
Article:
Brown, R., Cherian, K., Jones, K. orcid.org/0009-0002-5166-6462 et al. (3 more authors) (2022) Repetitive transcranial magnetic stimulation for post-traumatic stress disorder in adults. Cochrane Database of Systematic Reviews, 2022 (1). ISSN 1465-1858

https://doi.org/10.1002/14651858.cd015040

This review is published as a Cochrane Review in the Cochrane Database of Systematic Reviews [2022, Issue 1]. Cochrane Reviews are regularly updated as new evidence emerges and in response to comments and criticisms, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the Review. Randi Brown, Kirsten Cherian, Katherine Jones, Rowena Gomez, Robert Wickham, Gregory Sahlem. Repetitive transcranial magnetic stimulation for post-traumatic stress disorder in adults. Cochrane Database of Systematic Reviews 2022, Issue 1. Art. No.: CD015040. DOI: http://dx.doi.org/10.1002/14651858.CD015040

Cochrane Library

Cochrane Database of Systematic Reviews

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

Brown R, Cherian K, Jones K, Gomez R, Wickham R, Sahlem G

Brown R, Cherian K, Jones K, Gomez R, Wickham R, Sahlem G.
Repetitive transcranial magnetic stimulation for post-traumatic stress disorder in adults (Protocol).
Cochrane Database of Systematic Reviews 2022, Issue 1. Art. No.: CD015040.
DOI: 10.1002/14651858.CD015040.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

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

Randi Brown[1], Kirsten Cherian[2], Katherine Jones[3,4], Rowena Gomez[1,2], Robert Wickham[5], Gregory Sahlem[2]

[1]Clinical Psychology, Palo Alto University, Palo Alto, CA, USA. [2]Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA. [3]Cochrane Pain, Palliative and Supportive Care, Oxford University Hospitals NHS Foundation Trust, Oxford, UK. [4]Mental Health and Neuroscience Network and Acute and Emergency Care Network, Cochrane, London, UK. [5]Department of Psychological Sciences, Northern Arizona University, Flagstaff, AZ, USA

Contact: Randi Brown, rbrown@paloaltou.edu.

Editorial group: Cochrane Common Mental Disorders Group.
Publication status and date: New, published in Issue 1, 2022.

Citation: Brown R, Cherian K, Jones K, Gomez R, Wickham R, Sahlem G. Repetitive transcranial magnetic stimulation for post-traumatic stress disorder in adults (Protocol). *Cochrane Database of Systematic Reviews* 2022, Issue 1. Art. No.: CD015040. DOI: 10.1002/14651858.CD015040.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the safety and efficacy of repetitive transcranial magnetic stimulation (rTMS) for the treatment of post-traumatic stress disorder (PTSD) in adults.

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 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 subjects, 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 (PFC), and reduced fear extinction has been associated with hypoactivity of other brain regions, including the hippocampus and ventromedial PFC (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 academics, 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 may remain. A meta-analysis of trauma-focused psychotherapies for PTSD found these therapies to be associated with symptom improvement with large effect sizes; nonetheless, more than half of the participants remained at or above clinical criteria for PTSD post-treatment and dropout rates were high (Steenkamp 2015). Additionally, a recent chart review of nearly 3000 veterans receiving treatment for PTSD found that fewer than 20% achieved remission (i.e. no longer meeting 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 noninvasive 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 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 differentially impact brain activity (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 that have been 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 reduce neural activity (Chen 1997; Fitzgerald 2006; Huang 2005; Pascual-Leone 1994; Speer 2000). 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 normative functioning (Clark 2015; Koek 2019). Reviews and meta-analyses thus far indicate that treatment with rTMS is safe and well-tolerated in general as well as 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 some 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 as well as ignoring the ways in which stimulation frequency interacts with a host of other rTMS parameters (Huerta 2009; Koek 2019; Ziemann 2008). Current leading theory suggests the neurobiological basis of PTSD and other psychiatric conditions is a circuit dysfunction, 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 PFC and between the hippocampus and salience network (Philip 2018). The most effective rTMS treatment may require potentiation or inhibition of 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 normative, 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 demonstrated efficacy for the treatment of two psychiatric conditions with which PTSD shares key symptoms (Solomon 1991): specifically, the US Food and Drug Administration (FDA) has approved rTMS for the treatment of treatment-resistant major depressive disorder and obsessive compulsive disorder in adults (Voelker 2018). We have chosen not to explore the impact of rTMS on PTSD in children and adolescents in this review due to evidence for differences in the manifestation of PTSD symptoms in children and adolescents as well as the absence of FDA approval and relative dearth of studies examining 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 high 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 will add to this literature by providing the following: 1) an up-to-date synthesis of available data; 2) a detailed exploration of risk of bias using the Cochrane Collaboration's revised standards (the risk of bias 2 tool (RoB2); Sterne 2019); and 3) 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.

