meaning of SAE used in their study. This may seem inconsequential, as people may expect identification of serious adverse events to be obvious. However, evidence suggests determination of whether an adverse event qualifies as “serious” can be highly subjective. For example, we considered manic episodes to qualify as SAEs, whereas authors of the study reporting these events, Cohen 2004, did not (Wang 2022). Additionally, some studies recommend considering burns from magnetic coils that become heated during rTMS to be serious adverse events (Overvliet 2021). Another aspect that lowered our certainty of evidence rating was a lack of methodological detail regarding how SAEs would be monitored and reported. For example, many studies lacked reporting on which study staff were responsible for monitoring SAE occurrences, whether these staff were blind to treatment group, and whether participants were queried about experiences that may have qualified as SAEs. These omissions and inconsistencies suggest the field of rTMS would benefit from more standardized reporting on SAEs.

As outlined in our protocol, we only conducted formal GRADE assessments of our primary outcomes. Therefore, we can only provide a non-systematic summary of the certainty of evidence for our secondary outcomes. In our protocol, we had planned to complete GRADE assessments of dropout as a proxy for treatment tolerability. However, we decided against this as we determined that dropout could not be appropriately assessed with risk of bias standards. For example, ratings for domain 3 (attrition) are not applicable, and dropout is rarely reported as an outcome measure. Furthermore, study reporting on dropout often lacks details on plans for assessment and analysis.

Potential biases in the review process

We followed Cochrane guidelines when developing our protocol and review in an effort to minimize bias. We restricted our review to RCTs as these study designs are thought to provide the highest quality of evidence. However, this substantially reduced the number of studies eligible for inclusion. We also did not include two unpublished RCTs that provided some per-protocol data in ClinicalTrials.gov (NCT02268084; NCT02853032; see Characteristics of studies awaiting classification). We excluded these studies because they provided insufficient methodological detail to understand the study design and the potential risk of bias. We did include one unpublished study (Levasseur-Moreau 2018), as although this study did not provide ITT outcomes, it did provide a detailed description of the methodology. We hope that the aforementioned RCTs will be published and eligible for inclusion in future meta-analyses.

The largest contribution to risk of bias in the review process likely derives from our analytic choices; we summarize these below so that our findings can be interpreted in the context of potential limitations. For analyses of serious adverse events (SAEs), we used the randomized population as the safety population in the absence of more detailed information (the safety population is the number of participants exposed to the treatment, i.e. who completed at least one treatment visit; National Research Council 2010). The assumption we followed may cause underestimation of SAE rates, as the sample size potentially includes participants who did not attend any treatment visits. However, the potential underestimation of SAE rate is present across all treatment groups, so it is not expected to skew relative risk towards active or sham treatment.

Similarly, the methodological choices we made in the analysis of continuous data are not expected to bias outcomes in the direction of sham or active treatment, but may reduce the reliability of some of our outcomes. We followed imputation methods and formulae provided in the *Cochrane Handbook,* including imputation of standard deviation (SD) at endpoint and for baseline-to-endpoint change (Higgins 2021b). While these are accepted methods, they involve making assumptions about unknown data and are therefore recommended to be used sparingly. Given these concerns, we elected to only include studies requiring these forms of imputation in sensitivity analysis. We also split the control group sample to account for a multi-group comparison in exploratory analysis of subgroups for PTSD severity assessed immediately after treatment. We've detailed the limitations of this method in Effects of interventions, which introduces potential error due to unaccounted-for correlations among data derived from the same study. Network meta-analysis can more appropriately account for exploring potential differences across multiple treatment groups, and we hope there will be sufficient data to use this method in the near future. To aid interpretability, we also presented SMD outcomes transformed to a commonly-used scale (e.g. SMD to CAPS-IV) using a weighted average of SDs from studies that used that scale (Schünemann 2023). This technique may also introduce error as it depends on the reliability and generalizability of the study or studies contributing SDs for use in the transformation.

Finally, we did not include quality of life as a clinical outcome in our review. This is likely an outcome of interest to stakeholders and people with PTSD and may be recommended for inclusion in future systematic reviews and meta-analyses on this topic (we do not believe a sufficient number of papers provided this outcome for a reliable synthesis at the time of this review).

Agreements and disagreements with other studies or reviews

Several other meta-analyses and reviews of rTMS for PTSD have been published over the past decade. Overall, our review indicates

less favorable outcomes for rTMS for PTSD compared to preceding meta-analyses. We suspect this may be attributable to the more conservative methods we employed in our review, including restricting meta-analysis to ITT outcomes from RCTs. We opted for a conservative approach to guard against the overly-optimistic estimates that can sometimes emerge in new areas of research when many small-sample trials dominate the literature (IntHout 2015; Sterne 2001). We focus this discussion on comparison with the three most recently published meta-analyses: Belsher 2021; Harris 2021; McGirr 2021. These three reviews focused on efficacy and did not include exploration of serious adverse event occurrences.

McGirr 2021 conducted a systematic review and network meta-analysis of rTMS for PTSD. Consistent with our methods, McGirr 2021 also restricted their review to RCTs and focused on outcomes assessed immediately after treatment (although McGirr 2021 focused on change-from-baseline scores, while our main outcome was endpoint scores). McGirr 2021 included two studies in their review that were not included in ours (Yesavage 2018; Osuch 2009) and vice versa (Ahmadizadeh 2018; George 2014; Isserles 2021; Levasseur-Moreau 2018; Nam 2013; note: we included Isserles 2021 only in sensitivity analysis). There were also some important methodological differences between our systematic reviews. McGirr 2021 conducted network meta-analysis, supporting more accurate delineation of effects across different protocols than is possible with subgroup analyses. It is unclear what outcomes McGirr 2021 used for meta-analytic synthesis (ITT versus per-protocol outcomes); if per-protocol outcomes were used, this could have contributed to more favorable outcomes for rTMS presented in this paper than we observed in our analyses. McGirr 2021 reported that low-frequency right dorsolateral prefrontal cortex (rDLPFC) and high-frequency rDLPFC stimulation were associated with greater reduction of PTSD symptoms from baseline to immediately after treatment compared to sham rTMS, with low and very low quality of evidence, respectively. Additionally, the high-frequency left dorsolateral prefrontal cortex (lDLPFC), deep TMS, and intermittent theta-burst stimulation (iTBS) protocols did not show a significant difference in efficacy relative to sham treatment, with very low, low, and moderate quality of evidence, respectively. It is reasonable to expect that the outcomes favoring high-frequency rDLPFC and low-frequency rDLPFC stimulation, and neutral outcomes for high-frequency lDLPFC, dTMS, and iTBS compared to sham, as reported by McGirr 2021, may average together to a neutral estimate, and thus be consistent with the outcome we observed. Different reporting conventions may also give the impression of greater discrepancy between the two reviews' findings than actually obtains. Following Cochrane reporting recommendations based on GRADE evidence assessments, McGirr 2021's outcomes for high-frequency rDLPFC and low-frequency rDLPFC stimulation might be described as follows: “It is uncertain whether high-frequency rDLPFC rTMS decreases PTSD severity from baseline to immediately after treatment because the certainty of the evidence is very low”, and “Low-frequency rDLPFC rTMS may decrease severity of PTSD from baseline to immediately after treatment”. Consistent with our review, McGirr 2021 also did not observe differences in dropout between active and sham rTMS groups.

Belsher 2021 conducted a systematic review and meta-analysis of rTMS for PTSD. Consistent with our review, they also restricted inclusion to RCTs and focused on efficacy for PTSD severity immediately after treatment, focusing on change-from-baseline scores. Belsher 2021 included three studies in their review which were not included in ours (Kozel 2019; Osuch 2009; Philip 2019b), and we included three that were not included in theirs (George 2014; Isserles 2021; Levasseur-Moreau 2018; note: we included Isserles 2021 only in sensitivity analysis). Their meta-analytic synthesis excluded studies using synchronized TMS, dTMS, iTBS, or rTMS combined with psychotherapy. Outcomes from this synthesis found rTMS to be superior to sham at reducing PTSD severity and depression severity from baseline to immediately after treatment, with both rated as “very low” quality of evidence. As described above, using Cochrane’s reporting conventions, this might be rendered as: “It is uncertain whether rTMS decreases PTSD severity and depression severity from baseline to immediately after treatment”. They also reported high-frequency rTMS to be associated with slightly improved outcomes compared to low-frequency rTMS for PTSD severity and depression severity from baseline to immediately after treatment. This conclusion is in the opposite direction to that suggested by our subgroup analysis, which favored low-frequency rTMS over sham treatment for PTSD severity, but included the possibility of no difference between high-frequency rTMS and sham treatment. Together, inconsistent outcomes across the reviews, the aforementioned statistical limitations on our subgroup analysis, and the very low quality of evidence reported by Belsher 2021 suggest no conclusions can confidently be drawn yet, and that this remains an area ripe for further exploration. Belsher 2021 found high statistical heterogeneity for change in PTSD severity from baseline to immediately after treatment across high-frequency rTMS, low-frequency rTMS, and sham rTMS. This differs from our review, which did not detect significant heterogeneity for PTSD severity immediately after treatment in our main analysis. (However, we did identify significant heterogeneity for change-from-baseline to immediate post-treatment scores in sensitivity analysis). The estimate derived by Belsher 2021 included seven studies, compared to the three studies included in our main analysis of PTSD severity; this may partially explain the difference. Additionally, it is unclear whether Belsher 2021 restricted analysis to ITT data or per-protocol data, which may also significantly impact outcomes. Consistent with our outcomes, Belsher 2021 did not detect substantial statistical heterogeneity for depression severity or dropout (heterogeneity was minimal to moderate), and the margin of error for the dropout meta-analytic estimates across active and sham treatments had substantial overlap. Belsher 2021 examined the occurrence of adverse events (i.e. they focused on symptoms such as headache, discomfort, dizziness), but did not examine the occurrence of serious adverse events. They found rates of adverse event occurrence to be similar across high-frequency, low-frequency, and sham stimulation treatments.

Harris 2021 also conducted a meta-analysis of rTMS for PTSD. In contrast with our review and meta-analysis, Harris 2021 focused solely on active treatment; thus, they included both open-label and RCT studies, and excluded data from the sham arm of RCTs from analysis. Similar to our review, they also focused on immediate post-treatment outcomes. Authors did not clearly state whether they used ITT or per-protocol outcomes for synthesis. Overall, they found a strong, positive effect size for rTMS on change in PTSD severity from baseline to post-treatment, and high-frequency rTMS was associated with a larger treatment effect than low-frequency rTMS. They did not find evidence for differences in efficacy across targeting left versus right brain hemisphere, differences in dose, or

differences in stimulation intensity. Larger treatment effects were associated with RCTs compared to other (open-label, chart review) studies. This is somewhat unexpected, as open-label trials typically precede RCTs and are associated with larger effect-size findings (Lipsey 1993). However, this outcome may be influenced by the choice to combine open-label and chart reviews together as "other" study designs; additionally, the rigorous methodology associated with RCTs may increase placebo response. It is difficult to compare our results with theirs as they did not include comparison to sham treatment. Harris 2021 also acknowledged that the purpose of their review was meta-analysis of active treatment; thus, it was not a systematic review and did not include assessment of risk of bias and study quality.

Three additional studies also conducted meta-analysis of rTMS for PTSD within the last decade. Kan 2020 included 11 studies in meta-analytic synthesis and restricted analysis to RCTs. They found rTMS to be associated with decreases in PTSD severity from baseline to immediately after treatment with large effect size. It is unclear whether they used ITT or per-protocol data in their synthesis, which may contribute to differences between our outcomes. Cirillo 2019 included both RCTs and open-label studies (synthesizing pre- to post-treatment change scores for open-label studies with mean difference in change scores for RCTs). Their outcomes favored active rTMS with medium effect size. One element that may have biased outcomes in this direction is that, in the case of two active treatment groups, they excluded the group with smaller effect size from analysis. Finally, Yan 2017 included 11 studies in meta-analysis, including both RCTs and open-label studies. They found both high-frequency and low-frequency rTMS to be associated with a significant decrease in PTSD severity from baseline to immediately after treatment. We were unable to obtain access to six of the studies included in their meta-analytic synthesis (all conducted in China; for study references, see Appendix 2).

We also wish to address the discrepancy between outcomes identified by this meta-analysis and other recent literature on rTMS efficacy for depression. We found evidence for little to no effect of rTMS on depression severity immediately after treatment in our sample of participants with PTSD. This contrasts with a large body of literature demonstrating the efficacy of rTMS for treatment-refractory major depressive disorder (Berlim 2014; McClintock 2017). Multiple meta-analyses have reported improvements in depression with rTMS treatment compared to sham stimulation (Berlim 2014; McClintock 2017); accordingly, rTMS obtained approval from the US Food and Drug Administration (FDA) for the treatment of depression (Voelker 2018). There are multiple potential explanations for this discrepancy, including the possibility that depression may be less responsive to rTMS in people with comorbid diagnoses of PTSD, and differences in rTMS protocols used for the treatment of depression versus PTSD. Interestingly, a recent large-scale (n = 770) retrospective analysis of standard rTMS for depression (high-frequency stimulation delivered to the left DLPFC) in veterans with a diagnosis of major depressive disorder (and with or without PTSD) found similar reductions in depression severity in veterans with and without PTSD (Madore 2022). This suggests comorbid PTSD may not be a significant barrier to effective treatment of depressive symptoms in people with depression. However, this was not a synthesis of controlled trials and is therefore more susceptible to confounding effects. It appears likely that rTMS protocol differences may play an important role in the observed discrepancy. Studies of rTMS for depression have primarily used high-frequency rTMS targeting the left DLPFC, whereas all studies included in our primary analysis (and all but one study included in our sensitivity analyses) involved rTMS targeting the right DLPFC. This interpretation is consistent with our finding of statistical heterogeneity of outcomes across rTMS protocols (when we included more studies in sensitivity analysis estimates), and supports the recommendation for continued exploration of this area.

AUTHORS' CONCLUSIONS

Implications for practice

- On average, repetitive transcranial magnetic stimulation (rTMS) probably makes little to no difference in post-traumatic stress disorder (PTSD) symptom severity immediately post-treatment in adults relative to placebo effects produced by sham stimulation.
- Serious adverse events associated with rTMS among adults with PTSD appear to be very rare (< 1%). Our estimate indicated rTMS may increase the odds of experiencing a serious adverse event, but the margin of error was large and included no difference from sham treatment, and even increased odds of experiencing a serious adverse event in sham treatment.
- Longer-term effects of rTMS on PTSD severity in adults remain largely unknown as there is a dearth of rigorously conducted randomised controlled trials (RCTs) that have followed participants beyond immediate post-treatment.

Implications for research

- Research and clinical work on rTMS for PTSD may benefit from greater detail in reporting on serious adverse events (SAEs). This includes providing the definition of SAE used (preferably defined a priori in the protocol), how/when/by whom SAEs will be identified, and how SAEs will be assessed/analyzed. Additionally, inclusion of greater detail in participant flow diagrams is recommended to support accurate identification of the safety population size. Current ambiguities and inconsistencies in reporting create challenges for valid characterization of the safety of rTMS treatment for adults with PTSD.
- In line with recommendations proposed by other recent reviews and meta-analyses (Belsher 2021; McGirr 2021), we believe exploring the impact of various rTMS protocols on symptoms domains and biomarkers of PTSD is an exciting and potentially valuable objective for future research. Detection of substantial statistical heterogeneity in our analysis of change-from-baseline scores for PTSD severity suggests important differences in efficacy across protocols may exist, particularly if appropriately paired with subpopulations of people with PTSD most likely to benefit from different treatments.
- As noted above, we recommend that future RCTs include a delayed follow-up time point, as well-controlled data for follow-up time points is limited. There is some indication from uncontrolled trials in rTMS, as well as in other forms of brain stimulation (i.e. deep brain stimulation), that restricting analysis to immediate post-treatment may miss important effects.
- We recommend future RCTS and reviews include assessment of quality of life, as this is likely to be a valued outcome for individuals.

- Future research is warranted to establish the minimal clinically important difference for the PTSD Checklist for DSM-5 (PCL-5) and the Clinician-Administered PTSD Scale (CAPS-5), as these are the assessments most likely to be used in future rTMS for PTSD research trials conducted in the USA, as they have been rigorously developed to match current diagnostic criteria for PTSD in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and DSM-5 Text Revision (DSM-5-TR). Minimal clinically important differences provide important perspective on the interpretation of effect sizes.

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Toby Lasserson, Deputy Editor-in-Chief, Cochrane Central Executive;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Luisa Fernandez Mauleffinch, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Sara Hales-Brittain, Cochrane Central Editorial Service;
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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmadizadeh 2018

Study characteristics

Methods	Aim To compare the efficacy of unilateral right-sided rTMS, bilateral rTMS, and sham rTMS for the treatment of PTSD Design

Ahmadizadeh 2018 *(Continued)*

	Parallel RCT Unit of allocation Individual Ethical approval Yes (approved by Baqiyatallah University of Medical Science Ethics Committee) Study dates 2013 to 2016 (recruitment start and end dates)
Participants	ITT population Population description Male veterans with PTSD, recruited from the anxiety service at the Atieh Clinical Neuroscience Center, Baqiyatallah University of Medical Science Study setting Medical center Inclusion criteria Male veterans aged 42 to 69 with a diagnosis of PTSD (per SCID), PTSD Checklist Military Version (PCL-M) score > 50, and no change in psychotropic medication nor psychosocial treatment for at least 2 months prior to trial initiation Exclusion criteria Diagnosis of axis I psychiatric disorder or personality disorder, history of significant neurological or medical condition (e.g. seizure, brain tumor, moderate or severe TBI), cardiac pacemaker, history of heart disease, implanted medical pump, non-removable metal objects in or near head (excluding most dental work) Method of recruitment Not described Total number randomized 65 (across 3 groups) Age Mean age 50.45 (SD 7.31) in subsample (n = 58) of participants who completed treatment through session 5); statistics for fully randomized sample (n = 65) not provided. Sex 100% male (randomized sample) Comorbidities Not described (majority of comorbid disorders exclusionary)
Interventions	Active treatment Treatment duration 4 weeks (three sessions/week for weeks 1 & 2, two sessions per week for weeks 3 & 4 (10 sessions total)

Ahmadizadeh 2018 *(Continued)*

	Treatment target Unilateral: right DLPFC Bilateral: bilateral DLPFC (DLPFC targeted using beam method with head measurements and computerized program) Frequency Unilateral: 20 Hz Bilateral: same as unilateral Intensity Unilateral: 100% MT Bilateral: same as unilateral Session description: Unilateral: 30 minutes per session (30-second cycles of 2-second train, 28-second intertrain interval; total of 60 cycles/session) Bilateral: 30 minutes per session (30-second cycles of 2-second train, 28-second intertrain interval; total of 60 cycles/session, 30 cycles per side per session). Stimulation sequentially delivered to right, then left DLPFC Total pulses delivered Unilateral: 24,000 pulses Bilateral: same as unilateral (12,000 pulses per side) Coil type Figure-eight simulation coil (Neuro MS rTMS device [Neurosoft, Russia]; 70 mm figure-eight stimulation coil, air film coil) Sham treatment All procedural aspects for sham treatment reported to be consistent with active treatment. Not reported whether sham stimulation delivered unilaterally or bilaterally. Sham description Sham coil with similar appearance and sounds to active stimulation (no commentary provided on scalp sensations or stimulation of facial muscles produced by sham coil; presumably, none, as sham stimulator used plastic cap) Co-interventions administered None
Outcomes	(Assessments were not designated as primary, secondary, etc.) • **PTSD Checklist Military Version (PCL-M)** at session 5, **session 10** (i.e. immediately after treatment) • Responder status (greater than 2 SD decrease in PCL-M score from baseline), presumably at session 10 (post-treatment assessment time point not clearly stated) Outcomes in **bold** of interest to this review
Notes	We were unable to clarify with confidence which published outcomes correspond to ITT analysis (with last-observation-carried-forward imputation); we therefore chose not to include PTSD sever-

Ahmadizadeh 2018 *(Continued)*

ity outcomes from this study in meta-analysis. (Further details regarding this decision provided in supplementary data extraction form.)

We sought additional unpublished information regarding the following: 1) per-protocol outcomes at session 10 for PCL-M; 2) outcomes from questionnaire assessing integrity of treatment blind. Dr. Rezaee shared raw data (SPSS file; de-identified) to clarify question 2; treatment-blind outcomes were not available in the spreadsheet provided.

Although a statement regarding serious adverse events was reported in the results, there was no prespecified or analyzed serious adverse event outcome measurement; the study publication reports checking for side effects, but details of data collection (time points) not provided.