OBJECTIVES

To assess the safety and efficacy of repetitive transcranial magnetic stimulation (rTMS) for the treatment of post-traumatic stress disorder (PTSD) in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials assessing the therapeutic efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) for post-traumatic stress disorder (PTSD). We will include all eligible trials, irrespective of language and publication status. We will include cross-over trials (trials for which each participant undergoes multiple interventions sequentially) and exclude quasi-randomized trials (trials using a method of intervention assignment that is not truly random, such as allocation by date of birth or order of recruitment).

Types of participants

We will include adults (aged 18 years or older) who meet criteria for PTSD according to the Diagnostic and statistical manual of mental disorders: DSM-IV or subsequent revisions (DSM-IV-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 will be included irrespective of gender, nationality, ethnicity, veteran status, and treatment setting. If studies include a subset of participants who meet the above criteria, we will include the relevant subset of data, or we will contact the study authors to request these data if they are not reported separately.

Types of interventions

Interventions

We will include trials in which rTMS is 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 will include studies of any duration, dose, and stimulation intensity.

Comparators

To be included in this review, trials must include a sham (non-active rTMS) condition applied for a minimum of five sessions.

Combination interventions

We plan to include combination interventions, where a pharmacological agent or psychotherapy is combined with rTMS treatment. We will only include such trials for which the intervention and control groups receive the same pharmacological or psychological therapy.

Types of outcome measures

We will include any studies that meet the above criteria, irrespective of whether they report any of our outcomes of interest.

Primary outcomes

- PTSD severity: 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 will give preference to clinician-reported rather than self-reported scales in studies for which both are reported. Comparisons will be made at the following time points.
  - Immediately after treatment (scores immediately post-intervention or the earliest available follow-up not extending beyond one week post-intervention).
  - Between one and four weeks after treatment.
  - Four to twelve weeks after treatment.

If a study reports multiple time points within one of these follow-up windows, we will use data from the follow-up closest to the end of the treatment window.

- Serious adverse events: number of participants reporting one or more serious adverse events occurring during the period of active or sham treatment. We define '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 no longer meeting 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 exhibiting at least 30% decrease in severity from baseline to immediately post-intervention or the earliest available follow-up (not extending beyond one week post-intervention). There is no standard definition for treatment response, but 30% decrease in symptom severity is the most commonly-used response metric according to a recent meta-analysis (Varker 2020). Response versus non-response status will be based on reported response results (using the aforementioned definition) from 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 will give preference to clinician-reported rather than self-reported scales in studies for which both are reported.
- Dropout: number of participants who withdrew from the trial before the end of treatment. We will discuss the reasons for dropout (e.g. side effects) in narrative review.
- 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 (e.g. Hamilton Depression Rating Scale (Hamilton 1960), Montgomery-Asberg Depression Rating Scale (Montgomery 1979), 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 (e.g. Beck Anxiety Inventory (Beck 1988), Spielberger State-Trait Anxiety Inventory (Spielberger 1983)).

Search methods for identification of studies

Electronic searches

We will search the following databases and trial registers to identify randomized controlled trials of repetitive transcranial magnetic stimulation (rTMS) for post-traumatic stress disorder (PTSD). We will use relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

- Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR) (all available years).
- The Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, latest issue).
- Ovid MEDLINE (1946 to date) (Appendix 1).
- Ovid Embase (1974 to date).
- Ovid PsycINFO (all years to date).
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to date).
- ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (1990 to date).
- ClinicalTrials.gov (www.clinicaltrials.gov).
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

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

Searching other resources

Reference lists

We will check 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) will independently screen titles and abstracts of all identified records. We plan to use Covidence systematic review screening software to screen titles and abstracts, and to document eligibility and exclusion, and reasons for exclusion (Covidence). After any discrepancies are resolved through discussion, we will retrieve all potentially relevant articles. Two review authors (RB and KC) will then independently assess retrieved articles for inclusion, resolving discrepancies through discussion, or, if necessary, by consulting a third review author (GS).

Data extraction and management

Two review authors (RB and KC) will independently extract data from included studies. We will conduct data extraction using a form that has been piloted on at least one study, as recommended by Li 2021. We will resolve discrepancies through discussion, and, if necessary, by consulting a third review author (GS). We will present the details of included studies in a 'Characteristics of included studies' table. Data extracted from eligible trials will include 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.