Sources of funding

None to report

Conflicts of interest

No study-related conflicts of interest reported

Boggio 2010

Study characteristics

Methods	Aim To compare the efficacy of high-frequency right-sided rTMS, high-frequency left-sided rTMS, and sham stimulation for the treatment of PTSD Design Parallel RCT Unit of allocation Individual Ethical approval Yes (approved by "a local and national research ethics committee") Study dates October 2005 to July 2008
Participants	ITT population Population description Adults with PTSD Study setting University (Mackenzie University in São Paulo, Brazil) Inclusion criteria Persons aged 18 to 64 with PTSD (per SCID for DSM-IV) and no change in psychotropic medication nor psychotherapy for at least 3 weeks prior to trial initiation Exclusion criteria

Boggio 2010 *(Continued)*

	Diagnosis of a substance use disorder, presence of a severe major depressive episode immediately before the index traumatic event, head trauma, chronic medical conditions, or MRI contraindications Method of recruitment Newspaper advertisements and referral by psychiatrists Total number randomized 30 (across 3 groups) Age Mean age 44.5 (SD 4.4; randomized sample) Sex 30% male, 70% female (randomized sample) Comorbidities Not reported
Interventions	Active treatment Treatment duration 2 weeks, one session per day on weekdays (10 sessions total) Treatment target Right-sided rTMS: DLPFC targeted using methods outlined by Pascual-Leone 1996 involving measurements from site of optimal first dorsal interosseus muscle activation, Tailarach Atlas coordinates, and electrode positions of the 10-20 system Left-sided rTMS: DLPFC (same methods as for right-sided) Frequency Right-sided rTMS: 20 Hz Left-sided rTMS: 20 Hz Intensity Right-sided rTMS: 80% MT Left-sided rTMS: 80% MT Session description: Right-sided rTMS: 20 minutes per session (40 trains of 2 seconds with intertrain interval of 28 seconds) Left-sided rTMS: 20 minutes per session (40 trains of 2 seconds with intertrain interval of 28 seconds) Total pulses delivered Right-sided rTMS: 16,000 pulses Left-sided rTMS: 16,000 pulses Coil type

Boggio 2010 *(Continued)*

	Figure-eight coil (outside diameter of each wing = 7 cm) and a Magstim stimulator (1.5 Tesla version; Magstim Company Ltd, Wales, United Kingdom) Sham treatment All procedural aspects consistent with active treatment (treatment duration, session length and number, and co-interventions permitted). Half of participants allocated to sham received right-sided sham and half left-sided sham. Sham description Sham coil with similar appearance, weight, and scalp sensation (using small electrical stimulator) as active treatment Co-interventions administered None
Outcomes	(Assessments were not designated as primary, secondary, etc.) • **Treatment Outcome PTSD Scale** at day 5, **day 10** (i.e. immediate post-treatment), **2 weeks post-treatment** (i.e. 1 to 4 weeks post-treatment), **4 weeks post-treatment** (i.e. 1 month post-treatment), 8 weeks post-treatment, 12 weeks post-treatment • PTSD Checklist (PCL) at day 5, day 10, 2 weeks post-treatment, 4 weeks post-treatment, 8 weeks post-treatment, 12 weeks post-treatment • **Hamilton Depression Rating Scale-28 (HDRS-28)** at day 5, **day 10**, **2 weeks post-treatment**, **4 weeks post-treatment**, 8 weeks post-treatment, 12 weeks post-treatment • **Hamilton Anxiety Rating Scale (HARS)** at day 5, **day 10**, **2 weeks post-treatment**, **4 weeks post-treatment**, 8 weeks post-treatment, 12 weeks post-treatment Exploratory • Battery of neuropsychological tests to examine cognitive safety Outcomes in **bold** of interest to this review
Notes	A statement regarding serious adverse events was reported in the results, but there was no pre-specified or analyzed serious adverse event outcome measurement. We sought additional unpublished data for Treatment Outcome PTSD Scale, HDRS-28, and HARS as data only presented in figures, but received no response. Sources of funding Northstar Neuroscience and a research grant (Programa Institucional de Iniciação Cientifica [PIBIC]-Mackenzie) Conflicts of interest No study-related conflicts of interest reported

Cohen 2004

Study characteristics	
Methods	Aim To compare the efficacy of right-sided low-frequency (LF) rTMS, right-sided high-frequency (HF) rTMS, and sham rTMS for the treatment of PTSD Design

Cohen 2004 *(Continued)*

	Parallel RCT
	Unit of allocation
	Individual
	Ethical approval
	Yes (approved by Helsinki Ethics Committee of Ben-Gurion University)
	Study dates
	Not reported
Participants	ITT population
	Population description
	Participants recruited from inpatient or outpatient treatment programs at Be'er Sheva Mental Health Center
	Study setting
	Be'er Sheva Mental Health Center (Medical Hospital)
	Inclusion criteria
	Persons with PTSD (per SCID for DSM-IV)
	Exclusion criteria
	Substance use disorder, history of epilepsy, neurosurgery, or brain trauma, cardiac pacemaker implant, chronic medical condition
	Method of recruitment
	Not described
	Total number randomized
	29 (across 3 groups)
	Age
	Mean age 41.7 (SD 11.4; per-protocol sample, n = 24). Descriptive statistics not available for full randomized sample.
	Sex
	71% male, 29% female (per-protocol sample, n = 24)
	Comorbidities
	Not described; no chronic medical conditions (exclusionary)
Interventions	Active treatment
	Treatment duration
	2 weeks, one session per day on weekdays (10 sessions total)
	Treatment target
	Right DLPFC (5 cm anterior [in a parasagittal line] to the motor cortex)
	Frequency

Cohen 2004 *(Continued)*

	LF: 1 Hz HF: 10 Hz Intensity LF: 80% MT HF: 80% MT Session description: LF: 20 minutes/session (5 seconds/train, 55-second intertrain interval); estimated 100 pulses/session HF: 20 minutes/session (2 seconds/train, 58-second intertrain interval; estimated 400 pulses/session Total pulses delivered LF: not provided; estimated total 1000 pulses HF: not provided; estimated total 4000 pulses Coil type Magstim stimulator (Magstim Company, Whitland, U.K.), circular coil with a 9-cm diameter Sham treatment All procedural aspects consistent with active treatment (treatment duration, session length and number, targeting, and co-interventions permitted). Sham treatment involved use of the HF protocol with the coil placed at a 90-degree angle to the skull. Sham description Coil appearance and sound matched active treatment (same coil used); no sensations or stimulation of facial muscles Co-interventions administered None
Outcomes	(Assessments were not designated as primary, secondary, etc.) • Hebrew version of the **Clinician Administered PTSD Scale (CAPS**; DSM-IV version) at **2 weeks post-treatment** (i.e. 1 to 4 weeks post-treatment) • Treatment Outcome PTSD Scale at week 1, immediate post-treatment, 2 weeks post-treatment • PTSD Checklist (PCL) at week 1, immediate post-treatment, 2 weeks post-treatment • **Hamilton Depression Rating Scale-23 (HDRS-23)** at week 1, **immediate post-treatment**, 2 weeks post-treatment • **Hamilton Anxiety Rating Scale (HARS)** at week 1, **immediate post-treatment**, 2 weeks post-treatment Outcomes in **bold** of interest to this review
Notes	We sought additional unpublished data for ITT CAPS, HDRS, and HARS outcomes (mean and SD), but received no response; therefore, clinical outcomes not eligible for inclusion in primary meta-analysis (of ITT outcomes). Although a statement regarding serious adverse events was reported in the results, there was no prespecified or analyzed serious adverse event outcome measurement. Sources of funding

Cohen 2004 *(Continued)*

	Grant from the Israel Defense Force—Medical Corps Research and Development Branch Conflicts of interest No study-related conflicts of interest reported

Fryml 2019

Study characteristics	
Methods	Aim To assess the feasibility of simultaneous prolonged exposure and rTMS for PTSD Design Parallel RCT Unit of allocation Individual Ethical approval Yes (approved by institutional review boards of the Ralph H. Johnson VA Medical Center and the United States Army Medical Research Acquisition and Activity) Study dates July 2011 to March 2013 (start and end of active enrollment)
Participants	ITT population Population description Veterans with PTSD Study setting VA Medical Center (Ralph H. Johnson Veterans Administration) Inclusion criteria Veterans aged 21 to 50 with PTSD (per SCID for DSM-IV and CAPS) with a war-related index trauma and who served in Operation Iraqi Freedom/Operation Enduring Freedom Exclusion criteria Psychosis[a], substantial substance abuse, head trauma, seizures, unstable medical comorbidities, implanted metal in the head, and use of medications known to lower the seizure threshold or block activation of the anxiety circuit (methylphenidate, bupropion, or benzodiazepines) Method of recruitment Not described Total number randomized 8 (across 2 groups) Age

Fryml 2019 *(Continued)*

	Mean age sham treatment 30 (variability 2.6), mean age active treatment 27 (variability 2.1; randomized sample)[b] Sex 88% male, 12% female (randomized sample) Comorbidities Not described
Interventions	Active treatment Treatment duration 5 weeks, 1 session per week (5 sessions total)[c] Treatment target DLPFC (n = 3 left-sided, n = 2 right-sided; outcomes only available for active treatment groups combined). Targeted using 6 cm anterior to motor thumb area. Frequency 10 Hz Intensity 120% MT Session description: 30 minutes per session (5-second trains with 10-second intertrain intervals) Total pulses delivered 30,000 pulses[c] Coil type Figure-eight solid core coil (Neuronetics [Neuronetics Inc, Malvern, Pa] Model 2100 magnetic stimulator [NS 0226 A 15VAC-C]) Sham treatment All procedural aspects consistent with active treatment (treatment duration, session length and number, targeting, and co-interventions permitted). Sham and active treatment delivered using the same device; smart card program programmed to deliver active or sham treatment. Sham description No specific description of sham sensations or noises available; as the same coil was used as for active treatment, coil appearance and weight matched with that of active treatment Co-interventions administered Simultaneous prolonged exposure; participants received standard clinical prolonged exposure therapy, with sessions of at least 40 minutes' duration (concurrent rTMS for middle 30 minutes)
Outcomes	Primary • Treatment tolerability (**dropout**) at study endpoint (i.e. **immediate post-treatment**) Secondary

Fryml 2019 *(Continued)*

- **Clinician Administered PTSD Scale (CAPS)** at week 1, week 2, week 3, week 4, **week 5** (i.e. immediate post-treatment)
- **Hamilton Depression Rating Scale-24 (HDRS-24)** at week 1, week 2, week 3, week 4, **week 5** (i.e. immediate post-treatment)
- **Hamilton Anxiety Rating Scale** at week 1, week 2, week 3, week 4, **week 5** (i.e. immediate post-treatment)
- **PTSD Checklist (PCL)** at week 1, week 2, week 3, week 4, **week 5** (i.e. immediate post-treatment)

Outcomes in **bold** of interest to this review

Notes

[a]Current or past psychosis is listed as exclusionary, yet demographic table indicates 2 participants in the sham group experienced auditory hallucinations.
[b]Units for the variability metric (SD or SE) were not clearly stated.
[c]Treatment duration is unclear. Methods section stated 8 weeks' duration and Abstract stated 5 weeks. In personal communication with study authors, authors reported belief from memory that trial was 5 weeks' duration, but were unable to review study data to confirm.

We sought additional unpublished data to confirm variability metric, treatment duration, and CAPS and HDRS-24 scores at immediate post-treatment.

Clinical assessment scores were not reported in a usable form for meta-analysis; the measure of variability was not clearly stated for CAPS nor HDRS-24 and no outcomes were reported for PCL nor Hamilton Anxiety Rating Scale (due to incomplete datasets).

Although a statement regarding serious adverse events was reported in the results, there was no prespecified or analyzed serious adverse event outcome measurement.

Sources of funding

United States Department of Defense through Telemedicine and Advanced Technology Research (funding: award number W81XWH-10-2-0194)

Conflicts of interest

No study-related conflicts of interest reported

George 2014

Study characteristics

Methods

Aim

To assess the feasibility, safety, and potential efficacy of high-dose rTMS for suicidal thinking in in-patient veterans[a]

Design

Parallel RCT

Unit of allocation

Individual

Ethical approval

Yes (approved by all participating institutions [Ralph H. Johnson VA Medical Center, Walter Reed National Military Medical Center, University of California San Diego, US Army Medical Research and Materiel Command])

Study dates

George 2014 *(Continued)*

	December 2010 to March 2013 (enrollment start and end dates)
Participants	ITT population Population description Veterans receiving inpatient treatment due to suicidal ideation or suicide attempt with comorbid PTSD and/or mild traumatic brain injury (mTBI)[b] Study setting VA/military medical centers Inclusion criteria Must meet criteria for at least one of the following: diagnosis of PTSD (per DSM-IV), diagnosis of mTBI (per American College of Rehabilitation Medicine criteria). Veterans aged 18 to 70, receiving inpatient care for suicidal ideation and/or attempt, Beck Scale for Suicidal Ideation score ≥ 12, score on item #3 of HRSD ≥ 3, current depressive episode associated with unipolar or bipolar II depression (per DSM-IV), English-speaking and competent to give informed consent, negative pregnancy test (if female) Exclusion criteria Diagnosis of borderline personality disorder, schizophrenia, psychosis, bipolar disorder type I, or dementia, repeated abuse of drugs or dependent upon drugs within 6 days of study entry, signs of alcohol withdrawal, clinically unstable medical illnesses, metal in head, history of seizures, use of theophylline, stimulants such as methylphenidate, bupropion, homeless, committed to hospital under court order Method of recruitment Inpatient psychiatrists monitored admissions for eligible participants and attending physician would provide information about participation. Total number randomized 41 (across 2 groups)[c] Age Mean age 42.5 (SD 15.7) in the full sample (randomized population) Sex 85% male, 15% female (randomized population) Comorbidities 98% PTSD, 59% mTBI, 41% past substance abuse/dependence, 25% current substance abuse/dependence
Interventions	Active treatment Treatment duration 3 days, 3 sessions per day (9 sessions total) Treatment target Left PFC, 6-cm rule Frequency 10 Hz

George 2014 *(Continued)*

	Intensity 120% MT Session description: 30 minutes/session, 5-second stimulation train with 10-second intertrain interval, 6000 pulses/session; same-day sessions spaced by a minimum 1 hour Total pulses delivered 54,000 pulses Coil type Figure-eight solid core coil (Model 2100 magnetic stimulator [Neuronetics, Inc., Malvern, PA; NS 0226 A 15VAC-C]; controller/power supply and three solid iron core coils Sham treatment All procedural aspects consistent with active treatment (treatment duration, session length and number, targeting, and co-interventions administered and permitted). Sham description Coil with identical appearance, positioning, and noises; sham coil produced some sensation (via transcutaneous electrical nerve stimulation unit) Co-interventions administered No systematic co-interventions introduced as part of the study protocol Study was developed as an adjunctive treatment for suicidal inpatients; thus, treatment-as-usual occurred concurrently with trial (including counseling and medication adjustments)
Outcomes	Primary • Beck Suicidal Scale Inventory at end of each treatment day • Visual analog scale measures of emotions before and after each session • Visual analog scale measures of treatment painfulness after each session Secondary[d] • **Clinician Administered PTSD Scale for DSM-IV (CAPS-IV)** at **discharge**[e] (i.e. immediate post-treatment), **3 months post-treatment** (4 to 12 weeks post-treatment), and 6 months post-treatment • **Hamilton Rating Scale for Depression (HRSD)** at **discharge** (i.e. immediate post-treatment), **3 months post-treatment** (4 to 12 weeks post-treatment), and 6 months post-treatment • Montgomery-Åsberg Depression Rating Scale at discharge, 3 months post-treatment, and 6 months post-treatment • Columbia-Suicide Severity Rating Scale (C-SSRS) at discharge, 3 months post-treatment, and 6 months post-treatment Other • Number of adverse events at each session and follow-up visit • Length of hospital stay • Time to hospital re-admission • Integrity of treatment blind Outcomes in **bold** of interest to this review

George 2014 *(Continued)*

Notes	Information regarding serious adverse events were reported in the results, and adverse events were listed as an outcome of interest in the study protocol. However, authors provided no prespecified method for assessing the occurrence of adverse events or serious adverse events (i.e. it is unclear whether any systematic assessment of occurrence of serious adverse events was undertaken). [a]Study was not designed with the purpose of treating people with PTSD (rTMS parameters were not optimized for this population). [b]All but one participant (40/41) met criteria for PTSD. [c]Publication reports 42 participants underwent randomization, but one participant was excluded due to incorrect consent. [d]No data from secondary outcome clinical scales (CAPS, HRSD, MADRS, C-SSRS) were included in publication. [e]The discharge time point of assessment appears to meet criteria for "immediate post-treatment" (within 1 week of end of active treatment) on average, but variation exists. On average, participants' inpatient stays lasted 10 days, and treatment was initiated on the third day (thus resulting in an estimated 5 days between end of active treatment and discharge). Sources of funding US Army Medical Research and Materiel Command, Department of Defense Conflicts of interest No study-related conflicts of interest in relation to the review question. Study investigators denied any financial conflict of interest with the vendor (Neuronetics) at the time of the study as well as for 5 years preceding the study.

Isserles 2013

Study characteristics	
Methods	Aim To compare the effects of dTMS + brief exposure, dTMS + sham exposure, and sham TMS + brief exposure on fear extinction and PTSD symptoms Design Parallel RCT (followed by open-label dTMS) Unit of allocation Individual Ethical approval Yes (approved by Department of Psychiatry, Hadassah-Hebrew University Medical Center) Study dates March 2008 to March 2011 (enrollment start and end dates)
Participants	ITT population Population description Adults with treatment-refractory PTSD Study setting

Isserles 2013 *(Continued)*

	University Medical Center Inclusion criteria Adults diagnosed with PTSD who had experienced treatment failure with an antidepressant and/or trauma-focused psychotherapy, and no change in psychoactive medication for at least 4 weeks prior to trial initiation Exclusion criteria No other DSM-IV axis I or axis II disorders (excluding major depression), no TMS contraindications Method of recruitment Not described Total number randomized 30 (across 3 groups; n = 20 across the two groups relevant to current review; see footnote)[a] Age Exposure + dTMS: mean age 49 (SD 12.5; treatment criterion sample, n = 9) Exposure + sham TMS: mean age 40.4 (SD 10.5; treatment criterion sample, n = 9) Sex Exposure + dTMS: 78% male, 22% female (treatment criterion sample, n = 9) Exposure + sham TMS: 89% male, 11% female (treatment criterion sample, n = 9) Comorbidities Not described
Interventions	Active treatment Treatment duration 4 weeks, 3 sessions per week (12 treatments total) Treatment target Medial PFC (coil embedded in a helmet) Frequency 20 Hz Intensity 120% MT Session description 15.5 minutes stimulation per session (42 2-second trains of 20 Hz pulses with 20-second intertrain intervals) Total pulses delivered Calculated to be 20,160 pulses (1680 pulses/session) Coil type H coil (Magstim Rapid stimulator [Magstim, UK] with the novel H-coil [BrainsWay Inc., Jerusalem, Israel])

Isserles 2013 *(Continued)*

	Sham treatment All procedural aspects consistent with active treatment; same helmet used as for active treatment, but sham coil activated Sham description Sham coil with same appearance as active (same helmet used); similar noises and scalp sensations. Sham coil produced some "negligible" electrical field inside the brain Co-interventions administered A brief exposure administered immediately preceding each stimulation or sham treatment. Exposure consisted of a 30-second script (prerecorded by each participant) recounting the traumatic event associated with their PTSD.
Outcomes	Primary • **Clinician-Administered PTSD Scale-II (CAPS)** at **week 5** (i.e. immediate post-treatment), 2 weeks post-treatment, and 2 months post-treatment Secondary • PTSD Symptom Scale - Self Report version (PSS-SR) at week 1, week 2, week 3, week 4, week 5, 2 weeks post-treatment, and 2 months post-treatment • Hamilton Depression Rating Scale-24 (HDRS-24) at week 1, week 2, week 3, week 4, week 5, 2 weeks post-treatment, and 2 months post-treatment • Beck Depression Inventory II (BDI) at week 1, week 2, week 3, week 4, week 5, 2 weeks post-treatment, and 2 months post-treatment Other • Treatment response (> 50% decrease in CAPS relative to baseline) at week 5 • CAPS subscale totals (intrusion, avoidance, hyperarousal) at week 5, 2 weeks post-treatment, 2 months post-treatment • Average heart rate across treatment visits at week 1, week 2, week 3, week 4 • Average skin conductance across treatment visits at week 1, week 2, week 3, week 4 Outcomes in **bold** of interest to this review
Notes	[a]Descriptive statistics were provided for the "treatment criterion" sample of n = 26 who completed at least 8 sessions rather than the fully randomized sample of n = 30. Study outcomes at 2 weeks post-treatment and 2 months post-treatment were not eligible for inclusion in this review as after the 4-week double-blind phase, all participants were unblinded and those allocated to sham TMS had the option for open-label treatment. A statement regarding serious adverse events was reported in the results, but there was no prespecified or analyzed serious adverse event outcome measurement. Authors report that participants underwent weekly monitoring for adverse effects and subjective complaints. Study outcomes for CAPS and HDRS-24 not available in a usable format for meta-analysis. ITT sample CAPS scores only provided as change-from-baseline scores, which cannot be combined with endpoint scores for meta-analysis of standardized mean difference (Deeks 2021). HDRS-24 scores only available for treatment criterion sample. Sources of funding BrainsWay Conflicts of interest

Isserles 2013 *(Continued)*

	Dr Isserles receives financial support from BrainsWay, Inc which developed the H-coils and supported this study. Professor Zangen and Dr Roth are key-inventors of the H-coils, own equity in BrainsWay, Inc and receive financial support from this company. E. Zlotnick received financial support from BrainsWay, Inc.