Two review authors (RB and KC) will make note of trials where there is cause for suspicion of selective non-reporting of results (e.g. study authors state intention to assess certain outcomes but the outcomes are not reported, or summary statistics are only available for full sample). In studies for which pre-registered study plans (e.g. published protocols, trial registries) are available, we will extract discrepancies in outcomes reported in the study plan versus published results. We will contact study authors to attempt to clarify discrepancies. One review author (RB) will transfer extracted data into Review Manager 5 (RevMan 5) or RevMan Web (Review Manager 2020; RevMan Web 2020), and a second review author (KC) will check the data.

Assessment of risk of bias in included studies

Two review authors (RB and KC) will independently assess risk of bias using the Cochrane Risk of Bias tool version 2.0 (RoB2) for the following outcome measures: PTSD severity immediately post-intervention; serious adverse events; PTSD remission; and dropout (Sterne 2019). We will resolve any discrepancies through discussion, or, if necessary, in consultation with a third review author (GS). We will assess risk of bias in these domains: randomization process; deviations from intended interventions; missing outcome data; measurement of outcome; and selection of reported results. Our risk of bias assessment will focus on effect of assignment to intervention (intention-to-treat (ITT) outcomes), as this is the effect of interest for this review. We will rate the risk of bias for each domain and overall risk of bias as 'high', 'some concerns', or 'low', using the signalling questions and algorithms provided by the RoB2 tool. We plan to use the RoB2 Excel tool to implement RoB2 (available on the riskofbiasinfo.org website). We will store RoB2 data to be made available as supplemental files. Cross-over trials are associated with some unique risk of bias concerns not addressed by the standard RoB2 tool for parallel trials. We expect few, if any, cross-over trials. However, to maximize sample size while maintaining a cogent risk of bias assessment strategy, we will use the following strategy: 1) include only the first phase of cross-over trials; and 2) address potential risk of bias arising from first-phase results only being reported after identification of a carryover effect in narrative form (footnote in RoB table; Higgins 2021a).

Measures of treatment effect

The effect of assignment to intervention (ITT) is the effect of interest for this review; as such, our meta-analysis will be limited to ITT outcomes. We will explore adherence (per protocol) outcomes for primary outcome measures using sensitivity analysis.

Continuous outcomes

Continuous outcomes are PTSD severity, anxiety severity, and depression severity. We will calculate mean differences (MDs) and 95% confidence intervals (CIs) for data that used the same scale. If studies use different scales but outcomes are the same conceptually, we will use standardized mean differences (SMDs). Standardized mean differences equivalent to or higher than 0.2, 0.5, and 0.8 will be interpreted statistically as small, moderate, and large effect sizes, respectively (Cohen 1988). We will give preference to endpoint measures and we will convert change scores to endpoint data using formulae provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021b, hereafter referred to as the *Cochrane Handbook*).

Dichotomous outcomes

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

Hierarchy of outcomes

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

Unit of analysis issues

We will include only the first phase from cross-over trials in order to prevent confounding from carryover effects. For trials including multiple treatment groups, we will combine data from intervention arms that are sufficiently similar, using methods recommended by the *Cochrane Handbook* (Higgins 2021a; Higgins 2021b). We do not expect any other non-standard design features among eligible RCTs (e.g. cluster-randomized controlled trials). If such trials are found, we will provide a narrative summary.

Dealing with missing data

We will conduct meta-analysis of continuous and dichotomous outcomes using data from intention-to-treat (ITT) analyses; specifically, meta-analysis will include outcomes for which data from all randomized participants is included according to randomized treatment assignment (i.e. regardless of non-compliance or dropout). We will narratively review trials with more than 20% attrition, rather than include these trials in meta-analysis, as ITT analysis tends to be invalid beyond this level of attrition (Armijo-Olivo 2009). For trials with less than 20% missing data, we will use outcomes from appropriate imputation methods, including last observation carried forward, imputation of mean of the other group, multiple imputation, and repeated measures mixed-effects models (Armijo-Olivo 2009). We will give 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 will attempt to contact study authors to obtain ITT outcomes. If these data are not available, we will not attempt data imputation, as these methods require individual participant data. We will describe in narrative form the outcomes from such cases, rather than include them in meta-analysis. We will examine results from per-protocol analyses in sensitivity analysis. If a study reporting relevant outcome measures does not report a usable measure of variability, we will contact study authors in an

effort to obtain the missing data. If we cannot obtain these data, we will report the outcomes narratively.