Isserles 2021

Study characteristics	
Methods	Aim To evaluate the safety and efficacy of dTMS or sham stimulation combined with brief trauma script exposure for PTSD Design Parallel RCT Unit of allocation Individual Ethical approval Yes (multisite study approved by ethical review boards at all participating sites; p. 722) Study dates October 2015 to October 2019 (enrollment start and end for interim analysis)
Participants	ITT population Population description Individuals with PTSD recruited from the community Study setting Multicenter trial including 15 centers: 11 USA, 2 Israel, 1 Canada, 1 Europe Inclusion criteria People aged 22 to 68 with a diagnosis of PTSD (per DSM-5 criteria) and CAPS-5 score ≥ 25 Exclusion criteria Severe depression (HDRS > 26), other primary axis I disorder, severe personality disorder, significant suicidal risk, substance use within 6 months of study entry, significant TBI or brain disorder, previous TMS treatment Method of recruitment Public advertisements and physician referrals Total number randomized 125 (across 2 groups) Age Mean age sham treatment 43.7 (SD 12.25); mean age active treatment 44.8 (SD 13.19; randomized sample)

Isserles 2021 *(Continued)*

	Sex 35.2% male, 64.8% female (randomized sample) Comorbidities Not described (majority of comorbid disorders exclusionary)
Interventions	Active treatment Treatment duration 4 weeks, 3 sessions per week (12 treatments total). Additional booster session administered at week 5 (i.e. precedes week 9 follow-up assessments) Treatment target mPFC (helmet placed with front rim 1 cm above nasion) Frequency 18 Hz Intensity 100% MT Session description: 80 trains per session (2-second trains and 20-second intertrain intervals); session duration not provided (calculated: 30 minutes/session) Total pulses delivered Not provided. Calculated 34,560 pulses on the basis of 12 sessions of 2880 pulses. Coil type H coil, H7 type (Magstim Rapid2 TMS stimulator [Magstim Co. Ltd.]; coil type H7 [BrainsWay Ltd.]) Sham treatment All procedural aspects consistent with active treatment (treatment duration, session length and number, targeting, and co-interventions administered and permitted). Sham description Sham coil appearance, noise, and scalp sensations designed to mimic active coil Co-interventions administered Brief script-driven imagery (SDI) occurred immediately preceding each treatment session (SDI involved personalized 30- to 60-second script of traumatic event played followed by direction to imagine traumatic event for additional 30 seconds)
Outcomes	Primary • **Clinician Administered PTSD Scale for DSM-5 (CAPS-5)** at **week 5** (i.e. immediate post-treatment) and **week 9** (i.e. 4 to 12 weeks post-treatment) Secondary • Response rate (≥ 50% improvement in CAPS-5 score compared with baseline) at week 5 and week 9 • Modified PTSD Symptom Scale, Self-Report at week 3, week 5, and week 9 Other

Isserles 2021 *(Continued)*

	• At every visit, subjective report of any **adverse events** since previous treatment Outcomes in **bold** of interest to this review
Notes	We sought additional unpublished information to clarify the following: 1) range of days between final TMS treatment and week 5 assessment, and 2) whether per-protocol sample comprised N = 91 or N = 109 participants, but received no response. We designated week 5 assessment as "immediate-post" as this time point extends up to 1 week post-treatment. Although adverse events were monitored at each session, there was no prespecified or analyzed serious adverse event outcome measurement. Sources of funding BrainsWay, Inc. Conflicts of interest Two authors are reported inventors of deep TMS coils and multiple authors have financial interests in BrainsWay, a company involved in developing deep TMS.

Kozel 2018

Study characteristics	
Methods	Aim To compare the efficacy of active versus sham rTMS delivered immediately prior to Cognitive Processing Therapy (CPT) for the treatment of PTSD in veterans Design Parallel RCT Unit of allocation Individual Ethical approval Yes (approved by the University of Texas Southwestern Medical Center IRB, the University of Texas at Dallas IRB, and the Army Human Research Protection Office) Study dates July 2011 to January 2016
Participants	ITT population Population description Veterans deployed since 2001 with combat-related PTSD symptoms Study setting Not described Inclusion criteria Veterans aged 18 to 60 with current diagnosis of combat-related PTSD Exclusion criteria

Kozel 2018 *(Continued)*

	Psychiatric comorbidities including eating disorders, psychotic symptoms, and substance abuse or dependence (within previous 3 months), history of significant neurological or medical condition, including greater than mild TBI, medications with TMS contraindications; non-English-speaking Method of recruitment Not described Total number randomized 103 (across 2 groups) Age Mean age 32.65 (SD 6.91) in the full sample (randomized sample) Sex 94% male, 0.06% female (randomized sample) Comorbidities 33% major depressive disorder, 0.01% Depression NOS (not otherwise specified), 13% dysthymia, 0.05% generalized anxiety disorder, 0% obsessive-compulsive disorder, 0.02% bipolar disorder, 0.01% panic disorder, 0% psychotic disorder (assessed using SCID for DSM-IV; randomized population)
Interventions	Active treatment Treatment duration 12 to 15 weeks (12 planned sessions with up to 3 additional sessions upon agreement between patient and therapist), one session per week (12 to 15 sessions total) Treatment target Right DLPFC (targeted using head measurements and computerized program that locates the F4 electrode site under 10/20 electrode convention) Frequency 1 Hz Intensity 110% MT (intensity lowered for five participants with high MT; no participants received lower than 100% MT stimulation) Session description: 30 minutes per session Total pulses delivered Not provided. Calculated to be 21,600 to 27,000 pulses on the basis of 12 to 15 30-minute sessions using 1 Hz. Coil type Double coil (Magstim Rapid2 Stimulation using a Double 70 mm Air Cooled Coil, Magstim) Sham treatment All procedural aspects consistent with active treatment (treatment duration, session length and number, targeting, and co-interventions administered and permitted)

Kozel 2018 *(Continued)*

	Sham description Coil with similar appearance and sounds to active stimulation; sham coil did not produce any scalp sensations or stimulation of facial muscles Co-interventions administered CPT was administered for 60 minutes following each TMS session. CPT administered by two trained therapists; adherence to CPT protocol monitored via video recording (scored by fidelity supervisor)
Outcomes	Primary • **Clinician Administered PTSD Scale (CAPS)** at session 5, session 9, **1 month post-treatment** (i.e. 4 to 12 weeks post-treatment), 3 months post-treatment, and 6 months post-treatment Secondary • PTSD Checklist (PCL) at session 5, session 9, 1 month post-treatment, 3 months post-treatment, and 6 months post-treatment Other • Mississippi Scale for Combat Related PTSD (M-PTSD) at session 5, session 9, 1 month post-treatment, 3 months post-treatment, and 6 months post-treatment • Quick Inventory of Depressive Symptomology (QIDS) at session 5, session 9, 1 month post-treatment, 3 months post-treatment, and 6 months post-treatment (note: QIDS not assessed at time point of interest for this review - immediate post-treatment) • Inventory of Psychosocial Functioning (IPF) at 1 month post-treatment, 3 months post-treatment, and 6 months post-treatment Outcomes in **bold** of interest to this review
Notes	We sought additional unpublished data for PCL scores at immediate post-treatment (final CPT session) for treatment-completers. Data provided by study authors. Although a statement regarding serious adverse events was made in the results, there was no prespecified or analyzed serious adverse event outcome measurement. Publication did not report ITT outcomes for CAPS at one month post-treatment (per-protocol endpoint scores reported as well as mixed linear model outcomes); follow-up for these ITT outcomes not sought as outcomes are ineligible for inclusion in primary meta-analysis due to attrition > 20%. Sources of funding Department of Defense Grant: W81XWH-11-2-0132, Texas Health and Human Services Commission HHSC Contract 529-14-0084-00001 Conflicts of interest No study-related conflicts of interest in relation to the review question

Leong 2020

Study characteristics	
Methods	Aim To compare the efficacy of high-frequency (HF) rTMS, low-frequency (LF) right-sided rTMS, and sham stimulation for the treatment of PTSD Design Parallel RCT

Leong 2020 *(Continued)*

	Unit of allocation Individual Ethical approval Yes (approved by Clinical Research Ethics Board of the University of British Columbia) Study dates 2014 to 2018 (recruitment start and end dates)
Participants	ITT population Population description Civilians with PTSD Study setting Academic Medical Center (Vancouver General Hospital) Inclusion criteria People aged 19 to 70 with a primary diagnosis of non-combat related PTSD (per Mini-International Neuropsychiatric Interview [MINI]), no change in psychotropic medication nor psychotherapy for 4 weeks prior to trial initiation Exclusion criteria Diagnosis of a psychotic illness, bipolar disorder type 1, substance use disorder within 3 months preceding trial initiation (excluding nicotine), borderline personality disorder, antisocial personality disorder, active suicidal ideation, neurological disorders including previous stroke or history of seizure, unstable medical illnesses, intracranial ferromagnetic objects, implantable devices in the head or neck region Method of recruitment Recruited from the psychiatry outpatient and community programs of Vancouver Coastal Health Total number randomized 31 (across 3 groups)[a] Age Mean age sham treatment 49.5 (SD 6.9), mean age low-frequency (LF) 39.2 (SD 13.5), mean age high-frequency (HF) 43.5 (SD 12.4). Statistics from modified ITT sample n = 29 Sex 17.2% male, 82.8% female (modified ITT sample, n = 29) Comorbidities 93% MDD, 41% GAD, 31% social phobia, 69% panic disorder, 10% OCD, 7% eating disorder, 3% ADHD (modified ITT sample, n = 29)
Interventions	Active treatment Treatment duration 2 weeks, one session per day on weekdays (10 sessions total) Treatment target

Leong 2020 *(Continued)*

LF: right DLPFC, 6-cm rule

HF: right DLPFC, 6-cm rule

Frequency

LF: 1 Hz

HF: 10 Hz

Intensity

LF: 120% MT

HF: 120% MT

Session description:

LF: 37.5 minutes/session, 2250 pulses/session

HF: 37.5 minutes/session, 4-second stimulation train with 26-second intertrain interval, 3000 pulses/session

Total pulses delivered

LF: 22,500 pulses

HF: 30,000 pulses

Coil type

Double 70 mm Air Film Coil (Magstim Super Rapid2 [Magstim Company Ltd, United Kingdom] with a Double 70 mm Air Film Coil model 3910-00)

Sham treatment

All procedural aspects reported to be consistent with active treatment; authors describe sham treatment delivered to mimic either LF or HF (number of participants receiving each type not described).

Sham description

Sham coil with similar appearance, sounds, and vibration sensation as active stimulation

Co-interventions administered

None

Outcomes

Primary

- **Clinician Administered PTSD Scale for DSM-5 (CAPS-5)** at **immediate post-treatment**, **3 months post-treatment** (i.e. 4 to 12 weeks post-treatment)[b]

Secondary

- **Hamilton Depression Rating Scale-21 (HDRS-21)** at **immediate post-treatment**, 3 months post-treatment
- Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR) at immediate post-treatment, 3 months post-treatment
- PTSD Checklist for Civilians (PCL-C) at immediate post-treatment, 3 months post-treatment
- **Beck Anxiety Inventory (BAI)** at **immediate post-treatment**, 3 months post-treatment
- Generalized Anxiety Disorder Assessment (GAD-7) at immediate post-treatment, 3 months post-treatment

Leong 2020 *(Continued)*

	Outcomes in **bold** of interest to this review
Notes	[a]The ITT population was defined as n = 29 rather than the full randomized sample of n = 31. [b]Publication states that CAPS-5 data at 3 months post-treatment were acquired but not reported due to disproportionate attrition in the sham group. Although a statement regarding serious adverse events was reported in the results, there was no prespecified or analyzed serious adverse event outcome measurement. We sought additional unpublished summary statistics for ITT outcomes for the full randomized sample (n = 31) for CAPS-IV, HDRS-21, and BAI. Authors reported inability to release these statistics per ethical review board. Sources of funding Vancouver Coastal Health Research Institute Team Grant Conflicts of interest Author Peter Chan is the co-owner and practitioner at Brainstim Healthcare, a private rTMS clinic in Vancouver, Canada.

Levasseur-Moreau 2018

Study characteristics	
Methods	Aim To compare the efficacy of active versus sham intermittent theta-burst stimulation (iTBS) for the treatment of PTSD in military personnel Design Parallel RCT Unit of allocation Individual Ethical approval Yes (approved by "local Institutional Review Boards") Study dates March 2015 to July 2016 (recruitment start and end dates)
Participants	ITT population Population description Military personnel from the Canadian Forces diagnosed with combat-related PTSD Study setting Medical center Inclusion criteria Military personnel with a diagnosis of PTSD (per DSM-5), PTSD Checklist - Military Version > 50 at initial assessment and > 35 at screening, index traumatic event less than 25 years ago, and stable on psychotherapy and psychoactive medications for at least 3 weeks preceding study entry

Levasseur-Moreau 2018 *(Continued)*

	Exclusion criteria Other psychiatric disorder (except for anxiety disorders, depression, and tobacco use disorders), no history of neurological conditions Method of recruitment Not described Total number randomized 37 (across 2 groups) Age Mean age sham treatment 41.93 (SD 8.78); mean age active treatment 40.64 (SD 5.79; per-protocol [PP] sample, n = 28)[a] Sex 92.9% male, 7.1% female (PP sample, n = 28) Comorbidities 89% MDD, 61% GAD (PP sample, n = 28)
Interventions	Active treatment Treatment duration 1 week, one session per day (5 sessions total) Treatment target Right DLPFC (determined using participant's T1-weighted MRI scan using anatomical landmarks ([x = 35, y = 39, z = 27]) Frequency 50 Hz (iTBS) Intensity 80% MT Session description: 3.2 minutes and 600 pulses per session (bursts of three pulsations at 50 Hz repeated at intervals of 200 ms) Total pulses delivered 3000 (calculated from 600 per session) Coil type Magstim Rapid stimulator (Magstim Company Limited, UK) with a figure-eight double air film coil (7 cm in diameter) Sham treatment All procedural aspects consistent with active treatment (treatment duration, session length and number, targeting, and co-interventions permitted). Sham coil used. Sham description

Levasseur-Moreau 2018 *(Continued)*

	Sham coil with similar sounds (clicking) to active stimulation. No commentary provided on scalp sensations or stimulation of facial muscles produced by sham coil; presumably, none, as sham stimulator did not emit any magnetic pulses. Co-interventions administered None
Outcomes	Assessments were not designated as primary, secondary, etc. Primary study aim was to assess safety, tolerability, and clinical potential of iTBS; secondary aim was to characterize effects of iTBS on visual responses, neurobiological outcomes, and salivary cortisol. Clinical measures • **Modified PTSD Symptom Scale (MPSS-SR)** at **immediate post-treatment** and **1 month post-treatment** • **Beck Anxiety Inventory (BAI)** at **immediate post-treatment** and **1 month post-treatment** • **Beck Depression Inventory (BDI)** at **immediate post-treatment** and **1 month post-treatment** • Outcome Questionnaire-45 at immediate post-treatment and 1 month post-treatment • Side effects (type and severity) using a standardized questionnaire at each session • Self-reported mood at each session (14 visual analog scales) Other • Dot probe task at pre- and post-iTBS every treatment • Rapid Serial Visual Presentation task at pre- and post-iTBS every treatment • fMRI seed-based whole-brain correlation maps (pre- and post-treatment) • Spectroscopy GABA [gamma-aminobutyric acid] measurements (timepoints unclear; analysis dropped due to too many participant exclusions) • Cortisol assessment at pre-treatment, immediate post-treatment, and 1 month post-treatment Outcomes in **bold** of interest to this review
Notes	[a]No statistics available for ITT sample (n = 37); only per-protocol (n = 28) outcomes presented across demographic and outcome data Sources of funding Department of National Defense grant (11750878) to S. Fecteau and M. Bilodeau. J. Levasseur-Moreau was supported by Fonds de Recherche en Santé du Québec and Indspire scholarships. S. Fecteau was supported by the Canada Research Chair in Cognitive Neuroplasticity. This study applies tools developed under the Consortium d'imagerie en neuroscience et santé mentale de Québec via a Platform Support Grant from the Brain Canada Foundation for which S. Fecteau was part of a User Group, as co-applicant. Conflicts of interest No study-related conflicts of interest reported

Nam 2013

Study characteristics	
Methods	Aim To compare the efficacy of right prefrontal TMS versus sham stimulation for the treatment of PTSD

Nam 2013 *(Continued)*

	Design Parallel RCT Unit of allocation Individual Ethical approval Yes (approved by the Institutional Review Board of the Catholic University of Korea [SCMC 070T076]) Study dates Not described
Participants	ITT population Population description People with PTSD from a university medical clinic[a] Study setting University Medical Center Inclusion criteria People with a diagnosis of PTSD (per DSM-IV-TR)[b] Exclusion criteria Neurological illnesses or medico-surgical illnesses (e.g. history of seizure, estimated intelligence quotient lower than 80, heart disease with a pacemaker), currently pregnant, left-handed Method of recruitment Participants recruited from the PTSD clinic at the Catholic University of Korea, St. Mary's Hospital Total number randomized 18 (across 2 groups) Age Mean age sham treatment 32.8 (variability 6.9); mean age active treatment 36.3 (variability 8.8; per-protocol sample, n = 16)[c] Sex 37.5% male, 62.5% female (per-protocol sample, n = 16) Comorbidities Not described
Interventions	Active treatment Treatment duration 3 weeks, one session per day on weekdays (15 sessions total) Treatment target

Nam 2013 *(Continued)*

	Right prefrontal cortex (target defined as the location 5 cm anterior to and in a parasagittal plane from the site of maximal abductor pollicis brevis muscle stimulation) Frequency 1 Hz Intensity 100% MT Session description: 20 minutes per session (60 pulses per minute, 1200 pulses/session) Total pulses delivered 18,000 pulses Coil type TAMAS stimulator with a figure-eight coil (CR Tech, Daejon, Korea) Sham treatment All procedural aspects consistent with active treatment (treatment duration, session length and number, and targeting). The same coil was used as active treatment but with the lateral wing raised 90 degrees off the head. Sham description Sham coil with identical appearance and sounds as active coil (no commentary provided on scalp sensations or stimulation of facial muscles) Co-interventions administered None
Outcomes	Primary • **Clinician Administered PTSD Scale (CAPS)** at week 2, **week 4** (i.e. immediate post-treatment), and **week 8** (i.e. 4 to 12 weeks post-treatment)[d] • CAPS re-experiencing subscale at week 2, week 4, and week 8 • CAPS hyperarousal subscale at week 2, week 4, and week 8 • CAPS avoidance subscale at week 2, week 4, and week 8 Other • Adverse effects (number and type) reported for each group; not a prespecified outcome measure Outcomes in **bold** of interest to this review
Notes	[a]Text specifies the sham group consisted of 9 inpatients; it is unclear whether all participants in the active group were also receiving inpatient care. [b]Text also states that participant index traumas were non-military events for all participants (this appears to be descriptive rather than a formal exclusion criterion). Additionally, all participants appear to be adults (>18) given the ages available for 16 participants in table 1, but this was not formally stated as inclusion/exclusion criteria. [c]Units for the variability metric (SD or SE) were not clearly stated. [d]There exists ambiguity regarding assessment time points. Methods section and figures imply assessment time points outlined above, yet statements in the discussion section imply assessments took place at 2, 4, and 8 weeks post-treatment, respectively (see Notes in data extraction form for further details).

Nam 2013 *(Continued)*

We sought additional unpublished data to obtain ITT CAPS outcomes (mean and SD), but received no response. Outcomes were not reported in a usable form for meta-analysis; number of participants analyzed not clearly stated (18 randomized vs. 16 presented in table 1), and outcomes only available in graphical form without a variability metric.

Although a statement regarding serious adverse events was reported in the results, there was no prespecified or analyzed serious adverse event outcome measurement.

Sources of funding

No details provided

Conflicts of interest

No study-related conflicts of interest in relation to the review question

Philip 2019a

Study characteristics	
Methods	Aim To compare the efficacy of intermittent theta-burst stimulation (iTBS) versus sham iTBS for the treatment of PTSD in veterans Design Parallel RCT (followed by open-label iTBS) Unit of allocation Individual Ethical approval Yes (approved by Providence Veterans Affairs (VA) Medical Center IRB) Study dates May 2016 to December 2017 (recruitment start and end dates)
Participants	ITT population Population description Veterans Study setting VA Medical Center Inclusion criteria Veterans aged 18 to 70 with a diagnosis of PTSD (per SCID, DSM-5), trauma exposure (per Life Events Checklist), and no change in psychotropic medication nor psychotherapy for at least 6 weeks prior to trial initiation Exclusion criteria Primary psychotic disorder, bipolar I disorder, current moderate or severe substance use disorder, active suicidality, history of seizure or other significant neurological disorders, central nervous system tumors, stroke, cerebral aneurysm, lifetime history of moderate or severe traumatic brain injury (per VA/Department of Defense Clinical Practice Guidelines), current unstable medical condi-

Philip 2019a *(Continued)*

	tion(s), implanted devices (unless MRI-safe), internal metal above the upper thoracic spine, pregnancy risk Method of recruitment Not reported Total number randomized 50 (across 2 groups) Age Mean age 51 (SD 12) in the full sample (randomized sample) Sex 84% male, 16% female (randomized sample) Comorbidities 90% MDD, 10% bipolar II disorder, 54% substance use disorder (mild), 22% opioid use disorder (assessed using SCID for DSM-5; randomized sample) 24% mild TBI (randomized sample)
Interventions	Active treatment Treatment duration 2 weeks, one session per day on weekdays (10 sessions total) Treatment target Right DLPFC (scalp measurements using beam method to target F4) Frequency 50 Hz (iTBS) Intensity 80% MT Session description: 9.5 minutes and 1800 pulses per session (2-second trains of three pulses at 50 Hz, given every 200 ms; trains repeated every 10 seconds) Total pulses delivered 18,000 pulses Coil type Double 70 mm biphasic figure-eight air-cooled coil (Magstim Rapid 2+1 system [Magstim, Whitland, UK]) Sham treatment All procedural aspects consistent with active treatment (treatment duration, session length and number, targeting, and co-interventions permitted); Magstim sham coil used. Sham description No commentary provided on sensations or noises produced by sham stimulation

Philip 2019a *(Continued)*

	Co-interventions administered None
Outcomes	Primary • Treatment acceptability (retention rate; i.e. **dropout**) at **2 weeks** (i.e. immediate post-treatment) Secondary • **Clinician Administered PTSD Scale for DSM-5 (CAPS-5)** at **week 10** (i.e. immediate post-treatment), 1 month post-treatment • Social and Occupational Functioning Assessment Scale at week 10 and 1 month post-treatment • Quality of Life Enjoyment and Satisfaction Questionnaire at week 10 and 1 month post-treatment Other • PTSD Checklist for DSM-5 at week 10 and 1 month post-treatment • **Inventory of Depressive Symptomatology–Self-Report (IDS-SR)** at **week 10** and 1 month post-treatment • Safety assessed at every treatment visit by spontaneous adverse event reports (coded using the Medical Dictionary for Regulatory Activities) • Treatment satisfaction form administered at week 10 Exploratory • Neuroimaging connectivity patterns predictive of clinical improvement Outcomes in **bold** of interest to this review
Notes	Study outcomes at 1-month post-treatment not eligible for inclusion in this review as after the 2-week double-blind phase, all participants had the option for 2 weeks of open-label treatment. We sought additional unpublished data for CAPS scores at immediate post-treatment for treatment-completers. Data provided by study authors. Serious adverse events were reported in the results, but there was no prespecified serious adverse event outcome measurement (there was, however, prespecified measurement for adverse events/side effects). Sources of funding US Veterans Affairs grants and VA Rehabilitation Research and Development Service Center for Neurorestoration and Neurotechnology at the Providence VA Medical Center Conflicts of interest Dr. Philip reported grant support from Janssen, Neosync, and Neuronetics.