Assessment of heterogeneity

We will assess 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 percentage of heterogeneity not due to sampling error (Deeks 2021). If high levels of heterogeneity are indicated by visual inspection of the forest plots or an I^2 statistic of75% or higher, we will explore this through prespecified subgroup analyses and sensitivity analyses.

Assessment of reporting biases

For the primary outcome measures of PTSD severity immediately post-intervention and adverse events, if there are at least 10 included studies, we will examine potential reporting biases and interpret these using the recommendations of Sterne 2011. We will create funnel plots and visually inspected them for asymmetry. We will also use statistical tests for small study effects as follows: 1) for continuous outcomes, we will use Egger's test (Egger 1997); and 2) for dichotomous outcomes, if the estimated heterogeneity variance of log odds ratio is less than or equal to 0.1, then we will use tests proposed by Harbord 2006. If the estimated heterogeneity variance of log odds ratio is greater than 0.1, we will use the arcsine test including random effects proposed by Rücker 2008. We will interpret the results of these tests with caution, as recommended by Sterne 2011. For example, in the case of a relationship between sample size and effect size, we will consider alternative explanations to publication bias, such as systematic differences in populations included in larger versus smaller studies. Bias due to selective non-reporting of outcome domains can be difficult to detect (Page 2021). We will evaluate trial results for this possibility as outlined in our data extraction plan. For trials with suspected selective non-reporting of outcomes, we will evaluate the trial using the standards outlined in the *Cochrane Handbook* (Page 2021), including comparing published results against pre-publication study plans where available. We will describe suspected risk of bias and its implications in narrative form.

Data synthesis

Continuous outcomes

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

Dichotomous outcomes

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

If participants, interventions, and comparators are judged to be sufficiently similar to ensure clinically meaningful statistical synthesis, then for all primary and secondary outcome measures, we will conduct 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 TMS protocols and participant populations (Deeks 2021). We will conduct quantitative synthesis using all eligible studies (unrestricted by level of bias rating). We will discuss narratively results that are not appropriate for meta-analysis. We will meta-analyze continuous data using the inverse variance method in Review Manager 5 (Review Manager 2020). We will use 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; Kuss 2015; Deeks 2021). Analyses for dichotomous data will be conducted using SAS software (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 and persistence of PTSD symptoms and therefore may impact efficacy of rTMS treatment (Keane 2007; Sareen 2014). We will assess the following effect modifiers for impact on primary outcome comparisons of mean difference in PTSD severity immediately post-intervention and odds ratio for serious adverse events.

- rTMS dose (total pulses).
- rTMS protocol type.
- Combination treatment status.
- Comorbid psychiatric diagnosis.
- Presence of TBI.

We will assess the effect of total rTMS dose on the primary outcome measures outlined above using meta-regression. We will 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 effect of rTMS protocol, we will group trials by use of similar stimulation location, frequency, pattern, and intensity to form protocol types. We will examine 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 will examine the effect of comorbid psychiatric diagnosis by grouping trials according to the following conditions: comorbid depressive disorder, comorbid anxiety disorder, substance use disorder, or other DSM condition/no comorbid diagnosis identified (classifications made according to DSM-5 categories or corresponding ICD or earlier DSM classification). We will examine the effect of presence of TBI using the following comparison: with diagnosed TBI versus without diagnosed TBI. We will conduct subgroup analyses using the formal

test for subgroup differences in Review Manager 5 (Review Manager 2020).

Sensitivity analysis

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

Summary of findings and assessment of the certainty of the evidence

We will present a summary of findings table using GRADEpro GDT software (GRADEpro GDT). The summary of findings table will include the following outcomes: PTSD severity immediately post-intervention, serious adverse events, PTSD remission, and dropout. Outcome comparisons will be included regardless of risk of bias rating. For dichotomous outcomes, in addition to the odds ratio and corresponding 95% CI, we will provide an estimate of assumed (sham) intervention risk per 1000 and corresponding (active treatment) intervention risk per 1000 (and 95% CI). We will base the risk estimate for the sham group on the pooled estimate (median) from control groups of all included studies and we will calculate 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 relative risk estimate (Schünemann 2021). We will assess the certainty of the evidence using the methods and recommendations outlined by Schünemann 2021. These methods include assessing evidence across five GRADE domains for study design, overall risk of bias judgement, inconsistency, indirectness, and imprecision. Two review authors (RB and KC) will independently conduct grading of the evidence. We will resolve any disagreement through discussion, or, if required, by consulting a third review author (GS). We will give the reasons for downgrading and upgrading evidence in the summary of findings table footnotes. Using the standards recommended by the *Cochrane Handbook* (Schünemann 2021), *we* will categorize the certainty of the evidence as high, moderate, low, or very low. In the comments, we will summarize data from eligible studies that are inappropriate to be synthesized using meta-analysis, including whether the information is consistent or inconsistent with the meta-analysis results.