Watts 2012

Study characteristics	
Methods	Aim To compare the efficacy of active versus sham rTMS for the treatment of PTSD in veterans Design Parallel RCT

Watts 2012 *(Continued)*

	Unit of allocation Individual Ethical approval Yes (approved by the Dartmouth Committee for Protection of Human Subjects [CPHS ID16744]) Study dates Not reported
Participants	ITT population Population description Veterans recruited from the Behavioral Sciences Service Line at the White River Junction Veterans Affairs Medical Center in White River Junction, VT Study setting Not described Inclusion criteria Veterans aged 20 to 70 with a primary diagnosis of PTSD (per SCID, DSM-IV), CAPS score > 50, and no change in psychotropic medication nor therapy for 2 months prior to trial initiation Exclusion criteria Substance abuse in 3 months preceding trial entry, significant central nervous system disorder (e.g. epilepsy), seizure within prior year, acute medical illness, treatment with a medication known to decrease the seizure threshold, ferromagnetic materials in head/neck region, implantable devices (e.g. cardiac pacemaker) Method of recruitment Not described Total number randomized 20 (across 2 groups)[a] Age Mean age sham treatment 57.8 (SD 11.8); mean age active treatment 54.0 (SD 12.3; randomized sample) Sex 90% male, 10% female (randomized sample) Comorbidities 80% MDD, 20% OCD, 35% panic disorder, 15% substance-use disorder (assessed using SCID forDSM-IV; randomized sample)
Interventions	Active treatment Treatment duration 2 weeks, one session per day on weekdays (10 sessions total) Treatment target

Watts 2012 *(Continued)*

	Right DLPFC (coil placed 4 cm anterior parasagittally and 2 cm laterally of the motor strip location that caused hand movement for MT) Frequency 1 Hz Intensity 90% MT Session description 20 minutes per session (1-minute cycles of 20-second stimulation and 40-second intertrain interval) Total pulses delivered 4000 pulses Coil type Figure-eight coil (Neuronetic 2100 [Neuronetics, LLC, Marietta, GA]; MCB70 coil) Sham treatment All procedural aspects consistent with active treatment (treatment duration, session length and number, targeting, and co-interventions permitted). Sham description Sham coil with similar appearance and sounds to active stimulation (no commentary provided on scalp sensations or stimulation of facial muscles produced by sham coil) Co-interventions administered None
Outcomes	(Assessments were not designated as primary, secondary, etc.) • **Clinician Administered PTSD Scale (CAPS)** at **immediate post-treatment**, **1 month post-treatment** (i.e. 4 to 12 weeks post-treatment), 2 months post-treatment • PTSD Checklist (PCL) at immediate post-treatment, 1 month post-treatment, 2 months post-treatment • **Beck Depression Inventory (BDI)** at **immediate post-treatment**, 1 month post-treatment, 2 months post-treatment • **State Trait Anxiety Inventory (STAI)** at **immediate post-treatment**, 1 month post-treatment, 2 months post-treatment • Brief Neurobehavioral Cognitive Examination (BNCE) at immediate post-treatment, 1 month post-treatment, 2 months post-treatment Outcomes in **bold** of interest to this review
Notes	[a]Total number randomized is assumed to be 20. The methods refer to 20 people being recruited before describing inclusion/exclusion criteria, but there is no explicit statement in the publication for total recruited versus randomized; the abstract refers to 20 people being randomly assigned to interventions but this may not mean the total number randomised. Information on safety and adverse events not provided in the publication. We sought additional unpublished information for data on serious adverse events, dropouts, and randomization allocation strategy. From email correspondence with author Dr Bradley Watts: 1) adverse event data were collected via spontaneous report; there were no serious adverse events

Watts 2012 *(Continued)*

during the study; 2) there were no dropouts at any time period; 3) randomization allocation was carried out using envelopes that were sealed, shuffled, and randomly drawn.

Sources of funding

The Hitchcock Foundation

Conflicts of interest

No conflict of interest statement available; presumably, no study-related conflict of interest as this study was conducted under the purview of an institutional review board at a VA Medical Center.

ADHD: attention-deficit hyperactivity disorder; **CAPS:** Clinician Administered PTSD Scale; **DLPFC:** dorsolateral prefrontal cortex; **DSM (IV; 5; TR):** Diagnostic and Statistical Manual of Mental Disorders (fourth edition; fifth edition; Text Revision); **GAD:** generalized anxiety disorder; **HARS:** Hamilton Anxiety Rating Scale; **HDRS:** Hamilton Depression Rating Scale; **HF:** high-frequency; **ITT:** intention-to-treat; **LF:** low-frequency; **MADRS:** Montgomery–Åsberg Depression Rating Scale; **MDD:** major depressive disorder; **mPFC:** medial prefrontal cortex; **(f)MRI:** (functional) magnetic resonance imaging; **MT:** motor threshold; **OCD:** obsessive-compulsive disorder; **PCL:** PTSD Checklist; **PCL-M:** PTSD Checklist - Military Version; **PTSD:** post-traumatic stress disorder; **RCT:** randomized controlled trial; **rTMS:** repetitive transcranial magnetic stimulation; **SCID:** Structured Clinical Interview for DSM Disorders; **SD:** standard deviation; **SE:** standard error; **TBI:** traumatic brain injury

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Carpenter 2018	Ineligible study design (open-label trial)
Clarke 2019	Ineligible study design (non-RCT)
Grisaru 1998	Ineligible study design (open-label trial; identified in handsearch)
Holtzheimer 2010	Ineligible study design (open-label trial; identified in handsearch)
Kozel 2019	Ineligible comparator (no sham arm)
McCann 1998	Ineligible study design (non-RCT [review paper]; identified in handsearch)
NCT00685152	Recruitment terminated/study abandoned
NCT01196624	Ineligible comparator (no sham arm)
NCT02367521	Ineligible participant population (not targeted to people with PTSD)
NCT02369614	Recruitment terminated/study abandoned (reason for study termination listed as staffing issues)
NCT02584894	Ineligible comparator (no sham arm)
NCT02824445	Recruitment terminated/study abandoned
NCT02873299	Ineligible comparator (no sharm arm)
NCT03523507	Recruitment terminated/study abandoned
NCT03749967	Ineligible comparator (no sham arm)
NCT03924024	Ineligible participant population (not targeted to people with PTSD)

Study	Reason for exclusion
NCT03952468	Ineligible participant population (not targeted to people with PTSD)
NCT04906603	Ineligible study design (open-label trial)
NCT05368987	Ineligible study design (open-label trial)
Nemeroff 2018	Ineligible study design (non-RCT [opinion editorial])
Nursey 2020	Ineligible study design (case series; identified in handsearch)
Oathes 2015	Ineligible study design
Oathes 2022	Ineligible study design (non-RCT)
Osuch 2009	Ineligible study design (quasi-randomized trial)
Oznur 2014	Ineligible study design (non-RCT; identified in handsearch)
Philip 2016	Ineligible study design (non-RCT [chart review study]; identified in handsearch)
Philip 2019b	Ineligible intervention
Philip 2020	Ineligible study design (non-RCT [commentary])
Rao 2019	Ineligible participant population (not targeted to people with PTSD)
Rosenberg 2002	Ineligible study design (open-label trial; identified in handsearch)
Syed 2020	Ineligible study design (non-RCT [commentary/letter to the editor])
Tillman 2011	Ineligible study design (non-RCT; identified in handsearch)
Woodside 2017	Ineligible study design (open-label case series; identified in handsearch)

Characteristics of studies awaiting classification *[ordered by study ID]*

Adamson 2019

Methods	RCT (n = 33)
Participants	Veterans (aged 20 to 69) with mild or moderate TBI
Interventions	Active versus sham rTMS Protocol for active rTMS: targeted left DLPFC, 10 Hz, 120% MT intensity, 20-minute treatment (5-second train/ 10-s ITI), 4000 pulses/session, 20 sessions across 4 weeks.
Outcomes	Unknown - abstract indicates inclusion of: • **PTSD severity** (specific assessment not reported) • Measure of executive functions (including Trails B) • Resting state fMRI
Notes	Unclear what proportion of participants had PTSD.

Adamson 2019 *(Continued)*

	Insufficient information available in published abstract for inclusion. Study authors contacted; unable to provide us with ITT outcomes relevant to this review.

Bogdanova 2015

Methods	RCT
Participants	Veterans (aged 21 to 50) with blast exposure, mild TBI, PTSD
Interventions	Active rTMS with cognitive intervention versus sham rTMS with cognitive intervention Protocol for active rTMS: targeted right DLPFC, 20 Hz, 1 week
Outcomes	• Sleep efficiency (1-week actigraphy [ACT]) at follow-up • Pittsburgh Sleep Quality Index (PSQI) at follow-up • **PCL-M at follow-up** *It is unclear whether follow-up time point is at week 4 (i.e. 3 weeks post-treatment) or 4 weeks post-treatment
Notes	Insufficient information available in abstract for inclusion. We contacted study authors, but did not receive a response.

Garland 2020

Methods	RCT
Participants	Persons with PTSD and mild TBI
Interventions	Active versus sham rTMS Protocol for active rTMS: targeted bilateral DLPFC (10 Hz for left DLPFC; 1 Hz to right DLPFC), 70 - minute treatment, 3500 pulses/session to left DLPFC and 1500 pulses/session to right DLPFC, 30 sessions across 7 weeks (tapering schedule)
Outcomes	• Tolerability (pain ratings; specific measures not reported) • PTSD severity (specific assessment not reported) • mTBI symptomology (specific assessment not reported)
Notes	Abstract did not contain sufficient information for inclusion in review. We contacted abstract lead author; author unable to provide relevant data at the time of the query. (Abstract appears to be associated with data from protocol NCT02458521, also included under "awaiting classification".)

NCT02268084

Methods	RCT (target enrollment, n = 2004)
Participants	Non-active-duty military members with primary diagnosis of PTSD and PCL-M > 45
Interventions	Active versus sham rTMS

NCT02268084 *(Continued)*

	Active treatment described as EEG/ECG-guided magnetic resonant therapy (MRT) and as synchronized TMS Protocol for active rTMS: not described (30 minutes/session, 10 sessions across 2 weeks).
Outcomes	Primary: • PCL-M total score change from baseline to immediate post-treatment Secondary: • Pittsburgh Sleep Quality Index - Addendum for PTSD (PSQI-A) • HDRS-17 • WHO-QOL (World Health Organization quality of life assessment tool)
Notes	Not included due to limited information available about methods (for risk of bias assessment) and lack of ITT outcomes (per-protocol outcomes posted). Absence of detailed description of study protocol makes it unclear whether the active treatment qualifies as a form of rTMS. Trial sponsored by Wave Neuroscience.

NCT02458521

Methods	RCT
Participants	Adults with PCL > 30 and meeting criteria for mild TBI
Interventions	Active versus sham rTMS Protocol for active treatment: targeting bilateral DLPFC (10 Hz for left PFC followed by 1 Hz to right PFC), approximately 60-minute treatment, 3500 pulses/session to left PFC and 1500 pulses/session to right PFC, 30 sessions across 7 weeks (tapering schedule).
Outcomes	Primary outcomes: • Rivermead Post-Concussion Symptoms Questionnaire (RPQ; change from baseline to weeks 2, 4, and 6 of treatment as well as 1-month, 2-month, and 3-month post-treatment) • PCL-C change from baseline to weeks 2, 4, and 6 of treatment as well as 1-month, 2-month, and 3-month post-treatment Secondary outcomes: • Quick Inventory of Depressive Symptomatology, Self-Report • Beck Scale for Suicide Ideation • Mayo-Portland Adaptability Inventory-Military Edition • Satisfaction with Life Scale Other: • Pain rating • Automated Neuropsychological Assessment Metrics • Structural neuronal changes (assessed using MRI) • Metabolic neuronal changes (assessed using positron emission tomography [PET]) • Biomarker assessment of blood and saliva samples

NCT02458521 *(Continued)*

Notes	We attempted to contact study authors regarding obtaining relevant unpublished data and/or study status, but did not receive a response.

NCT02853032

Methods	RCT (n = 119)
Participants	Active duty or veterans deployed post 9/11 (aged 18 to 65) with a diagnosis of PTSD (per CAPS-5) and minimum PCL score > 24
Interventions	Active versus sham rTMS Protocol for active rTMS: targeted right DLPFC using connectivity-based, image-guided aiming with robotic arm, 20 Hz frequency, 20-minute treatment (2-second train/ 14-second ITI), 1600 pulses/session, 20 sessions across 3 weeks
Outcomes	Primary outcomes: • PCL-5 at immediate post-treatment Secondary outcomes: • Patient Health Questionnaire - 9 (PHQ-9) total • MADRS total • PCL-5 total (at 1 month, 3 months post-treatment) • CAPS-5 total • PTSD response and remission (PCL-5) • PTSD response and remission (CAPS-5) • Depression response and remission (PHQ-9) • Depression response and remission (MADRS) • Resting state functional connectivity changes • Number of participants experiencing a treatment-emergent adverse event • Number of participants experiencing a treatment-emergent serious adverse event
Notes	Not included due to limited information available about methods (for risk of bias assessment) and lack of ITT outcomes (per-protocol outcomes posted)

Yesavage 2018

Methods	RCT (n = 81 with PTSD; n = 164 total)
Participants	Veterans (aged 18 to 80) with treatment-resistant depression (subsample of n = 81 with PTSD)
Interventions	Active versus sham rTMS Protocol for active rTMS: targeted left PFC, 10 Hz, 120% MT intensity, 4000 pulses/session, 20 to 36 sessions with tapering schedule
Outcomes	Primary: • Depression remission (HDRS-24) at immediate post-treatment Secondary:

Yesavage 2018 *(Continued)*

	• Depression severity (MADRS) • Depression severity (Beck Depression Inventory - II) • PTSD severity (PCL-M) • PTSD severity (CAPS-IV) • Suicidality (Beck Scale for Suicidal Ideation) • Suicidality (Columbia Suicide Severity Rating Scale) • Quality of life (Veterans RAND 36-item Health Survey)
Notes	Did not include in review as unable to obtain data for subsample of participants with PTSD diagnosis.

CAPS: Clinician Administered PTSD Scale; **DLPFC:** dorsolateral prefrontal cortex; **DSM (IV; 5; TR):** Diagnostic and Statistical Manual of Mental Disorders (fourth edition; fifth edition; Text Revision); **ECG:** electrocardiogram; **EEG:** electroencephalogram; **(f)MRI:** (functional) magnetic resonance imaging; **HDRS:** Hamilton Depression Rating Scale; **ITI:** intertrain interval; **ITT:** intention-to-treat; **MADRS:** Montgomery–Åsberg Depression Rating Scale; **MT:** motor threshold; **PCL:** PTSD Checklist; **PCL-M:** PTSD Checklist - Military Version; **PFC:** prefrontal cortex; **PTSD:** post-traumatic stress disorder; **RCT:** randomized controlled trial; **rTMS:** repetitive transcranial magnetic stimulation; **(m)TBI:** (mild) traumatic brain injury;

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12621000342819

Study name	The Effect of Transcranial Magnetic Stimulation and Oral Ketamine Combination Treatment on severity of symptoms in Post-Traumatic Stress Disorder (TMS-OK PTSD)
Methods	RCT (target sample size, n = 100)
Participants	Adults (age 18+) with a diagnosis of PTSD
Interventions	Active rTMS + oral ketamine versus sham rTMS + oral ketamine Protocol for active rTMS: targeting left DLPFC, iTBS (twenty 2-second trains per session. Each train involves 10 HF bursts [3 pulses at 50 Hz per burst] delivering at 5 bursts/ second (5 Hz) for a total of 2 seconds), 80% MT intensity, 30 sessions across 6 weeks. Protocol for ketamine: sub-anesthetic dose (1 mg/kg of body weight) once a week for 6 weeks (during active or sham rTMS)
Outcomes	Primary: • PCL-5 (1 week post-treatment) Secondary: • Clinical side effects (Patient Rated Inventory of Side Effects [PRISE]) at 24 hours after ketamine and at 1 week and 4 weeks post-treatment • Neural communication assessed using EEG • World Health Organization Well-being Index (WHO-5) • Self-rated anxiety, depression, stress (subscales of Depression Anxiety Stress Scales [DASS-21]) • Sleep quality (PSQI-A) • Snaith Hamilton Pleasure Scale (SHAPS-C) • PTSD severity (PCL-5) • PTSD remission (CAPS-5) • Cognitive functioning (Cambridge Neuropsychological Test Automated Battery [CANTAB]) • Clinical psychiatric side effects (composite of Clinician-Administered Dissociative States Scale [CADSS], Brief Psychiatric Rating Scale [BPRS], and Young Mania Rating Scale [YMRS]) • Social and Occupational Assessment Scale (SOFAS)

ACTRN12621000342819 *(Continued)*

	• Beck Scale for Suicide Ideation (BSS) • Depression severity (MADRS)
Starting date	8 July 2021 (first enrollment)
Contact information	Ms Megan Dutton: email: TI_ClinicalResearch@usc.edu.au; phone: +61 07 5456 5386
Notes	Primary sponsor: Thompson Institute, University of the Sunshine Coast

ChiCTR2100046475

Study name	The neuroimaging of the post-traumatic stress disorder patients by losing their relative before and after the treatment
Methods	RCT (target sample size, n = 30)
Participants	People (aged 45 to 65) who meet criteria for PTSD (per CAPS) related to the death of an immediate family member
Interventions	3 comparator arms: HF rTMS + paroxetine hydrochloride versus LF rTMS + paroxetine hydrochloride versus sham rTMS + paroxetine hydrochloride Information about HF and LF rTMS protocols is not available.
Outcomes	Not reported
Starting date	May 2021 (first enrollment)
Contact information	Primary contact: Cao Zhihong. Email: staff877@yxph.com; phone: +86 510 87921010
Notes	Primary sponsor: Yixing People Hospital

NCT02990793

Study name	Clinical Trial to Evaluate the Safety and Efficacy of MeRT Treatment in Post-Traumatic Stress Disorder (MeRT-005-B)
Methods	RCT (target sample size of n = 176)
Participants	People (aged 18 to 65) with a diagnosis of PTSD (CAPS-5), meeting DSM-5 criteria for a minimum of 6 months prior to study entry, PCL-5 > 30
Interventions	Active MeRT versus sham MeRT MeRT is a personalized biometrics-guided protocol known as magnetic EEG/ECG resonance therapy that is tailored specifically to each participant's EEG intrinsic alpha frequency. Study involves 5 weeks of treatment (week 5 appears to be primary endpoint) with option for additional two weeks (i.e. 25 to 35 treatments across 5 to 7 weeks).
Outcomes	Primary outcome: • PCL-5 change from baseline to immediate post-treatment Secondary outcome:

NCT02990793 *(Continued)*

	• Persistent Post-Concussion Symptoms (Rivermead Post-Concussion Symptoms Questionnaire [RPQ-16]) Other outcomes: • Number and type of adverse events (AEs) and serious adverse events (SAEs) through 6 months post-treatment
Starting date	April 2022 (study start date)
Contact information	Primary contact: Adele Gilpin, PhD, JD. Email: mert005b@gmail.com; phone: +1 949-229-2869
Notes	Sponsor: Wave Neuroscience The active treatment may not qualify as a form of rTMS.

NCT03819608

Study name	Neuromodulation and Neurorehabilitation for mTBI Plus PTSD
Methods	RCT
Participants	Adults (aged 18 to 60), co-occurring PTSD (per CAPS-5) and mild TBI (per Symptom Attribution and Classification Algorithm [SACA]); 3 months to 10 years post-exposure to TBI
Interventions	4 comparator arms: real APT+ active iTBS versus real APT+ sham iTBS versus placebo APT+ active iTBS versus placebo APT+ sham iTBS Active rTMS protocol: targeting right DLPFC, iTBS involves 2-second trains, each train involves 10 HF bursts (3 pulses at 50 Hz per burst) delivering at 5 bursts/second [5 Hz] for a total of 2 seconds, 80% MT intensity, ~3 minutes/session, 600 pulses/session, 30 sessions across 10 weeks. **APT:** interactive computer attention processing training (APT-III). 60 minutes/session across 10 weeks
Outcomes	Primary outcome: • Self-reported ability, adjustment and community participation (Mayo Portland Adaptability Inventory [MPAI]) change from baseline to week 5, week 10 (immediate post-treatment), and week 20 Secondary outcome: • PCL change from baseline to week 5, week 10 (immediate post-treatment), and week 20
Starting date	October 2020 (start date)
Contact information	Primary contact: Catherine M Kestner. Email: Catherine.Kestner@va.gov; phone: 708-878-0578
Notes	

NCT03932773

Study name	Multi-site Confirmatory Efficacy Treatment Trial of Combat-related PTSD

NCT03932773 *(Continued)*

Methods	RCT
Participants	Veterans (aged 18 to 60) with a diagnosis of PTSD (per CAPS-5) related to post-9/11 conflicts
Interventions	3 comparator arms: active rTMS + CPT versus sham rTMS + CPT versus rTMS standalone Active rTMS protocol: targeting right DLPFC, 1 Hz, 110% MT intensity, 30-minute sessions, 12 sessions across 12 weeks. rTMS sessions to occur immediately preceding CPT.
Outcomes	Primary outcome: • CAPS-5 total score change from baseline to 6 months post-treatment Secondary outcomes: • CAPS-5 total score and cluster scores • PCL-5 total score and cluster scores • Mississippi Scale for Combat Related Posttraumatic Stress Disorder total score • MADRS total score • QIDS • Inventory of Psychosocial Functioning (IPF) • Short Impulsive Behavior Scale (UPPS-P) total score and subscale scores • Buss-Perry Aggression Questionnaire total score and subscale scores • ERP [event-related potentials] response to trauma-specific auditory and visual stimuli, change from baseline • EEG power in response to trauma-specific auditory and visual stimuli, change from baseline • ERP response to inhibitory control task (Go/No-go task), change from baseline • EEG power, change from baseline • fMRI BOLD signal difference between trauma-specific versus non-trauma-specific threatening and non-threatening visual stimuli, change from baseline • Resting-state functional connectivity, change from baseline
Starting date	May 2019
Contact information	Primary contact: Elizabeth "Ellen" Morris, PhD. Email: neurolab@utdallas.edu; phone: 214-883-3171
Notes	

NCT03995173

Study name	Pilot rTMS for AUD+mTBI (TMS_AUD+mTBI)
Methods	RCT (target sample size, n = 20)
Participants	Veterans (aged 22 to 65) who meet AUDIT-C [Alcohol Use Disorders Identification Test-Concise] criteria for an alcohol-use disorder as well as a diagnosis of mild TBI or PTSD
Interventions	Active rTMS versus sham rTMS Active rTMS protocol: targeting left DLPFC, 10 Hz rate, 4.9-seconds/train, with 30-second ITI, 20 trains per session, 10 sessions across 2 weeks

NCT03995173 *(Continued)*

Outcomes	Primary outcomes: • Penn Alcohol Craving Rating Scale, change from baseline to immediate post-treatment as well as 1 day, 1 week, and 1 month post-treatment • Total adverse events occurring through 2 weeks post-treatment Secondary outcomes: not reported
Starting date	March 2019
Contact information	Principal Investigators: Amy A Herrold, PhD BA, Edward Hines Jr. VA Hospital, Hines, IL (primary study contact not provided)
Notes	

NCT04046536

Study name	rTMS in Alleviating Pain and Co-Morbid Symptoms in Gulf War Veterans Illness (GWVI)
Methods	RCT
Participants	Veterans (aged < 65) who served in the military for at least 30 consecutive days between 1 August 1990 and 31 July 1991 in the Persian Gulf War region, and: • meet CDC [Centers for Disease Control and Prevention] and Kansas criteria for GWVI; • meet International Headache Society Criteria for migraine headache without aura; • have an average overall daily muscle pain intensity > 3 on a 0 to 10 numerical pain rating scale (NPS), and average overall daily extremities joint pain intensity > 3 on a 0 to 10 NPS; • headache exacerbation/attack once a week with the average intensity > 3 on a 0 to 10 NPS that lasts > 1 hour in the past three months; • HDRS-17 ≥ 14.
Interventions	4 comparator arms: active rTMS (left DLFPC) versus sham rTMS (left DLPFC) versus active rTMS (left motor cortex) versus sham rTMS (left motor cortex) Active rTMS protocol not described
Outcomes	Primary outcomes: *all primary outcomes assessed as change from baseline to 1 week, 1 month, 2 month, and 3 months post-treatment • GWVI-related pain and headaches rated 0 to 10 • Quality and intensity of pain (Short Form McGill Pain Questionnaire [SF-MPQ]) • Headache Impact Test (HIT-6) • Depression severity (HDRS-17) • Short Form Health Survey-36 (SF-36) • Brief Pain Inventory-Short Form (BPI-SF) • Muscle pain (New Clinical Fibromyalgia Diagnostic Criteria - Part 1) • Revised Fibromyalgia Impact Questionnaire • Neurobehavioral Symptoms Inventory (NSI) • Pittsburgh Sleep Quality Index (PSQI) • Insomnia Severity Index • Flinders Fatigue Scale

NCT04046536 *(Continued)*

	Secondary outcomes: • CAPS-5 • Opioid-based pain medication use • Supraspinal resting state functional connectivity (fMRI)
Starting date	October 2019
Contact information	Primary contact: Caleb T Lopez, BS. Email: caleb.lopez@va.gov; phone: (858) 552-8585 ext 2638
Notes	Secondary outcome measures suggest some participants may have PTSD. It is unclear whether outcomes will be provided for the subsample of the population with PTSD. *Study appears to be run in parallel with NCT04182659 (which targets participants with HDRS-17 **< 14**)

NCT04182659

Study name	Long Term Efficacy of Neuronavigation Guided rTMS in Alleviating Gulf War Illness Related Headaches and Pain Symptoms
Methods	RCT
Participants	Veterans (aged < 65) who served in the military for at least 30 consecutive days between 1 August 1990 and 31 July 1991 in the Persian Gulf War region, and: • meet CDC [Centers for Disease Control and Prevention] and Kansas criteria for GWVI; • meet International Headache Society Criteria for migraine headache without aura; • have an average overall daily muscle pain intensity > 3 on a 0 to 10 numerical pain rating scale (NPS), and average overall daily extremities joint pain intensity > 3 on a 0 to 10 NPS; • headache exacerbation/attack once a week with the average intensity > 3 on a 0 to 10 NPS that lasts > 4 hours in the past three months; • HDRS-17 ≥ 14.
Interventions	Active rTMS (left motor cortex) versus sham rTMS (left motor cortex) Active rTMS protocol not described
Outcomes	Primary outcomes: *all primary outcomes assessed as change from baseline to 1 week, 1 month, 2 month, and 3 months post-treatment • GWI-related pain and headaches rated 0-10 • Quality and intensity of pain (Short Form McGill Pain Questionnaire [SF-MPQ]) • Headache Impact Test (HIT-6) • Depression severity (HDRS-17) • Short Form Health Survey-36 (SF-36) • Brief Pain Inventory-Short Form (BPI-SF) • Muscle pain (New Clinical Fibromyalgia Diagnostic Criteria - Part 1) • Revised Fibromyalgia Impact Questionnaire • Neurobehavioral Symptoms Inventory (NSI) • Pittsburgh Sleep Quality Index (PSQI) • Insomnia Severity Index • Flinders Fatigue Scale

NCT04182659 *(Continued)*

	Secondary outcomes: • CAPS-5 • Opioid-based pain medication use • Supraspinal resting state functional connectivity (fMRI)
Starting date	October 2019
Contact information	Primary contact: Caleb T Lopez, BS. Email: caleb.lopez@va.gov; phone: (858) 552-8585 ext 2638
Notes	Secondary outcome measures suggest some participants may have PTSD. It is unclear whether outcomes will be provided for the subsample of the population with PTSD. *Study appears to be run in parallel with NCT04046536 (which targets participants with HDRS-17 **≥ 14**

NCT04207346

Study name	Transcranial Magnetic Stimulation to Improve Functioning in Veterans With PTSD (rTMS for PTSD)
Methods	RCT (target sample size, n = 91)
Participants	Adults eligible for VA health care (aged 19 to 70) with moderate to severe PTSD (per CAPS)
Interventions	Active rTMS versus sham rTMS Active rTMS protocol: targeting right DLPFC, 1 Hz, 2 weeks of treatment
Outcomes	Outcomes: • CAPS at immediate post-treatment as well as 3 months and 6 months post-treatment • WHODAS [World Health Organization Disability Assessment Scale] at immediate post-treatment as well as 3 months and 6 months post-treatment • QIDS SR-16 at immediate post-treatment as well as 3 months and 6 months post-treatment
Starting date	December 2020
Contact information	Primary contact: Bradley V Watts, MD MPH. Email: Bradley.Watts@va.gov; phone: (802) 295-9363 ext 5235
Notes	

NCT04563078

Study name	Effect of TMS on PTSD Biomarkers
Methods	RCT
Participants	Adults (aged 18 to 65) who meet criteria for partial PTSD, defined as 3 out of 4 symptom clusters always including cluster E (alterations in arousal and reactivity) using the Clinician-Administered PTSD Scale (CAPS-5)
Interventions	Active rTMS versus sham rTMS

NCT04563078 *(Continued)*

	Active rTMS protocol: treatment parameters not described. 10-day treatment (2 treatments/day with 10-minute break, 20 sessions in total)
Outcomes	Primary outcomes • Amygdala reactivity during fear processing, change from baseline to immediate post-treatment • Skin conductance response to trauma cues, change from baseline to immediate post-treatment Secondary outcomes • Inhibition-related activation in the ventromedial prefrontal cortex (vmPFC) • Inhibition-related activation in the hippocampus • Ventromedial prefrontal cortex (vmPFC)-amygdala functional connectivity • Dorsolateral prefrontal cortex (DLPFC)-amygdala functional connectivity • Fear-Potentiated Startle Responses to danger and safety cues • Discrimination between danger and safety cues • Post-traumatic stress disorder (PTSD) hyperarousal symptoms
Starting date	February 2021
Contact information	Primary contact: Sanne van Rooij, PhD. Email: sanne.van.rooij@emory.edu; phone: 404-251-8926
Notes	

NCT05149534

Study name	rTMS-augmented Written Exposure Therapy for PTSD
Methods	RCT (target sample size, n = 98)
Participants	Veterans (aged 18 to 50) with a diagnosis of PTSD and right-handed
Interventions	Active rTMS + Written Exposure Therapy (WET) versus sham rTMS + WET Active rTMS protocol not described Written Exposure Therapy involves written disclosure of trauma administered in an evidence-based protocol
Outcomes	Primary outcomes: • CAPS-5 total score, change from baseline to immediate post-treatment and 3 months post-treatment Secondary outcomes: • PCL-5, change from baseline to immediate post-treatment and 3 months post-treatment
Starting date	January 2022
Contact information	Primary contact: Crystal M Lantrip. Email: crystal.lantrip@va.gov; phone: (254) 297-5155
Notes	

NCT05426967

Study name	ADEPT: Adaptive Trial for the Treatment of Depressive Symptoms Associated With Concussion Using Repetitive Transcranial Magnetic Stimulation Protocols
Methods	RCT
Participants	Veterans (aged 18 to 50) with a history of concussion (mild TBI), > 6 months, but < 20 years prior to consent, MADRS > 13
Interventions	16-arm, Bayesian adaptive trail Arm 1: Active rTMS/Individualized Connectome Targeting (ICT)/Bilateral/Standard rTMS protocol Arm 2: Active rTMS/ICT/Bilateral/Theta Burst Stimulation (TBS) rTMS protocol Arm 3: Active rTMS/ICT/Unilateral/Standard rTMS protocol Arm 4: Active rTMS/ICT/Unilateral/TBS rTMS protocol Arm 5: Active rTMS/Structural targeting/Bilateral/Standard rTMS protocol Arm 6: Active rTMS/Structural targeting/Bilateral/TBS rTMS protocol Arm 7: Active rTMS/Structural targeting/Unilateral/Standard rTMS protocol Arm 8: Active rTMS/Structural targeting/Unilateral/TBS rTMS protocol Arm 9: Active rTMS/Scalp targeting/Bilateral/Standard rTMS protocol Arm 10: Active rTMS/Scalp targeting/Bilateral/TBS rTMS protocol Arm 11: Active rTMS/Scalp targeting/Unilateral/Standard rTMS protocol Arm 12: Active rTMS/Scalp targeting/Unilateral/TBS rTMS protocol Arm 13: Sham rTMS/Scalp targeting/Bilateral laterality/Standard rTMS protocol Arm 14: Sham rTMS/Scalp targeting/Bilateral laterality/TBS rTMS protocol Arm 15: Sham rTMS/Scalp targeting/Unilateral/Standard rTMS protocol Arm 16: Sham rTMS/Scalp targeting/Unilateral/TBS rTMS protocol
Outcomes	Primary outcomes • MADRS, change from baseline to post-intervention (within 10 days of final rTMS session), 6 months post-intervention • MADRS, change from baseline to post-intervention (within 10 days of final rTMS session) for participants who completed ≥ 80% of rTMS sessions • Treatment response (≥ 50% improvement in MADRS) post-intervention (within 10 days of final rTMS session) • Treatment remission (MADRS ≤ 10) post-intervention (within 10 days of final rTMS session) • Adverse event occurrence up to 10 days post-treatment Secondary outcomes • Inventory of Depressive Symptomatology-Self Report (IDS-SR) • Symptoms of Major Depressive Disorder Scale • TBI Quality of Life Scale (TBI-QOL) • PCL-5 • Compliance (completed ≥ 16 rTMS sessions) • Resting-state fMRI connectivity

NCT05426967 *(Continued)*

Starting date	August 2022
Contact information	Principal Investigator: David L Brody, MD, PhD (contact information not available)
Notes	Secondary outcome measures suggest some participants may have PTSD. It is unclear whether outcomes will be provided for the subsample of the population with PTSD.

NCT05544110

Study name	Study on the Effect and Mechanism of Individualized and Precise Location Transcranial Magnetic Stimulation Based on Magnetic Resonance Imaging on Post-traumatic Stress Disorder
Methods	RCT
Participants	Persons admitted to the psychosomatic outpatient department of the First Affiliated Hospital of Air Force Medical University (aged 18 to 65) diagnosed with PTSD (per DSM-5), PCL-5 > 33
Interventions	Active rTMS versus sham rTMS Active rTMS protocol not described. Stimulation target identified using fMRI. 10 sessions across 10 days.
Outcomes	Primary outcomes • PCL-5, change from baseline to 4 weeks post-treatment Secondary outcomes • PCL-5, change from baseline to immediate post-treatment • HDRS-17 • HARS • Resting-state fMRI • Behavioral changes (expression, language and body movements as assessed by video recording)
Starting date	February 2023
Contact information	Primary contact: Yaochi Zhang. Email: a18294037117@163.com; phone: 86-18294037117
Notes	

NCT05682677

Study name	Combined Neuromodulation and Cognitive Training for Post-mTBI Depression
Methods	RCT
Participants	Adults (aged 18 to 65) with a history of mild TBI (as defined by the Department of Defense/Veterans' Affairs criteria used in conjunction with the Ohio State University TBI-identification method) over 3 months prior to study entry, meet criteria for current major depressive episode and MDD per MINI (Mini International Neuropsychiatric Interview), HDRS-17 ≥ 18
Interventions	Active iTBS + PACT versus sham iTBS + PACT

NCT05682677 *(Continued)*	Active iTBS protocol: targeting left DLPFC, 20 sessions across 4 weeks **PACT:** Personalized Augmented Cognitive Training, 6 sessions across 4 weeks
Outcomes	Primary outcome • HDRS, "change over 8 weeks" (presumably, 4 weeks post-treatment) Secondary outcomes • PHQ-9 • Neurobehavioral Symptom Inventory • PCL-5 • Headache Impact Test • Pittsburgh Sleep Quality Index • WHO Disability Assessment Schedule • Glasgow Outcome Scale - Extended • PROMIS (Patient-Reported Outcome Measurement Information System) Cognitive Function Abilities Short Form • Patient Global Impression of Change • Traumatic Brain Injury Quality of Life (TBI-QOL) • Cognitive measures (D-KEFS Trail Making Test, D-KEFS Color Word Interference Test, WMS-IV Digit Span, WAIS-IV Processing Speed, Hopkins Verbal Learning Test - Revised) • UCSD Performance-Based Skills Assessment-Brief
Starting date	September 2023
Contact information	Primary contact: Michelle Schy. Email: mschy@health.ucsd.edu; phone: +1 858-642-3848
Notes	

ADHD: attention-deficit hyperactivity disorder; **CAPS:** Clinician Administered PTSD Scale; **DLPFC:** dorsolateral prefrontal cortex; **DSM (IV; 5; TR):** Diagnostic and Statistical Manual of Mental Disorders (fourth edition; fifth edition; Text Revision); **EEG:** electroencephalogram; **(f)MRI:** (functional) magnetic resonance imaging; **GAD:** generalized anxiety disorder; **HARS:** Hamilton Anxiety Rating Scale; **HDRS:** Hamilton Depression Rating Scale; **HF:** high-frequency; **iTBS:** intermittent theta-burst stimulation; **ITT:** intention-to-treat; **LF:** low-frequency; **MADRS:** Montgomery–Åsberg Depression Rating Scale; **MDD:** major depressive disorder; **mPFC:** medial prefrontal cortex; **MT:** motor threshold; **OCD:** obsessive-compulsive disorder; **PCL:** PTSD Checklist; **PCL-M:** PTSD Checklist - Military Version; **PSQI:** Pittsburgh Sleep Quality Index; **PTSD:** post-traumatic stress disorder; **QIDS:** Quick Inventory of Depressive Symptomatology; **RCT:** randomized controlled trial; **rTMS:** repetitive transcranial magnetic stimulation; **SCID:** Structured Clinical Interview for DSM Disorders; **SD:** standard deviation; **SE:** standard error; **TBI:** traumatic brain injury; **VA:** Veterans' Affairs

RISK OF BIAS

Legend: Low risk of bias High risk of bias Some concerns

Risk of bias for analysis 1.1 PTSD symptom severity: immediately after treatment, SMD (ITT, endpoint)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Leong 2020	✓	~	~	✓	✓	~
Philip 2019a	✓	✓	✓	✓	✓	✓
Watts 2012	~	~	~	✓	✓	~

DATA AND ANALYSES

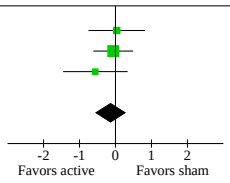
Comparison 1. PTSD symptom severity (immediately after treatment) – as measured by validated scale

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 PTSD symptom severity: immediately after treatment, SMD (ITT, endpoint)	3	99	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.54, 0.27]
1.2 PTSD symptom severity: immediately after treatment, SMD (ITT, endpoint; with data imputation)	5	232	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.35, 0.51]
1.3 PTSD symptom severity: change from baseline to immediately after treatment, SMD (ITT, with data imputation)	6	252	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-0.98, 0.10]
1.4 PTSD symptom severity: immediately after treatment, SMD (per-protocol, endpoint)	3	85	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.69, 0.17]

Analysis 1.1. Comparison 1: PTSD symptom severity (immediately after treatment) – as measured by validated scale, Outcome 1: PTSD symptom severity: immediately after treatment, SMD (ITT, endpoint)

Study or Subgroup	Active Mean [SMD]	Active SD [SMD]	Active Total	Sham Mean [SMD]	Sham SD [SMD]	Sham Total	Weight	Std. Mean Difference IV, Random, 95% CI [SMD]	Std. Mean Difference IV, Random, 95% CI [SMD]	Risk of Bias A B C D E F
Leong 2020	66.19	33.65	20	65.12	14.97	9	26.4%	0.04 [-0.75 , 0.82]		+ ? ? + + ?
Philip 2019a	38.6	11.4	25	39.4	13.8	25	53.2%	-0.06 [-0.62 , 0.49]		+ + + + + +
Watts 2012	53.9	15.3	10	61.7	11.1	10	20.3%	-0.56 [-1.46 , 0.34]		? ? ? + + ?
Total (95% CI)			**55**			**44**	**100.0%**	**-0.14 [-0.54 , 0.27]**		

Heterogeneity: Tau² = 0.00; Chi² = 1.10, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.51)
Test for subgroup differences: Not applicable

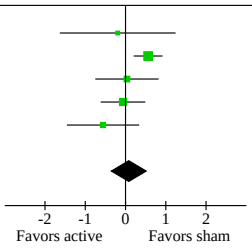


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: PTSD symptom severity (immediately after treatment) – as measured by validated scale, Outcome 2: PTSD symptom severity: immediately after treatment, SMD (ITT, endpoint; with data imputation)

Study or Subgroup	Active Mean [SMD]	Active SD [SMD]	Active Total	Sham Mean [SMD]	Sham SD [SMD]	Sham Total	Weight	Std. Mean Difference IV, Random, 95% CI [SMD]	Std. Mean Difference IV, Random, 95% CI [SMD]
Fryml 2019	37.8	25.7	5	43.8	28.9	3	7.5%	-0.19 [-1.63 , 1.24]	
Isserles 2021	27.32	9.36	60	22.15	8.99	65	33.8%	0.56 [0.20 , 0.92]	
Leong 2020	66.19	33.65	20	65.12	14.97	9	17.9%	0.04 [-0.75 , 0.82]	
Philip 2019a	38.6	11.4	25	39.4	13.8	25	25.5%	-0.06 [-0.62 , 0.49]	
Watts 2012	53.9	15.3	10	61.7	11.1	10	15.2%	-0.56 [-1.46 , 0.34]	
Total (95% CI)			**120**			**112**	**100.0%**	**0.08 [-0.35 , 0.51]**	