ACKNOWLEDGEMENTS

The authors thank the Cochrane Methods Support Unit for consultation support regarding choice of pairwise random-effects model for meta-analysis.

Cochrane Common Mental Disorders (CCMD) supported the authors in the development of this protocol.

The following people conducted the editorial process for this article.

Sign-off Editor (final editorial decision): Nick Meader, CCMD, Centre for Reviews and Dissemination, University of York

Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Jessica Hendon, CCMD, Centre for Reviews and Dissemination, University of York

Information Specialist (developed the search strategy in consultation with review authors, provided editorial guidance to authors, edited the article): Sarah Dawson, CCMD and University of Bristol

Peer reviewers (provided comments and recommended an editorial decision): Andrew Leuchter, Department of Psychiatry and Biobehavioral Sciences, and Neuromodulation Division, Semel Institute for Neuroscience and Human Behavior, UCLA (clinical/content review); Jean Sellar-Edmunds, York (consumer review); Rachel Richardson, Associate Editor, Cochrane (methods review).

Copy Editor (copy-editing and production): Faith Armitage

The authors and the CCMD Editorial Team are grateful to the peer reviewers for their time and comments. They would also like to thank Cochrane Copy Edit Support for the team's help.

Cochrane Group funding acknowledgement: the UK National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Common Mental Disorders Group.

Disclaimer: the views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the NIHR, National Health Service (NHS), or the Department of Health and Social Care.

REFERENCES

Additional references

Adenauer 2010

Adenauer H, Pinöscha S, Catani C, Gola H, Keil J, Kißler J, et al. Early processing of threat cues in posttraumatic stress disorder—evidence for a cortical vigilance-avoidance reaction. *Biological Psychiatry* 2010;**68**(5):451-8.

Akiki 2017

Akiki TJ, Averill CL, Abdallah CG. A network-based neurobiological model of PTSD: evidence from structural and functional neuroimaging studies. *Current Psychiatry Reports* 2017;**19**(11):81. [DOI: 10.1007/s11920-017-0840-4]

Allen 2017

Allen CH, Kluger BM, Buard I. Safety of transcranial magnetic stimulation in children: a systematic review of the literature. *Pediatric Neurology* 2017;**68**:3-17.

APA 1994

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-IV). 4th edition. Washington, DC: American Psychiatric Association, 1994.

APA 2000

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (Text Revision)(DSM-IV-TR). 4th edition. Washington, DC: American Psychiatric Association, 2000.

APA 2013

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 5th edition. Washington, DC: American Psychiatric Association, 2013.

Armijo-Olivo 2009

Armijo-Olivo S, Warren S, Magee D. Intention to treat analysis, compliance, drop-outs and how to deal with missing data in clinical research: a review. *Physical Therapy Reviews* 2009;**14**(1):36-49.

Badura-Brack 2018

Badura-Brack A, McDermott TJ, Heinrichs-Graham E, Ryan TJ, Khanna MM, Pine DS, et al. Veterans with PTSD demonstrate amygdala hyperactivity while viewing threatening faces: a MEG study. *Biological Psychiatry* 2018;**132**:228-32.

Beck 1961

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Archives of General Psychiatry* 1961;**4**:561-71.

Beck 1988

Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety; psychometric properties. *Journal of Consulting and Clinical Psychology* 1988;**56**(6):893-7.

Belsher 2021

Belsher BE, Beech EH, Reddy MK, Smolenski DJ, Rauch SA, Kelber M, et al. Advances in repetitive transcranial magnetic stimulation for posttraumatic stress disorder: a systematic review. *Journal of Psychiatric Research* 2021;**138**:598-606.

Blake 1995

Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, et al. The development of a clinician-administered PTSD scale. *Journal of Traumatic Stress* 1995;**8**(1):75-90.

Brewin 2017

Brewin CR, Cloitre M, Hyland F, Shevlin M, Maercker A, Bryant RA, et al. A review of current evidence regarding the ICD-11 proposals for diagnosing PTSD and complex PTSD. *Clinical Psychology Review* 2017;**58**:1-15.

Buckholtz 2012

Buckholtz JW, Meyer-Lindenberg A. Psychopathology and the human connectome: toward a transdiagnostic model of risk for mental illness. *Neuron* 2012;**74**(6):990-1004.

Chang 2017

Chang B-H, Hoaglin DC. Meta-analysis of odds ratios: current good practices. *Medical Care* 2017;**55**(4):328-35.