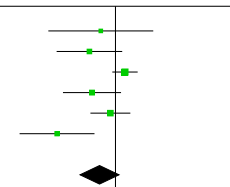
Heterogeneity: Tau² = 0.11; Chi² = 7.87, df = 4 (P = 0.10); I² = 49%
Test for overall effect: Z = 0.37 (P = 0.72)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: PTSD symptom severity (immediately after treatment) – as measured by validated scale, Outcome 3: PTSD symptom severity: change from baseline to immediately after treatment, SMD (ITT, with data imputation)

Study or Subgroup	Active Mean [SMD]	Active SD [SMD]	Active Total	Sham Mean [SMD]	Sham SD [SMD]	Sham Total	Weight	Std. Mean Difference IV, Random, 95% CI [SMD]	Std. Mean Difference IV, Random, 95% CI [SMD]	Risk of Bias A B C D E F
Fryml 2019	-46.2	36.71	5	-29.2	35.23	3	9.1%	-0.41 [-1.87 , 1.05]		? ? ? + ? −
Isserles 2013	-24.3	23.4	10	-9.1	16.13	10	15.3%	-0.72 [-1.64 , 0.19]		+ ? ? + + ?
Isserles 2021	-15.48	14.23	60	-19.05	12.63	65	24.2%	0.26 [-0.09 , 0.62]		+ ? − + + −
Leong 2020	-4.81	25.12	20	9.9	11.02	9	16.9%	-0.65 [-1.46 , 0.15]		+ ? ? + + ?
Philip 2019a	-9.3	8.26	25	-8	9.76	25	21.0%	-0.14 [-0.70 , 0.41]		+ + + + + +
Watts 2012	-27.7	10.99	10	-10.6	9.08	10	13.5%	-1.62 [-2.67 , -0.58]		? ? ? + + ?
Total (95% CI)			**130**			**122**	**100.0%**	**-0.44 [-0.98 , 0.10]**		

Heterogeneity: Tau² = 0.28; Chi² = 16.11, df = 5 (P = 0.007); I² = 69%
Test for overall effect: Z = 1.60 (P = 0.11)
Test for subgroup differences: Not applicable

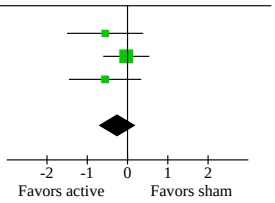


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: PTSD symptom severity (immediately after treatment) – as measured by validated scale, Outcome 4: PTSD symptom severity: immediately after treatment, SMD (per-protocol, endpoint)

Study or Subgroup	Active Mean [SMD]	Active SD [SMD]	Active Total	Sham Mean [SMD]	Sham SD [SMD]	Sham Total	Weight	Std. Mean Difference IV, Random, 95% CI [SMD]
Isserles 2013	63.7	16.4	9	77	27.7	9	20.6%	-0.56 [-1.50 , 0.39]
Philip 2019a	38.6	11.2	24	39	13.6	23	56.5%	-0.03 [-0.60 , 0.54]
Watts 2012	53.9	15.3	10	61.7	11.1	10	22.9%	-0.56 [-1.46 , 0.34]
Total (95% CI)			**43**			**42**	**100.0%**	**-0.26 [-0.69 , 0.17]**

Heterogeneity: Tau² = 0.00; Chi² = 1.42, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.19 (P = 0.23)
Test for subgroup differences: Not applicable

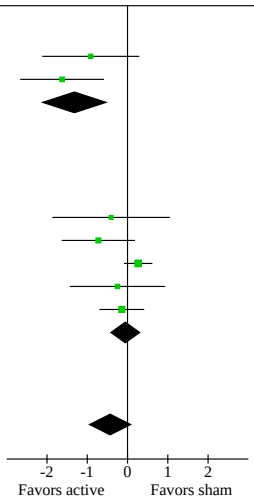


Comparison 2. PTSD symptom severity (change from baseline to immediately after treatment): subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Stimulation frequency: low versus high frequency	6	251	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.94, 0.08]
2.1.1 Low frequency (1 Hz)	2	35	Std. Mean Difference (IV, Random, 95% CI)	-1.32 [-2.11, -0.53]
2.1.2 High frequency (10 Hz to 50 Hz)	5	216	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.41, 0.30]
2.2 Combination treatment status: rTMS alone versus rTMS paired with exposure/psychotherapy	6	252	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-0.98, 0.10]
2.2.1 rTMS stand-alone treatment	3	99	Std. Mean Difference (IV, Random, 95% CI)	-0.71 [-1.51, 0.09]
2.2.2 rTMS combined with exposure/psychotherapy	3	153	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.86, 0.56]

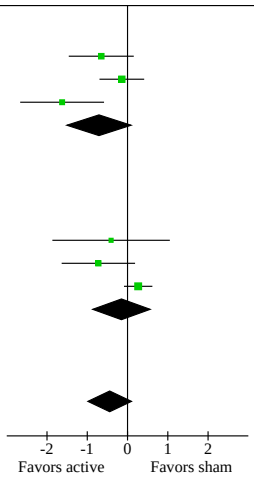
Analysis 2.1. Comparison 2: PTSD symptom severity (change from baseline to immediately after treatment): subgroup analyses, Outcome 1: Stimulation frequency: low versus high frequency

Study or Subgroup	Active Mean [SMD]	Active SD [SMD]	Active Total	Sham Mean [SMD]	Sham SD [SMD]	Sham Total	Weight	Std. Mean Difference IV, Random, 95% CI [SMD]
2.1.1 Low frequency (1 Hz)								
Leong 2020	-12.47	25.59	11	9.9	11.02	4	10.7%	-0.91 [-2.12 , 0.29]
Watts 2012	-27.7	10.99	10	-10.6	9.08	10	12.5%	-1.62 [-2.67 , -0.58]
Subtotal (95% CI)			**21**			**14**	**23.2%**	**-1.32 [-2.11 , -0.53]**
Heterogeneity: Tau² = 0.00; Chi² = 0.77, df = 1 (P = 0.38); I² = 0%								
Test for overall effect: Z = 3.28 (P = 0.001)								
2.1.2 High frequency (10 Hz to 50 Hz)								
Fryml 2019	-46.2	36.71	5	-29.2	35.23	3	8.4%	-0.41 [-1.87 , 1.05]
Isserles 2013	-24.3	23.4	10	-9.1	16.13	10	14.3%	-0.72 [-1.64 , 0.19]
Isserles 2021	-15.48	14.23	60	-19.05	12.63	65	23.3%	0.26 [-0.09 , 0.62]
Leong 2020	4.56	22.38	9	9.9	11.02	4	10.9%	-0.25 [-1.43 , 0.93]
Philip 2019a	-9.3	8.26	25	-8	9.76	25	20.0%	-0.14 [-0.70 , 0.41]
Subtotal (95% CI)			**109**			**107**	**76.8%**	**-0.06 [-0.41 , 0.30]**
Heterogeneity: Tau² = 0.04; Chi² = 5.26, df = 4 (P = 0.26); I² = 24%								
Test for overall effect: Z = 0.31 (P = 0.76)								
Total (95% CI)			**130**			**121**	**100.0%**	**-0.43 [-0.94 , 0.08]**
Heterogeneity: Tau² = 0.26; Chi² = 16.14, df = 6 (P = 0.01); I² = 63%								
Test for overall effect: Z = 1.66 (P = 0.10)								
Test for subgroup differences: Chi² = 8.20, df = 1 (P = 0.004), I² = 87.8%								



Analysis 2.2. Comparison 2: PTSD symptom severity (change from baseline to immediately after treatment): subgroup analyses, Outcome 2: Combination treatment status: rTMS alone versus rTMS paired with exposure/psychotherapy

Study or Subgroup	Active Mean [SMD]	Active SD [SMD]	Active Total	Sham Mean [SMD]	Sham SD [SMD]	Sham Total	Weight	Std. Mean Difference IV, Random, 95% CI [SMD]
2.2.1 rTMS stand-alone treatment								
Leong 2020	-4.81	25.12	20	9.9	11.02	9	16.9%	-0.65 [-1.46 , 0.15]
Philip 2019a	-9.3	8.26	25	-8	9.76	25	21.0%	-0.14 [-0.70 , 0.41]
Watts 2012	-27.7	10.99	10	-10.6	9.08	10	13.5%	-1.62 [-2.67 , -0.58]
Subtotal (95% CI)			**55**			**44**	**51.4%**	**-0.71 [-1.51 , 0.09]**
Heterogeneity: Tau² = 0.33; Chi² = 6.21, df = 2 (P = 0.04); I² = 68%								
Test for overall effect: Z = 1.74 (P = 0.08)								
2.2.2 rTMS combined with exposure/psychotherapy								
Fryml 2019	-46.2	36.71	5	-29.2	35.23	3	9.1%	-0.41 [-1.87 , 1.05]
Isserles 2013	-24.3	23.4	10	-9.1	16.13	10	15.3%	-0.72 [-1.64 , 0.19]
Isserles 2021	-15.48	14.23	60	-19.05	12.63	65	24.2%	0.26 [-0.09 , 0.62]
Subtotal (95% CI)			**75**			**78**	**48.6%**	**-0.15 [-0.86 , 0.56]**
Heterogeneity: Tau² = 0.22; Chi² = 4.44, df = 2 (P = 0.11); I² = 55%								
Test for overall effect: Z = 0.41 (P = 0.68)								
Total (95% CI)			**130**			**122**	**100.0%**	**-0.44 [-0.98 , 0.10]**
Heterogeneity: Tau² = 0.28; Chi² = 16.11, df = 5 (P = 0.007); I² = 69%								
Test for overall effect: Z = 1.60 (P = 0.11)								
Test for subgroup differences: Chi² = 1.05, df = 1 (P = 0.31), I² = 4.4%								



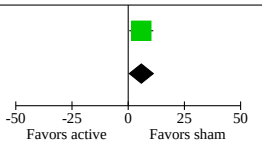
Comparison 4. PTSD symptom severity (4 to 12 weeks after treatment) – as measured by validated scale

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 PTSD symptom severity: change from baseline to 4 to 12 weeks after treatment (ITT)	1	125	Mean Difference (IV, Random, 95% CI)	5.83 [0.49, 11.17]

Analysis 4.1. Comparison 4: PTSD symptom severity (4 to 12 weeks after treatment) – as measured by validated scale, Outcome 1: PTSD symptom severity: change from baseline to 4 to 12 weeks after treatment (ITT)

Study or Subgroup	Active Mean [CAPS-5]	Active SD [CAPS-5]	Active Total	Sham Mean [CAPS-5]	Sham SD [CAPS-5]	Sham Total	Weight	Mean Difference IV, Random, 95% CI [CAPS-5]
Isserles 2021	-17.03	16.06	60	-22.86	14.27	65	100.0%	5.83 [0.49 , 11.17]
Total (95% CI)			**60**			**65**	**100.0%**	**5.83 [0.49 , 11.17]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.14 (P = 0.03)
Test for subgroup differences: Not applicable



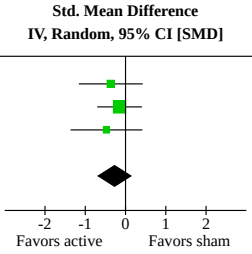
Comparison 6. Depression severity (immediately after treatment) – as measured by validated scale

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Depression severity: immediately after treatment, SMD (ITT, endpoint)	3	99	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.68, 0.13]
6.2 Depression severity: immediately after treatment, SMD (ITT, endpoint, with data imputation)	4	224	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.40, 0.32]
6.3 Depression severity: change from baseline to immediately after treatment, SMD (ITT, with data imputation)	4	224	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-1.05, 0.17]

Analysis 6.1. Comparison 6: Depression severity (immediately after treatment) – as measured by validated scale, Outcome 1: Depression severity: immediately after treatment, SMD (ITT, endpoint)

Study or Subgroup	Active Mean [SMD]	Active SD [SMD]	Active Total	Sham Mean [SMD]	Sham SD [SMD]	Sham Total	Weight	Std. Mean Difference IV, Random, 95% CI [SMD]
Leong 2020	11.81	8.03	20	14.44	3.32	9	26.1%	-0.37 [-1.16 , 0.43]
Philip 2019a	31.3	14.8	25	33.5	14.3	25	53.3%	-0.15 [-0.70 , 0.41]
Watts 2012	17.7	6.3	10	21.4	8.5	10	20.6%	-0.47 [-1.37 , 0.42]
Total (95% CI)			**55**			**44**	**100.0%**	**-0.27 [-0.68 , 0.13]**

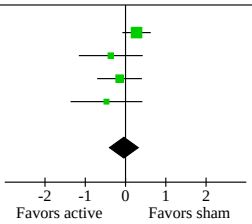
Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 2 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Depression severity (immediately after treatment) – as measured by validated scale, Outcome 2: Depression severity: immediately after treatment, SMD (ITT, endpoint, with data imputation)

Study or Subgroup	Active Mean [SMD]	Active SD [SMD]	Active Total	Sham Mean [SMD]	Sham SD [SMD]	Sham Total	Weight	Std. Mean Difference IV, Random, 95% CI [SMD]
Isserles 2021	12.45	5.05	60	11.02	5.32	65	43.9%	0.27 [-0.08 , 0.63]
Leong 2020	11.81	8.03	20	14.44	3.32	9	16.0%	-0.37 [-1.16 , 0.43]
Philip 2019a	31.3	14.8	25	33.5	14.3	25	26.9%	-0.15 [-0.70 , 0.41]
Watts 2012	17.7	6.3	10	21.4	8.5	10	13.3%	-0.47 [-1.37 , 0.42]
Total (95% CI)			**115**			**109**	**100.0%**	**-0.04 [-0.40 , 0.32]**

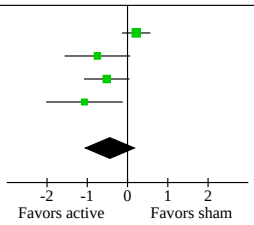
Heterogeneity: Tau² = 0.04; Chi² = 4.42, df = 3 (P = 0.22); I² = 32%
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable



Analysis 6.3. Comparison 6: Depression severity (immediately after treatment) – as measured by validated scale, Outcome 3: Depression severity: change from baseline to immediately after treatment, SMD (ITT, with data imputation)

Study or Subgroup	Active Mean [SMD]	Active SD [SMD]	Active Total	Sham Mean [SMD]	Sham SD [SMD]	Sham Total	Weight	Std. Mean Difference IV, Random, 95% CI [SMD]
Isserles 2021	-3.45	5.95	60	-4.68	5.43	65	31.9%	0.22 [-0.14 , 0.57]
Leong 2020	-4.63	6.7	20	0	3.92	9	21.8%	-0.75 [-1.56 , 0.06]
Philip 2019a	-11.5	11.26	25	-5.7	10.88	25	27.3%	-0.52 [-1.08 , 0.05]
Watts 2012	-7.8	5.28	10	-1.3	6.31	10	19.0%	-1.07 [-2.02 , -0.12]
Total (95% CI)			**115**			**109**	**100.0%**	**-0.44 [-1.05 , 0.17]**

Heterogeneity: Tau² = 0.27; Chi² = 11.41, df = 3 (P = 0.010); I² = 74%
Test for overall effect: Z = 1.42 (P = 0.16)
Test for subgroup differences: Not applicable



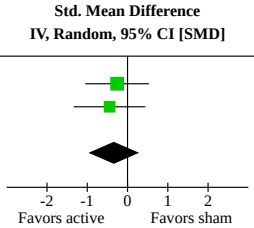
Comparison 7. Anxiety severity (immediately after treatment) – as measured by validated scale

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Anxiety severity: immediately after treatment, SMD (ITT, endpoint)	2	49	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.93, 0.25]
7.2 Anxiety severity: change from baseline to immediately after treatment, SMD (ITT, with data imputation)	2	49	Std. Mean Difference (IV, Random, 95% CI)	-0.51 [-1.31, 0.30]

Analysis 7.1. Comparison 7: Anxiety severity (immediately after treatment) – as measured by validated scale, Outcome 1: Anxiety severity: immediately after treatment, SMD (ITT, endpoint)

Study or Subgroup	Active Mean [SMD]	Active SD [SMD]	Active Total	Sham Mean [SMD]	Sham SD [SMD]	Sham Total	Weight	Std. Mean Difference IV, Random, 95% CI [SMD]
Leong 2020	23.83	17.99	20	28.14	10.97	9	55.9%	-0.26 [-1.05 , 0.53]
Watts 2012	47.4	13.4	10	52.2	5.6	10	44.1%	-0.45 [-1.34 , 0.44]
Total (95% CI)			**30**			**19**	**100.0%**	**-0.34 [-0.93 , 0.25]**

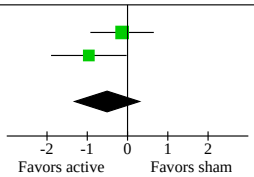
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable



Analysis 7.2. Comparison 7: Anxiety severity (immediately after treatment) – as measured by validated scale, Outcome 2: Anxiety severity: change from baseline to immediately after treatment, SMD (ITT, with data imputation)

Study or Subgroup	Active Mean [SMD]	Active SD [SMD]	Active Total	Sham Mean [SMD]	Sham SD [SMD]	Sham Total	Weight	Std. Mean Difference IV, Random, 95% CI [SMD]
Leong 2020	-8.8	14.39	20	-7	8.46	9	54.9%	-0.14 [-0.92 , 0.65]
Watts 2012	-9.9	9.69	10	-2.3	4.55	10	45.1%	-0.96 [-1.90 , -0.02]
Total (95% CI)			**30**			**19**	**100.0%**	**-0.51 [-1.31 , 0.30]**

Heterogeneity: Tau² = 0.15; Chi² = 1.75, df = 1 (P = 0.19); I² = 43%
Test for overall effect: Z = 1.24 (P = 0.22)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Study sample characteristics

Study	Sample size	Age (mean)	Gender (Male:Female)	Race/ethnicity	Veteran status	Traumatic brain injury (TBI) status (I: inclusion criteria; E: exclusion criteria)	[a]Comorbid psychiatric diagnoses (I: inclusion criteria; E: exclusion criteria)
Ahmadizadeh 2018	N = 65	50.5[b]	65:0	-	Veterans	I: - E: moderate/severe TBI	I: - E: any comorbid axis I disorder, PD
Boggio 2010	N = 30	44.6	9:21	-	-	I: - E: "head trauma"	I: - E: SUD
Cohen 2004	N = 29	41.7[b]	17:7[b]	-	Assumed to be veterans[c]	I: - E: "brain trauma"	I: - E: SUD
Fryml 2019	N = 8	28.1	7:1	-	Veterans	I: - E: "head trauma"	I: - E: psychosis, "substantial" substance abuse
George 2014	N = 41	42.5	35:6	White: 70.7%; non-white: 29.3%	Assumed to be veterans[d]	I: PTSD or mild TBI (n = 1, TBI only; n = 17 PTSD only; n = 23 both) E: -	I: current MDE, hospitalized for SI or SA E: psychotic disorder, bipolar I disorder, borderline PD, current drug dependence
Isserles 2013	N = 20	44.7[b]	15:3[b]	-	Assumed to be veterans[c]	-	I: - E: any comorbid psychiatric diagnosis other than depression
Isserles 2021	N = 125	44.2	44:81	White: 85.6% Black: 5.6% Hispanic: 5.6% Other: 4.8%	-	I: - E: head trauma with loss of consciousness > 5 minutes	I: - E: psychotic disorder, bipolar disorder, OCD, severe PD, SUD past 6 months
Kozel 2018	N = 103	31.7	97:6	White: 81.6% Black: 12.6%	Veterans	I: -	n = 34 (33%) with MDD

Table 1. Study sample characteristics *(Continued)*

				Other: 5.8% Hispanic/non-hispanic: 21.4%/ 78.6%		E: moderate/severe TBI	I: - E: eating disorder, psychosis, SUD
Leong 2020	N = 31	43.7[b]	5:24[b]	-	Civilians	-	n = 27[b] (93%) with MDD I: - E: psychotic disorder, bipolar I disorder, SUD, borderline PD, antisocial PD
Levasseur-Moreau 2018	N = 37	41.3[b]	26:2[b]	-	Veterans	-	[b]n = 25 (89%) with MDD I: - E: any comorbid psychiatric diagnoses other than, MDD, anxiety, tobacco use disorder
Nam 2013	N = 18	34.3[b]	6:10[b]	-	Assumed to be civilians[e]	-	-
Philip 2019	N = 50	50.5	42:8	White: 84% Black: 4% American Indian/Alaskan Native: 2% Multiracial: 6% Hispanic: 4%	Veterans	n = 12 (24%) with mild TBI I: - E: moderate or severe TBI	n = 45 (90%) with MDD I: - E: primary psychotic disorder, bipolar I disorder, current moderate or severe SUD
Watts 2012	N = 20	55.9	18:2	White: 100%	Veterans	-	I: - E: SUD

Note: I: study inclusion criteria; E: study exclusion criteria; absence of information indicated by "-"
Diagnostic abbreviations: **BPD:** borderline personality disorder; **MDE:** major depressive episode; **MDD:** major depressive disorder; **OCD:** obsessive compulsive disorder; **PD:** personality disorder; **SA:** suicide attempt; **SI:** suicidal ideation; **SUD:** substance use disorder
[a]Comorbid psychiatric diagnoses include the following: statistics for percentage of study sample with major depressive disorder (MDD), inclusion/exclusion criteria involving comorbid psychiatric diagnoses. Statistics were included for MDD but not other psychiatric diagnoses due to data availability (MDD was the only psychiatric diagnosis for which several studies provided statistics).
[b]Statistics provided for subsample of randomized population. Subsamples as follows: Ahmadizadeh 2018 (n = 58); Cohen 2004 (n = 24, per-protocol sample), Isserles 2013 (n = 18, treatment criterion sample), Leong 2020 (n = 29, modified ITT sample), Levasseur-Moreau 2018 (n = 28, per-protocol sample), Nam 2013 (n = 16, per-protocol sample)

[c]Sample assumed to be comprised of veterans on the basis of study location in Israel and associated mandatory military service
[d]Sample assumed to be comprised of veterans on the basis of study having been conducted at two USA Veterans Administration centers and funded by the Department of Defense
[e]Sample assumed to be comprised of civilians on the basis of descriptions of participants' traumatic incidents and recruitment center

Table 2. Stimulation characteristics

Study	Target	Frequency	Intensity	Pattern	Total pulses	Number of sessions	Sham description
Ahmadizadeh 2018	Right DLPFC	20 Hz	100% MT	30 min/session (60 cycles 2s train/ 28s ITI)	24,000	10 sessions (across 4 weeks)	Similar appearance & sounds as active. Plastic cap to prevent stimulation.
	Bilateral DLPFC	(same as above)	(same as above)	(same as above)	(same as above; 12,000 per side)	(same as above)	
Boggio 2010	Right DLPFC	20 Hz	80% MT	20 min/session (40 cycles 2s train/ 28s ITI)	16,000	10 sessions (across 2 weeks)	Similar appearance, weight, and scalp sensation (small electrical stimulator installed) as active.
	Left DLPFC	(same as above)	(same as above)	(same as above)	(same as above)	(same as above)	
Cohen 2004	Right DLPFC	1 Hz	80% MT	20 min/session (5s train/ 55s ITI)	*1000	10 sessions (across 2 weeks)	Same appearance, similar sounds as active; active coil placed 90° to skull and HF (10 Hz) protocol used.
	(same as above)	10 Hz	80% MT	20 min/session (2s train/ 58s ITI)	*4000	(same as above)	
Fryml 2019	DLPFC (n = 3 left-sided, n = 2 right-sided)	10 Hz	120% MT	30 min/session (5s train/ 10s ITI)	30,000[a]	5 sessions[a]	Same coil used and smart card determined delivery of active vs. sham stimulation.
George 2014	Left PFC	10 Hz	120% MT	30 min/session (5s train/10s ITI) Same-day sessions spaced by minimum 1 hr	54,000	9 sessions (3 sessions/day across 3 days)	Similar appearance, noise, temperature, and scalp sensation (TENS) as active.
Isserles 2013	Medial PFC	20 Hz	120% MT	15.5 min/ session	20,160*	12 sessions	Similar acoustic artifact and scalp sensation as active.