Chen 1997

Chen R, Classen J, Gerloff C, Celnik P, Wasserman EM, Hallet M, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* 1997;**48**(5):1398-403.

Cirillo 2019

Cirillo P, Gold AK, Nardi AE, Ornelas AC, Nierenberg AA, Camprodon J, et al. Transcranial magnetic stimulation in anxiety and trauma-related disorders: a systematic review and meta-analysis. *Brain and Behavior* 2019;**9**(6):e01284.

Clark 2015

Clark C, Cole J, Winter C, Williams K, Grammer G. A review of transcranial magnetic stimulation as a treatment for post-traumatic stress disorder. *Current Psychiatry Reports* 2015;**17**(10):1-9.

Cocchi 2018

Cocchi L, Zalesky A. Personalized transcranial magnetic stimulation in psychiatry. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 2018;**3**(9):731-41.

Cohen 1988

Cohen J. Statistical Power Analysis in the Behavioral Sciences. 2nd edition. Hillsdale (NJ): Lawrence Erlbaum Associates, Inc, 1988.

Covidence [Computer program]

Veritas Health Innovation Covidence. Melbourne, Australia: Veritas Health Innovation. Available at covidence.org.

Deeks 2021

Deeks JJ, Higgins JP, Altman DG. Chapter 10: Analyzing data and undertaking meta-analysis. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34.

FDA 2009

US Department of Health and Human Services, Food and Drug Administration (FDA), Office of the Commissioner (OC), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH), Office of Good Clinical Practice (OGCP). Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection; January 2009. www.fda.gov/media/72267/download (accessed 9 December 2021).

Fitzgerald 2006

Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clinical Neurophysiology* 2006;**117**(12):2584-96.

Fox 2012

Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biological Psychiatry* 2012;**72**:595-603.

Fulton 2015

Fulton JJ, Calhoun PS, Wagner HR, Schry AR, Hair LP, Feeling N, et al. The prevalence of posttraumatic stress disorder in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans: a meta-analysis. *Journal of Anxiety Disorders* 2015;**31**:98-107.

George 2002

George MS, Nahas Z, Kozel FA, Li X, Denslow S, Yamanaka K, et al. Mechanisms and state of the art of transcranial magnetic stimulation. *Journal of ECT* 2002;**18**(4):170-81.

Goldstein 2016

Goldstein RB, Smith SM, Chou SP, Saha TD, Jung J, Zhang H, et al. The epidemiology of DSM-5 posttraumatic stress disorder in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *Social Psychiatry and Psychiatric Epidemiology* 2016;**51**:1137–48.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Version accessed 9 December 2021. Hamilton (ON): McMaster University (developed by Evidence Prime). Available at gradepro.org.

Hamilton 1960

Hamilton M. A rating scale for depression. *Journal of Neurology, Neuroscience, and Psychiatry* 1960;**23**:56-62.

Harbord 2006

Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;**25**:3443-57.

Higgins 2021a

Higgins JP, Eldridge S, Li T. Chapter 23: Including variants on randomized trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Higgins 2021b

Higgins JP, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Huang 2005

Huang Y-Z, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron* 2005;**45**(2):201-6.

Huerta 2009

Huerta PT, Volpe BT. Transcranial magnetic stimulation, synaptic plasticity and network oscillations. *Journal of Neuroengineering and Rehabilitation* 2009;**6**(1):1-10.

Hughes 2011

Hughes KC, Shin LM. Functional neuroimaging studies of post-traumatic stress disorder. *Expert Review of Neurotherapeutics* 2011;**11**(2):275-85.

Kan 2020

Kan RL, Zhang BB, Zhang JJ, Kranz GS. Non-invasive brain stimulation for posttraumatic stress disorder: a systematic review and meta-analysis. *Translational Psychiatry* 2020;**10**(1):1-12.

Keane 2007

Keane TM, Brief DJ, Pratt EM, Miller MW. Assessment of PTSD and its comorbidities in adults. In: Friedman MJ, Keane TM, Resick PA, editors(s). Handbook of PTSD: Science and Practice. 1st edition. New York (NY): The Guilford Press, 2007:279–305.

Klomjai 2015

Klomjai W, Katz R, Lackmy-Vallee A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Annals of Physical and Rehabilitation Medicine* 2015;**58**(4):208-13.

Koek 2019

Koek RJ, Roach J, Athanasiou N, van't Wout-Frank M, Phillip NS. Neuromodulatory treatments for post-traumatic stress disorder

(PTSD). *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2019;**92**:148-60.

Koenen 2017

Koenen KC, Ratanatharathorn A, Ng L, McLaughlin KA, Bromet EJ, Stein DJ, et al. Posttraumatic stress disorder in the World Mental Health Surveys. *Psychological Medicine* 2017;**47**(13):2260-74.

Kuss 2015

Kuss O. Statistical methods for meta-analyses including information from studies without any events - add nothing to nothing and succeed nevertheless. *Statistics in Medicine* 2015;**34**(7):1097-116.

Li 2021

Li T, Higgins JP, Deeks JJ. Chapter 5: Collecting data. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Memon 2021

Memon AM. Transcranial magnetic stimulation in treatment of adolescent attention deficit/hyperactivity disorder: a narrative review of literature. *Innovations in Clinical Neuroscience* 2021;**18**(1-3):43-6.

Milad 2009

Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, et al. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biological Psychiatry* 2009;**66**(12):1075-82.

Montgomery 1979

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* 1979;**134**:382-9. [DOI: 10.1192/bjp.134.4.382]

Page 2021

Page MJ, Higgins JP, Sterne JA. Chapter 13: Assessing risk of bias due to missing results in a synthesis. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Pascual-Leone 1994

Pascual-Leone A, Valss-Solé J, Wasserman EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain* 1994;**117**:847-58.

Pell 2011

Pell GS, Roth Y, Zangen A. Modulation of cortical excitability induced by repetitive transcranial magnetic stimulation: influence of timing and geometrical parameters and underlying mechanisms. *Progress in Neurobiology* 2011;**93**(1):59-98.

Philip 2018

Philip NS, Barredo J, van't Wout-Frank M, Tyrka AR, Price LH, Carpenter LL. Network mechanisms of clinical response to transcranial magnetic stimulation in posttraumatic stress disorder and major depressive disorder. *Biological Psychiatry* 2018;**83**(3):263-72.

Quirk 2006

Quirk GJ, Garcia R, González-Lima F. Prefrontal mechanisms in extinction of conditioned fear. *Biological Psychiatry* 2006;**60**(4):337-43.

Racine 1995

Racine RJ, Chapman CA, Trepel C, Teskey GC, Milgram NW. Post-activation potentiation in the neocortex. IV. Multiple sessions required for induction of long-term potentiation in the chronic preparation. *Brain Research* 1995;**702**(1-2):87-93.

Rauch 2000

Rauch SL, Whalen PJ, Shin LM, McInerney SC, Macklin ML, Lasko NB, et al. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biological Psychiatry* 2000;**47**(9):769-76.

Ressler 2007

Ressler KJ, Mayberg HS. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. *Nature Neuroscience* 2007;**10**(9):1116-24.

Review Manager 2020 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.4. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2020.

RevMan Web 2020 [Computer program]

The Cochrane Collaboration Review Manager Web (RevMan Web). Version 3.14.1. The Cochrane Collaboration, 2020. Available at revman.cochrane.org.

Rodriguez 2012

Rodriguez P, Holowka DW, Marx BP. Assessment of posttraumatic stress disorder-related functional impairment: a review. *Journal of Rehabilitation Research and Development* 2012;**49**(5):649-66.

Rossi 2004

Rossi S, Rossini PM. TMS in cognitive plasticity and the potential for rehabilitation. *Trends in Cognitive Sciences* 2004;**8**(6):273-9.

Rossi 2009

Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neuropsychology* 2009;**120**:2008-39.

Rossi 2021

Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmöller J, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues. Expert Guidelines. *Clinical Neuropsychology* 2021;**132**:269-306.

Rücker 2008

Rücker G, Schwarzer G, Carpenter J. Arcsine test for publication bias in meta-analyses with binary outcomes. *Statistics in Medicine* 2008;**27**:746-63.

Sareen 2014

Sareen J. Posttraumatic stress disorder in adults: impact, comorbidity, risk factors, and treatment. *Canadian Journal of Psychiatry* 2014;**59**(9):460-7.

SAS 2013 [Computer program]

SAS Institute, Inc SAS/STAT. Version 13.1. Cary (NC): SAS Institute, Inc, 2013.

Sathappan 2019

Sathappan AV, Luber BM, Lisanby SH. The Dynamic Duo: combining noninvasive brain stimulation with cognitive interventions. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2019;**89**(8):347-60.

Scheeringa 2011

Scheeringa MS, Zeanah CH, Cohen JA. PTSD in children and adolescents: toward an empirically based algorithm. *Depression and Anxiety* 2011;**28**:770-82.

Schünemann 2021

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Shin 2006

Shin LM, Rauch SL, Pitman RK. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Annals of the New York Academy of Sciences* 2006;**1071**(1):67-79.