Table 2. Stimulation characteristics *(Continued)*

				(42 cycles 2s train/ 20s ITI)		(across 4 weeks)	Same coil used and electronic system determined delivery of active vs. sham stimulation.
Isserles 2021	Medial PFC	18 Hz	100% MT	30 min*/ session (80 cycles 2s train/ 20s ITI)	34,560*[b]	12 sessions[b] (across 4 weeks)	Similar noise and scalp sensations as active. Same coil used and coded magnetic card determined delivery of active vs. sham stimulation.
Kozel 2018	Right DLPFC	1 Hz	110% MT	30 min/session (continuous stimulation; 1 pulse/s)	21,600 to 27,000*	12 to 15 sessions (1 session per week)	Similar appearance & sounds as active (no significant magnetic fields or stimulation of facial muscles)
Leong 2020	Right DLPFC	1Hz	120% MT	37.5 min/ session (continuous stimulation; 1 pulse/s)	22,500	10 sessions (across 2 weeks)	Similar appearance, sounds, and vibration sensation as active.
	Right DLPFC	10 Hz	(same as above)	37.5 min/ session (4s train/ 26s ITI)	30,000	(same as above)	
Levasseur-Moreau 2018	Right DLPFC	50 Hz	80% MT	3.2 min/session (bursts of 3 pulses repeated every 200 ms)	3000*	5 sessions (across 1 week)	Similar sounds as active.
Nam 2013	Right PFC	1 Hz	100% MT	20 min/ session (continuous stimulation; 1 pulse/s)	18,000	15 sessions (across 3 weeks)	Similar appearance and sounds as active.
Philip 2019	Right DLPFC	50 Hz	80% MT	9.5 min/session (2s trains of 3 pulses (at 50 Hz), given every 200 ms; 10s ITI)	18,000	10 sessions (across 2 weeks)	Sham coil not described
Watts 2012	Right DLPFC	1 Hz	90% MT	20 min/session (20s train/ 40s ITI)	4000	10 sessions (across 2 weeks)	Similar appearance and sounds as active.

Note: total pulses marked with asterisks (*) were not provided in the publication and were estimated by review authors using information about session length and stimulation pattern provided.

Abbreviations: DLPFC: dorsolateral prefrontal cortex; **dTMS:** deep transcranial magnetic stimulation; **HF:** high-frequency; **ITI:** intertrain interval; **min:** minute(s); **MT:** motor threshold; **PFC:** prefrontal cortex; **s/ms:** second(s)/millisecond(s); **TENS:** transcutaneous electrical nerve stimulation

[a]Treatment duration (5 versus 8 weeks) for Fryml 2019 was unclear; we assumed 5 weeks based on available information.

[b]Isserles 2021 administered additional dTMS ("booster") sessions at week 5 and week 9 post-treatment visits. We did not include TMS delivered at these visits in the pulse total and session durations reported above.

APPENDICES

Appendix 1. Search strategies

Search strategies TMS for PTSD (2022)

Database: Ovid MEDLINE(R) ALL <1946 to February 02, 2022>

Searched on: 3rd February 2022

Search Strategy:

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1 Stress Disorders, Traumatic/ (745)

2 Stress Disorders, Post-Traumatic/ (37429)

3 Stress Disorders, Traumatic, Acute/ (516)

4 Combat Disorders/ (3191)

5 PTSD.ti,ab,kf. (29469)

6 ((posttrauma* or post-trauma*) adj3 (stress* or neuros* or disorder* or psych* or symptom* or syndrome*)).ti,ab,kf. (42231)

7 acute stress disorder*.ti,ab,kf. (738)

8 (CPTSD or C-PTSD).ti,ab,kf. (277)

9 (disorder$ adj2 extreme stress).ti,ab,kf. (53)

10 DESNOS.ti,ab,kf. (36)

11 (combat adj (stress* or neuros* or disorder* or syndrome*)).ti,ab,kf. (489)

12 war neuros*.ti,ab,kf. (143)

13 or/1-12 (57399)

14 Transcranial Magnetic Stimulation/ (13370)

15 (transcrani* magnetic or TMS or rTMS or iTMS or sTMS or dTMS or nTMS).ti,ab,kf. (24303)

16 ((non-invasive or noninvasive) adj brain stimulat*).ti,ab,kf. (2460)

17 (theta-burst* or thetaburst* or TBS or iTBS or aiTBS).ti,ab,kf. (4836)

18 or/14-17 (30763)

19 13 and 18 (185)

20 controlled clinical trial.pt. (94678)

21 randomized controlled trial.pt. (557721)

22 Clinical Trials as Topic/ (199064)

23 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kf. (727805)

24 randomly.ti,ab,kf. (376128)

25 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or crossover or cross-over or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or subsitut* or treat*))).ti,ab,kf. (645181)

26 (placebo or sham).ab,ti,kf. (321701)

27 trial.ti. (255916)

28 (groups or (control* adj3 group*)).ab. (2542884)

29 ((control* or trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kf,hw. (44502)

30 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,kf. (187205)

31 double-blind method/ or random allocation/ or single-blind method/ (296503)

32 or/20-30 (3618061)

33 exp animals/ not humans.sh. (4953238)

34 32 not 33 (3081489)

35 19 and 34 (78)

Database: Embase <1974 to 2022 February 02>

Searched on: 3rd February 2022

Search Strategy:

---

1 acute stress disorder/ (1594)

2 posttraumatic stress disorder/ (69186)

3 combat stress/ (44)

4 PTSD.ti,ab,kw. (38210)

5 ((posttrauma* or post-trauma*) adj3 (stress* or neuros* or disorder* or psych* or symptom* or syndrome*)).ti,ab,kw. (50234)

6 acute stress disorder*.ti,ab,kw. (985)

7 (CPTSD or C-PTSD).ti,ab,kw. (239)

8 (disorder$ adj2 extreme stress).ti,ab,kw. (60)

9 DESNOS.ti,ab,kw. (52)

10 (combat adj (stress* or neuros* or disorder* or syndrome*)).ti,ab,kw. (598)

11 war neuros*.ti,ab,kw. (104)

12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (79955)

13 exp transcranial magnetic stimulation/ (27558)

14 (transcrani* magnetic or TMS or rTMS or iTMS or sTMS or dTMS or nTMS).ti,ab,kw. (33384)

15 ((non-invasive or noninvasive) adj brain stimulat*).ti,ab,kw. (2997)

16 (theta-burst* or thetaburst* or TBS or iTBS or aiTBS).ti,ab,kw. (7637)

17 13 or 14 or 15 or 16 (46072)

18 12 and 17 (502)

19 randomized controlled trial/ (694072)

20 randomization/ (92934)

21 controlled clinical trial/ (464906)

22 clinical trial/ (1026618)

23 placebo/ (376425)

24 (placebo or sham).ti,ab. (461077)

25 trial.ti. (349655)

26 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kw. (1040394)

27 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster* or control* or crossover or cross-over or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or substitut* or treat*))).ti,ab,kw. (879657)

28 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$ or dumm$)).mp. (336847)

29 (groups or (control* adj3 group*)).ab. (3546636)

30 ((control* or trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kw,hw. (64548)

31 or/19-30 (5299840)

32 ((animal or nonhuman) not human).de. (6049201)

33 31 not 32 (4568931)

34 18 and 33 (193)

Database: APA PsycInfo <1806 to January Week 5 2022>

Searched on: 3rd February 2022

Search Strategy:

---

1 exp posttraumatic stress disorder/ (36597)

2 posttraumatic stress/ (1309)

3 acute stress disorder/ (633)

4 traumatic neurosis/ (305)

5 combat experience/ (3131)

6 PTSD.ti,ab,id. (37495)

7 ((posttrauma* or post-trauma*) adj3 (stress* or neuros* or disorder* or psych* or symptom* or syndrome*)).ti,ab,id. (47553)

8 acute stress disorder*.ti,ab,id. (861)

9 (CPTSD or C-PTSD).ti,ab,id. (327)

10 (disorder* adj2 extreme stress).ti,ab,id. (114)

11 DESNOS.ti,ab,id. (62)

12 (combat adj (stress* or neuros* or disorder* or syndrome*)).ti,ab,id. (685)

13 war neuros*.ti,ab,id. (453)

14 or/1-13 (56139)

15 transcranial magnetic stimulation/ (9290)

16 (transcrani* magnetic or TMS or rTMS or iTMS or sTMS or dTMS or nTMS).ti,ab,id. (11004)

17 ((non-invasive or noninvasive) adj brain stimulat*).ti,ab,id. (1431)

18 (theta-burst* or thetaburst* or TBS or iTBS or aiTBS).ti,ab,id. (1599)

19 15 or 16 or 17 or 18 (13783)

20 14 and 19 (154)

21 randomized clinical trials/ (307)

22 randomized controlled trials/ (823)

23 clinical trials/ (12015)

24 clinical trial.md. (32577)

25 (random* or RCT).ti,ab,id. (223034)

26 (groups or (control* adj3 group*)).ab. (573867)

27 ((control* or trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,id,hw. (16965)

28 ((single or double or triple or treble) adj2 (blind* or mask* or dumm*)).ti,ab,id. (27891)

29 trial.ti. (34416)

30 (placebo or sham).ti,ab,id,hw. (55570)

31 treatment outcome.md. (22284)

32 treatment effectiveness evaluation/ (26454)

33 mental health program evaluation/ (2256)

34 or/21-33 (800484)

35 20 and 34 (72)

Science Citation Index

1900-present

Conference Proceedings Citation Index – Science

1990-present

via Web of Science, Clarivate

Searched on: 3rd February 2022

Records retrieved: 197

15 #14 AND #11 197

14 #12 OR #13 8,584,298

13 TS= (random* or quasi-random* or quasirandom* or control* or trial* or placebo or sham or RCT) 8,532,592

12 TS=((singl* or doubl* or tripl* or trebl*) NEAR/2 (blind* or mask* or dumm*)) 311,252

11 #6 AND #10 367

10 #7 OR #8 OR #9 65,925

9 TS=((theta-burst* or thetaburst* or *TBS)) 10,617

8 TS=(((non-invasive or noninvasive) NEAR/0 brain NEAR/0 stimulat*)) 3,381

7 TS=((transcrani* NEAR/0 magnetic) or *TMS) 55,642

6 #1 OR #2 OR #3 OR #4 OR #5 46,676

5 TS=(war NEXT/0 neuros*) 0

4 TS=((combat NEAR/0 (stress* or neuros* or disorder* or syndrome*))) 534

3 TS=("acute stress disorder*" or CPTSD or C-PTSD or (disorder* NEAR/2 "extreme stress") or DESNOS) 695

2 TS=(((posttrauma* or post-trauma*) NEAR/3 (stress* or neuros* or disorder* or psych* or symptom* or syndrome*))) 41,836

1 TS=(PTSD) 23,272

PTSDPubs

via ProQuest

Searched on: 3rd February 2022

Records retrieved: 70

(MAINSUBJECT.EXACT("Repetitive Transcranial Magnetic Stimulation") OR TI,AB,SU,IF((transcrani* NEAR/1 magnetic) OR TMS OR rTMS OR iTMS OR sTMS OR dTMS OR nTMS) OR TI,AB,SU,IF((non-invasive OR noninvasive) NEAR/1 brain stimulat*) OR TI,AB,SU,IF(theta-burst* OR thetaburst* OR TBS OR iTBS OR aiTBS)) AND ((MAINSUBJECT.EXACT.EXPLODE("Randomized Clinical Trial") OR MAINSUBJECT.EXACT.EXPLODE("Clinical Trial")) OR TI,AB,SU,IF(random* OR quasi-random* OR quasirandom* OR control* OR trial* OR placebo OR sham OR RCT) OR TI,AB,SU,IF((singl* OR doubl* OR tripl* OR trebl*) NEAR/2 (blind* OR mask* OR dumm*))) 70 hits

CENTRAL

via Cochrane Library

Searched on: 3rd February 2022

Records retrieved: 135

#1 MeSH descriptor: [Stress Disorders, Traumatic] this term only 804

#2 MeSH descriptor: [Stress Disorders, Post-Traumatic] this term only 2977

#3 MeSH descriptor: [Stress Disorders, Traumatic, Acute] this term only 56

#4 MeSH descriptor: [Combat Disorders] this term only 132

#5 PTSD:ti,ab,kw 4941

#6 ((posttrauma* or post-trauma*) near/3 (stress* or neuros* or disorder* or psych* or symptom* or syndrome*)):ti,ab,kw 6605

#7 (acute stress disorder*):ti,ab,kw 1231

#8 (CPTSD or C-PTSD):ti,ab,kw 20

#9 (disorder* near/2 extreme stress):ti,ab,kw 6

#10 DESNOS:ti,ab,kw 3

#11 (combat next (stress* or neuros* or disorder* or syndrome*)):ti,ab,kw 161

#12 (war next neuros*):ti,ab,kw 0

#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 8099

#14 MeSH descriptor: [Transcranial Magnetic Stimulation] this term only 1569

#15 ((transcrani* next magnetic) or *TMS):ti,ab,kw 7012

#16 ((non-invasive or noninvasive) next brain next stimulat*):ti,ab,kw 1016

#17 (theta-burst* or thetaburst* or *TBS):ti,ab,kw 1435

#18 #14 or #15 or #16 or #17 8360

#19 #13 and #18 in Trials 135

Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR)

searched via CRS-Web (4-Feb-2022, records up-to-date as of June 2016 only)

#1 (PTSD or CPTSD or C-PTSD or DESNOS or ((posttrauma* or post-trauma* or "post trauma*") adj3 (stress* or neuros* or disorder* or psych* or symptom* or syndrom*)) or ((traumatic or acute or extreme) adj3 stress) or (combat adj (stress* or neuros* or disorder* or syndrom*)) or "war neuros*") (2661)

#2 ((transcrani* and (magnet* or stimulat*)) or TMS or rTMS or iTMS or sTMS or dTMS or nTMS or ((non-invasive or noninvasive) adj "brain stimulat*") or theta-burst* or thetaburst* or TBS or iTBS or aiTBS) (570)

#3 (#1 and #2) (28)

ProQuest Dissertations & Theses A&I

via ProQuest

Searched on: 4th February 2022

Records retrieved: 12

S1 TI,AB,SU,IF(PTSD OR CPTSD OR C-PTSD OR DESNOS) ProQuest Dissertations & Theses A&I 6263

S2 TI,AB,SU,IF((posttrauma* or post-trauma*) NEAR/3 (stress* or neuros* or disorder* or psych* or symptom* or syndrome*)) ProQuest Dissertations & Theses A&I 7470

S3 TI,AB,SU,IF("acute stress" NEAR/1 disorder*) ProQuest Dissertations & Theses A&I 67

S4 TI,AB,SU,IF("extreme stress" NEAR/1 disorder*) ProQuest Dissertations & Theses A&I 33

S5 TI,AB,SU,IF(combat NEAR/1 (stress* or neuros* or disorder* or syndrome*)) ProQuest Dissertations & Theses A&I 318

S6 TI,AB,SU,IF(war NEAR/1 neuros*) ProQuest Dissertations & Theses A&I 42

S7 TI,AB,SU,IF(PTSD OR CPTSD OR C-PTSD OR DESNOS) OR TI,AB,SU,IF((posttrauma* OR post-trauma*) NEAR/3 (stress* OR neuros* OR disorder* OR psych* OR symptom* OR syndrome*)) OR TI,AB,SU,IF("acute stress" NEAR/1 disorder*) OR TI,AB,SU,IF("extreme stress" NEAR/1 disorder*) OR TI,AB,SU,IF(combat NEAR/1 (stress* OR neuros* OR disorder* OR syndrome*)) OR TI,AB,SU,IF(war NEAR/1 neuros*) ProQuest Dissertations & Theses A&I 9193

S8 TI,AB,SU,IF((transcrani* NEAR/1 magnetic) OR TMS OR rTMS OR iTMS OR sTMS OR dTMS OR nTMS) OR TI,AB,SU,IF((non-invasive OR noninvasive) NEAR/1 brain stimulat*) OR TI,AB,SU,IF(theta-burst* OR thetaburst* OR TBS OR iTBS OR aiTBS) ProQuest Dissertations & Theses A&I 3211

S9 (TI,AB,SU,IF(PTSD OR CPTSD OR C-PTSD OR DESNOS) OR TI,AB,SU,IF((posttrauma* OR post-trauma*) NEAR/3 (stress* OR neuros* OR disorder* OR psych* OR symptom* OR syndrome*)) OR TI,AB,SU,IF("acute stress" NEAR/1 disorder*) OR TI,AB,SU,IF("extreme stress" NEAR/1 disorder*) OR TI,AB,SU,IF(combat NEAR/1 (stress* OR neuros* OR disorder* OR syndrome*)) OR TI,AB,SU,IF(war NEAR/1 neuros*)) AND (TI,AB,SU,IF((transcrani* NEAR/1 magnetic) OR TMS OR rTMS OR iTMS OR sTMS OR dTMS OR nTMS) OR TI,AB,SU,IF((non-invasive OR noninvasive) NEAR/1 brain stimulat*) OR TI,AB,SU,IF(theta-burst* OR thetaburst* OR TBS OR iTBS OR aiTBS)) ProQuest Dissertations & Theses A&I 12

ClinicalTrials.gov

https://clinicaltrials.gov/

Searched on: 4th February 2022

Records retrieved: 62 before deduplication (53 after duplicates removed)

1. 46 Studies found for: "Transcranial Magnetic Stimulation" OR TMS OR rTMS OR iTMS OR sTMS OR dTMS OR nTMS | PTSD OR "posttraumatic stress" OR "post-traumatic stress" OR "post traumatic stress" OR CPTSD OR C-PTSD OR DESNOS OR "acute stress" OR "extreme stress"

2. 16 Studies found for: non invasive brain stimulation OR "theta burst" OR theta-burst or thetaburst or TBS or iTBS or aiTBS | PTSD OR "posttraumatic stress" OR "post-traumatic stress" OR "post traumatic stress" OR CPTSD OR C-PTSD OR DESNOS OR "acute stress" OR "extreme stress"

WHO International Clinical Trials Registry Platform

https://trialsearch.who.int/AdvSearch.aspx

Searched on: 4th February 2022

Records retrieved: 40 records before deduplication (36 after duplicates removed)

Advanced search screen. Recruitment status set to ALL. Synonyms included.

1. Condition field: PTSD OR posttraumatic stress OR post-traumatic stress OR post traumatic stress OR CPTSD OR C-PTSD OR DESNOS OR acute stress OR extreme stress AND Intervention field: Transcranial Magnetic Stimulation OR TMS OR rTMS OR iTMS OR sTMS OR dTMS OR nTMS (32 hits)

2. Condition field: PTSD OR posttraumatic stress OR post-traumatic stress OR post traumatic stress OR CPTSD OR C-PTSD OR DESNOS OR acute stress OR extreme stress AND Intervention field: non invasive brain stimulation OR theta burst OR theta-burst or thetaburst or TBS or iTBS or aiTBS (8 hits)

Search strategies TMS for PTSD – Jan 2023 update

Database: Ovid MEDLINE(R) ALL <1946 to January 10, 2023>

Searched on: 11th January 2023

Records retrieved: 83

Search Strategy:

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1 Stress Disorders, Traumatic/ (749)

2 Stress Disorders, Post-Traumatic/ (40043)

3 Stress Disorders, Traumatic, Acute/ (533)

4 Combat Disorders/ (3210)

5 PTSD.ti,ab,kf. (32140)

6 ((posttrauma* or post-trauma*) adj3 (stress* or neuros* or disorder* or psych* or symptom* or syndrome*)).ti,ab,kf. (45826)

7 acute stress disorder*.ti,ab,kf. (787)

8 (CPTSD or C-PTSD).ti,ab,kf. (335)

9 (disorder$ adj2 extreme stress).ti,ab,kf. (55)

10 DESNOS.ti,ab,kf. (38)

11 (combat adj (stress* or neuros* or disorder* or syndrome*)).ti,ab,kf. (500)

12 war neuros*.ti,ab,kf. (145)

13 or/1-12 (61762)

14 Transcranial Magnetic Stimulation/ (14422)

15 (transcrani* magnetic or TMS or rTMS or iTMS or sTMS or dTMS or nTMS).ti,ab,kf. (26079)

16 ((non-invasive or noninvasive) adj brain stimulat*).ti,ab,kf. (2846)

17 (theta-burst* or thetaburst* or TBS or iTBS or aiTBS).ti,ab,kf. (5327)

18 or/14-17 (33146)

19 13 and 18 (205)

20 controlled clinical trial.pt. (95158)

21 randomized controlled trial.pt. (584289)

22 Clinical Trials as Topic/ (200738)

23 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kf. (781459)

24 randomly.ti,ab,kf. (400432)

25 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or crossover or cross-over or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or substitut* or treat*))).ti,ab,kf. (696870)

26 (placebo or sham).ab,ti,kf. (335630)

27 trial.ti. (277171)

28 (groups or (control* adj3 group*)).ab. (2712809)

29 ((control* or trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kf,hw. (48361)

30 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,kf. (195230)

31 double-blind method/ or random allocation/ or single-blind method/ (301853)

32 or/20-31 (3885361)

33 exp animals/ not humans.sh. (5081501)

34 32 not 33 (3307356)

35 19 and 34 (83)

Database: Embase <1974 to 2023 January 10>

Searched on: 11th January 2023

Records retrieved: 214

Search Strategy:

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1 acute stress disorder/ (1715)

2 posttraumatic stress disorder/ (75615)

3 combat stress/ (75)

4 PTSD.ti,ab,kw. (41903)

5 ((posttrauma* or post-trauma*) adj3 (stress* or neuros* or disorder* or psych* or symptom* or syndrome*)).ti,ab,kw. (54774)

6 acute stress disorder*.ti,ab,kw. (1061)

7 (CPTSD or C-PTSD).ti,ab,kw. (308)

8 (disorder$ adj2 extreme stress).ti,ab,kw. (62)

9 DESNOS.ti,ab,kw. (58)

10 (combat adj (stress* or neuros* or disorder* or syndrome*)).ti,ab,kw. (621)

11 war neuros*.ti,ab,kw. (108)

12 or/1-11 (87468)

13 exp transcranial magnetic stimulation/ (29781)

14 (transcrani* magnetic or TMS or rTMS or iTMS or sTMS or dTMS or nTMS).ti,ab,kw. (35776)

15 ((non-invasive or noninvasive) adj brain stimulat*).ti,ab,kw. (3405)

16 (theta-burst* or thetaburst* or TBS or iTBS or aiTBS).ti,ab,kw. (8399)

17 13 or 14 or 15 or 16 (49684)

18 12 and 17 (564)

19 randomized controlled trial/ (745275)

20 randomization/ (95953)

21 controlled clinical trial/ (467967)

22 clinical trial/ (1052444)

23 placebo/ (390476)

24 (placebo or sham).ti,ab. (484206)

25 trial.ti. (379574)

26 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kw. (1117288)

27 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster* or control* or crossover or cross-over or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or substitut* or treat*))).ti,ab,kw. (948216)

28 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$ or dumm$)).mp. (354012)

29 (groups or (control* adj3 group*)).ab. (3784988)

30 ((control* or trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kw,hw. (70514)

31 or/19-30 (5623625)

32 ((animal or nonhuman) not human).de. (6283985)

33 31 not 32 (4855113)

34 18 and 33 (214)

Database: APA PsycInfo <1806 to January Week 2 2023>

Searched on: 11th January 2023

Records retrieved: 79

Search Strategy:

---

1 exp posttraumatic stress disorder/ (38525)

2 posttraumatic stress/ (1716)

3 acute stress disorder/ (658)

4 traumatic neurosis/ (306)

5 combat experience/ (3230)

6 PTSD.ti,ab,id. (39783)

7 ((posttrauma* or post-trauma*) adj3 (stress* or neuros* or disorder* or psych* or symptom* or syndrome*)).ti,ab,id. (50387)

8 acute stress disorder*.ti,ab,id. (902)

9 (CPTSD or C-PTSD).ti,ab,id. (397)

10 (disorder* adj2 extreme stress).ti,ab,id. (115)

11 DESNOS.ti,ab,id. (62)

12 (combat adj (stress* or neuros* or disorder* or syndrome*)).ti,ab,id. (698)

13 war neuros*.ti,ab,id. (455)

14 or/1-13 (59575)

15 transcranial magnetic stimulation/ (9733)

16 (transcrani* magnetic or TMS or rTMS or iTMS or sTMS or dTMS or nTMS).ti,ab,id. (11563)

17 ((non-invasive or noninvasive) adj brain stimulat*).ti,ab,id. (1592)

18 (theta-burst* or thetaburst* or TBS or iTBS or aiTBS).ti,ab,id. (1703)

19 15 or 16 or 17 or 18 (14494)

20 14 and 19 (166)

21 randomized clinical trials/ (412)

22 randomized controlled trials/ (937)

23 clinical trials/ (12130)

24 clinical trial.md. (35651)

25 (random* or RCT).ti,ab,id. (234887)

26 (groups or (control* adj3 group*)).ab. (596699)

27 ((control* or trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,id,hw. (18164)

28 ((single or double or triple or treble) adj2 (blind* or mask* or dumm*)).ti,ab,id. (28711)

29 trial.ti. (36695)

30 (placebo or sham).ti,ab,id,hw. (57251)

31 treatment outcome.md. (23075)

32 treatment effectiveness evaluation/ (27329)

33 mental health program evaluation/ (2305)

34 or/21-33 (833981)

35 20 and 34 (79)

Science Citation Index

1900-present

Conference Proceedings Citation Index – Science

1990-present

via Web of Science, Clarivate

Searched on: 11th January 2023

Records retrieved: 221

1: TS=(PTSD) Results: 25438

2: TS=(((posttrauma* or post-trauma*) NEAR/3 (stress* or neuros* or disorder* or psych* or symptom* or syndrome*))) Results: 45282

3: TS=("acute stress disorder*" or CPTSD or C-PTSD or (disorder* NEAR/2 "extreme stress") or DESNOS) Results: 773

4: TS=((combat NEAR/0 (stress* or neuros* or disorder* or syndrome*))) Results: 557

5: TS=("war neurosis" or "war neuroses") Results: 222

6: #1 OR #2 OR #3 OR #4 OR #5 Results: 50731

7: TS=((transcrani* NEAR/0 magnetic) or *TMS) Results: 60284

8: TS=(((non-invasive or noninvasive) NEAR/0 brain NEAR/0 stimulat*)) Results: 3893

9: TS=((theta-burst* or thetaburst* or *TBS)) Results: 11715

10: #7 OR #8 OR #9 Results: 71642

11: #10 AND #6 Results: 413

12: TS=((singl* or doubl* or tripl* or trebl*) NEAR/2 (blind* or mask* or dumm*)) Results: 328711

13: TS= (random* or quasi-random* or quasirandom* or control* or trial* or placebo or sham or RCT) Results: 9041630

14: #12 OR #13 Results: 9097181

15: #14 AND #11 Results: 221

PTSDPubs

via ProQuest

Searched on: 13th January 2023

Records retrieved: 72

(MAINSUBJECT.EXACT("Repetitive Transcranial Magnetic Stimulation") OR TI,AB,SU,IF((transcrani* NEAR/1 magnetic) OR TMS OR rTMS OR iTMS OR sTMS OR dTMS OR nTMS) OR TI,AB,SU,IF((non-invasive OR noninvasive) NEAR/1 brain stimulat*) OR TI,AB,SU,IF(theta-burst* OR thetaburst* OR TBS OR iTBS OR aiTBS)) AND ((MAINSUBJECT.EXACT.EXPLODE("Randomized Clinical Trial") OR MAINSUBJECT.EXACT.EXPLODE("Clinical Trial")) OR TI,AB,SU,IF(random* OR quasi-random* OR quasirandom* OR control* OR trial* OR placebo OR sham OR RCT) OR TI,AB,SU,IF((singl* OR doubl* OR tripl* OR trebl*) NEAR/2 (blind* OR mask* OR dumm*)))

CENTRAL

via Cochrane Library

Issue 12 of 12, December 2022

Searched on: 11th January 2023

Records retrieved: 148

#1 MeSH descriptor: [Stress Disorders, Traumatic] this term only 862

#2 MeSH descriptor: [Stress Disorders, Post-Traumatic] this term only 3209

#3 MeSH descriptor: [Stress Disorders, Traumatic, Acute] this term only 57

#4 MeSH descriptor: [Combat Disorders] this term only 134

#5 PTSD:ti,ab,kw 5394

#6 ((posttrauma* or post-trauma*) near/3 (stress* or neuros* or disorder* or psych* or symptom* or syndrome*)):ti,ab,kw 7239

#7 (acute stress disorder*):ti,ab,kw 1401

#8 (CPTSD or C-PTSD):ti,ab,kw 28

#9 (disorder* near/2 extreme stress):ti,ab,kw 7

#10 DESNOS:ti,ab,kw 4

#11 (combat next (stress* or neuros* or disorder* or syndrome*)):ti,ab,kw 166

#12 (war next neuros*):ti,ab,kw 0

#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 8921

#14 MeSH descriptor: [Transcranial Magnetic Stimulation] this term only 1698

#15 ((transcrani* next magnetic) or *TMS):ti,ab,kw 7914

#16 ((non-invasive or noninvasive) next brain next stimulat*):ti,ab,kw 1175

#17 (theta-burst* or thetaburst* or *TBS):ti,ab,kw 1693

#18 #14 or #15 or #16 or #17 9453

#19 #13 and #18 in Trials 148

ProQuest Dissertations & Theses A&I

via ProQuest

Searched on: 13th January 2023

Records retrieved: 16

(TI,AB,SU,IF(PTSD OR CPTSD OR C-PTSD OR DESNOS) OR TI,AB,SU,IF((posttrauma* OR post-trauma*) NEAR/3 (stress* OR neuros* OR disorder* OR psych* OR symptom* OR syndrome*)) OR TI,AB,SU,IF("acute stress" NEAR/1 disorder*) OR TI,AB,SU,IF("extreme stress" NEAR/1 disorder*) OR TI,AB,SU,IF(combat NEAR/1 (stress* OR neuros* OR disorder* OR syndrome*)) OR TI,AB,SU,IF(war NEAR/1 neuros*)) AND (TI,AB,SU,IF((transcrani* NEAR/1 magnetic) OR TMS OR rTMS OR iTMS OR sTMS OR dTMS OR nTMS) OR TI,AB,SU,IF((non-invasive OR noninvasive) NEAR/1 brain stimulat*) OR TI,AB,SU,IF(theta-burst* OR thetaburst* OR TBS OR iTBS OR aiTBS))

ClinicalTrials.gov

https://clinicaltrials.gov/

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1. 58 Studies found for: PTSD OR "posttraumatic stress" OR "post-traumatic stress" OR "post traumatic stress" OR CPTSD OR C-PTSD OR DESNOS OR "acute stress" OR "extreme stress" | "Transcranial Magnetic Stimulation" OR TMS OR rTMS OR iTMS OR sTMS OR dTMS OR nTMS

2. 13 Studies found for: non invasive brain stimulation OR "theta burst" OR theta-burst or thetaburst or TBS or iTBS or aiTBS | PTSD OR "posttraumatic stress" OR "post-traumatic stress" OR "post traumatic stress" OR CPTSD OR C-PTSD OR DESNOS OR "acute stress" OR "extreme stress"

WHO International Clinical Trials Registry Platform

https://trialsearch.who.int/AdvSearch.aspx

Searched on: 13th January 2023

Records retrieved: 46

Advanced search screen. Recruitment status set to ALL. Synonyms included.

1. Condition field: PTSD OR posttraumatic stress OR post-traumatic stress OR post traumatic stress OR CPTSD OR C-PTSD OR DESNOS OR acute stress OR extreme stress AND Intervention field: Transcranial Magnetic Stimulation OR TMS OR rTMS OR iTMS OR sTMS OR dTMS OR nTMS (37 hits)

2. Condition field: PTSD OR posttraumatic stress OR post-traumatic stress OR post traumatic stress OR CPTSD OR C-PTSD OR DESNOS OR acute stress OR extreme stress AND Intervention field: non invasive brain stimulation OR theta burst OR theta-burst or thetaburst or TBS or iTBS or aiTBS (9 hits)

Appendix 2. Additional excluded studies (unable to locate)

We identified the following six references from the meta-analysis, Yan 2017, as potentially eligible during the handsearch. We were unable to locate/access these articles; therefore, they are not included in this review.

- Bie HX, Wang XY. Effectiveness of high-frequency repetitive transcranial magnetic stimulation as an augmention in posttraumatic stress disorder. J. Guangdong Med. Chin. 2011;32:222-3. [CRS ID: 24030320]
- Huang X, Wang JL. Research on the therapeutic effects of high frequency repetitive transcranial magnetic stimulation to post-traumatic stress disorder and its related mechanisms. Chin. Ed. Hebei Med. Univ, Shijiazhuang. 2015. [CRS ID: 24030332]
- Wang Y, Peng L, Zhou XL, Liu HL, Li M. Effect of repetitive transcranial magnetic stimulation on core symptoms, positive and negative affects and resilience in rehabilitation patients with post-traumatic stress disorder after traumatic injury. J. Third Mil. Med. Univ. Chin. 2015;37:1571-5. [CRS ID: 24030406]
- Wu H, Zhao Y, Hou Y, Yang X. Acupuncture combined with repetitive transcranial magnetic stimulation in the treatment of post-traumatic stress disorder. J. Brain Neurol. Dis. 2013;21. [CRS ID: 24030410]
- Wu WJ, Peng ZW, Zhang RG, Tan QR. Effects of high-frequency repetitive transcranial magnetic stimulation combined with paroxetine in treatment of posttraumatic stress disorder. J Neurosci Ment. Health 2014;14:450-3. [CRS ID: 24030412]
- Zhou P, Zhang Y, Tan QR. Effect of repetitive transcranial magnetic stimulation (rTMS) combined with paroxetine in the treatment of posttraumatic stress disorder. Journal of Psychiatry (Chinese ed.) 2016;26:89-92. [CRS ID: 24030414]

HISTORY

Protocol first published: Issue 1, 2022

CONTRIBUTIONS OF AUTHORS

RB: conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, validation, visualization, writing – original draft, writing – review & editing

KC: conceptualization, data curation, investigation, methodology, validation, writing – original draft, writing – review & editing

KJ: data curation, methodology, supervision (methodology, Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards), validation, writing – review & editing

RW: methodology, software, supervision (statistical methods)

RG: supervision (content), writing – review & editing

GS: supervision (content), writing – review & editing

DECLARATIONS OF INTEREST

RB: no known conflict of interest.
KC: no known conflict of interest.
KJ: no known conflict of interest.
RG: no known conflict of interest.
RW: no known conflict of interest.
GS: no known conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We conducted analysis of dichotomous outcomes using R rather than SAS (statistical software). We found R to be more compatible with Cochrane methods and systems, including calculation of heterogeneity and production of figures. We checked our estimates and 95% confidence intervals (CIs) for odds ratios of dichotomous outcomes in SAS (estimates obtained were similar across programs).
- Compared to our protocol, we provided additional details for our definition of serious adverse events (SAEs). As stated in the Results section, we defined serious adverse events following the criteria outlined by Wang 2022: events warranting hospitalization, including

but not limited to seizure, increased suicidal ideation, mania, and syncope. We made this change because we discovered that SAEs were often not clearly defined during data extraction. We acknowledge that lack of a prespecified definition of SAEs is a limitation of this review, as well as of the randomised controlled trials (RCTs) we included.

- We conducted meta-analysis of SAEs using the safety population rather than the intention-to-treat (ITT) sample as our protocol stated. Analysis of the safety population is recommended and was confirmed by consultation with Cochrane methods support (National Research Council 2010).
- A third review author (KJ) was involved in data extraction and risk of bias ratings who was not described as undertaking these roles in the protocol. Two authors still systematically undertook all data extraction and risk of bias ratings (RB and KC or KJ).
- We clarified that PTSD severity assessed immediately after treatment was our primary efficacy outcome, and PTSD severity at one to four weeks and four to 12 weeks after treatment were secondary outcomes. We implied this distinction in the outcomes by designating only the first time point (PTSD severity assessed immediately after treatment) for risk of bias assessment and inclusion in the summary of findings table, but failed to convey this distinction explicitly in our list of primary and secondary outcomes.
- In the protocol, we provisionally identified dropouts (i.e. number of participants who withdraw from a trial before the end of treatment) as a key outcome for the summary of findings table. Instead, we reported this outcome in the main results section of the review.
- We were more explicit about our analysis and presentation of endpoint scores and change scores in the review. Specifically, we reference the sections of the *Cochrane Handbook for Systematic Reviews of Interventions* from which we obtained the formulae to use, and clarified plans to include estimates of endpoint scores with imputed data and change scores with imputed data as sensitivity analyses.
- We excluded two unpublished studies that otherwise met our inclusion criteria but provided limited methodological information (only study protocols were available when we were carrying out this review). We did not believe we had sufficient information to provide valid interpretation and summary of these studies, but we hope they can be included in future reviews (see NCT02268084; NCT02853032; in Studies awaiting classification).
- Our threshold for exclusion on the basis of attrition was increased from 20% (protocol) to 40%. Upon undertaking data extraction, we realized limiting inclusion to studies with less than 20% attrition would severely limit the number of included studies. Additionally, our original threshold of excluding studies with more than 20% missingness was based upon a review published in 2009 (Armijo-Olivo 2009), which, in turn, heavily drew from a seminal simulation study published in 2001 (Unnebrink 2001). We learned that more sophisticated methods of imputation (e.g. full information maximum likelihood relative to last observation carried forward) have been developed and widely implemented in the intervening years, and so a cap at 20% is likely to be over-restrictive. For example, a review and guide for multiple imputation published in 2017 suggested outcomes from trials with missingness greater than 40% should be viewed as hypothesis-generating only (and thus, not included in meta-analysis; Jakobsen 2017). An exclusion threshold of 40% attrition is also consistent with that used by other systematic reviews in the mental health domain published by Cochrane (for examples, see Li 2014, Rodriguez-Martin 2003, and Sin 2017. Sin 2017 used a slightly higher threshold of 50%). For these reasons, we concluded that to best balance the competing aims of achieving a comprehensive review of studies to date (maximizing the number of studies included) and limiting the impact of questionably-valid statistical comparison (inclusion of ITT outcomes with moderate to high levels of attrition), 40% attrition was a more appropriate limit. We planned to conduct a sensitivity analysis excluding trials with attrition exceeding 20% to provide further clarity on our outcomes and explore potential bias resulting from this protocol deviation.
- On the basis of reviewer comments recommending alignment of stated objectives with Cochrane's preferred format, we modified the original objective from, "to provide a comprehensive synthesis of RCTs to assess the safety and efficacy of repetitive transcranial magnetic stimulation (rTMS) for the treatment of post-traumatic stress disorder (PTSD) in adults", to "to assess the effects of repetitive transcranial magnetic stimulation (rTMS) for post-traumatic stress disorder (PTSD) in adults". We believe this formulation captures the review's focus on the efficacy of rTMS for PTSD, and while safety (SAEs) was an important outcome, the review was optimized for investigation of rTMS efficacy and not for detection of safety risks (e.g. search was restricted to RCTs).
- We adjusted the order of the presentation of the secondary outcomes throughout the review to ensure consistency.
- At the recommendation of peer reviewers, we expanded the discussion of the neurobiological effects of rTMS and the variation in rTMS outcomes that may result from variability across protocols and participant characteristics to the Abstract and Background sections.
- We added additional context/explanation for I^2 and assessment of heterogeneity to the Methods section, Assessment of heterogeneity, at the recommendation of peer reviewers.
- We provided more detail about sham rTMS stimulation to the Methods section, Types of interventions, at the recommendation of peer reviewers.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; *Randomized Controlled Trials as Topic; *Stress Disorders, Post-Traumatic [therapy]; *Transcranial Magnetic Stimulation [adverse effects] [methods]; Treatment Outcome

MeSH check words

Adult; Female; Humans; Male