Shiner 2018

Shiner B, Westgate CL, Gui J, Maguen S, Young-Xu Y, Schnurr PP, et al. A retrospective comparative effectiveness study of medications for posttraumatic stress disorder in routine practice. *Journal of Clinical Psychiatry* 2018;**79**(5):18m12145.

Solomon 1991

Solomon A, Bleich A, Koslowsky M, Kron S, Lerer B, Waysman M. Post-traumatic stress disorder: issues of co-morbidity. *Journal of Psychiatric Research* 1991;**25**(3):89-94.

Speer 2000

Speer AM, Kimbrell TA, Wassermann EM, Repella JD, Willis MW, Herscovitch P, et al. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. *Biological Psychiatry* 2000;**48**(12):1133-41.

Spielberger 1983

Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory. Palo Alto (CA): Consulting Psychologists Press, 1983.

Steenkamp 2015

Steenkamp MM, Litz BT, Hoge CW, Marmar CR. Psychotherapy for military-related PTSD: a review of randomized clinical trials. *JAMA* 2015;**314**(5):489-500.

Sterne 2011

Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**:d4002. [DOI: 10.1136/bmj.d4002]

Sterne 2019

Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898. [DOI: 10.1136/bmj.l4898]

VanElzakker 2014

VanElzakker MB, Dahlgren MK, Davis FC, Dubois S, Shin LM. From Pavlov to PTSD: the extinction of conditioned fear in rodents, humans, and anxiety disorders. *Neurobiology of Learning and Memory* 2014;**113**:3-18.

Varker 2020

Varker T, Kartal D, Watson L, Freijah I, O'Donnell M, Forbes D, et al. Defining response and nonresponse to posttraumatic stress disorder treatments: a systematic review. *Clinical Psychology Science and Practice* 2020;**27**(4):e12355.

Voelker 2018

Voelker, R. Brain stimulation approved for obsessive-compulsive disorder. *JAMA* 2018;**320**(11):1098. [DOI: 10.1001/jama.2018.13301]

Vogt 2017

Vogt D, Smith BN, Fox AB, Amoroso T, Taverna E, Schnurr PP. Consequences of PTSD for the work and family quality of life of female and male U.S. Afghanistan and Iraq War veterans. *Social Psychiatry and Psychiatric Epidemiology* 2017;**52**:341-52.

Wassermann 1998

Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section* 1998;**108**(1):1-16.

Weathers 1999

Weathers FW, Ruscio AM, Keane TM. Psychometric properties of nine scoring rules for the Clinican-Administered Posttraumatic Stress Disorder Scale. *Psychological Assessment* 1999;**11**:124-33.

Weathers 2013

Weathers FW, Litz BT, Keane TM, Palmieri PA, Marx BP, Schnurr PP. The PTSD Checklist for DSM-5 (PCL-5); 2013. www.ptsd.va.gov/professional/assessment/adult-sr/ptsd-checklist.asp (accessed prior to 27 December 2021).

WHO 1993

World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. 2nd edition. Geneva (Switzerland): World Health Organization, 1993.

WHO 1997

World Health Organization. Composite International Diagnostic Interview (CIDI) 2.1. Geneva, Switzerland: World Health Organization 1997.

Williams 2017

Williams LM. Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation. *Depression and Anxiety* 2017;**34**(1):9-24.

Ziemann 2008

Ziemann U, Paulus W, Nitsche MA, Pascual-Leone A, Byblow WD, Berardelli A, et al. Consensus: motor cortex plasticity protocols. *Brain Stimulation* 2008;**1**(3):164-82.

APPENDICES

Appendix 1. Ovid MEDLINE search

Ovid MEDLINE(R) ALL <1946 to July 13, 2021>

Search Strategy:

---

1 stress disorders, traumatic/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ (36209)

2 (PTSD or ((posttrauma* or post-trauma* or post trauma*) adj3 (stress* or disorder* or psych* or symptom?)) or acute stress disorder* or combat disorder* or war neuros*).ti,ab,kf. (43309)

3 1 or 2 (52925)

4 (transcrani* magnetic or TMS or rTMS or non-invasive brain stimulation* or noninvasive brain stimulation* or theta-burst* or thetaburst* or TBS).ti,ab,kf. (27145)

5 transcranial magnetic stimulation/ (12515)

6 4 or 5 (28486)

7 3 and 6 (172)

8 controlled clinical trial.pt. (94293)

9 randomized controlled trial.pt. (537579)

10 clinical trials as topic/ (196652)

11 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kf. (697218)

12 randomly.ti,ab,kf. (362387)

13 (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. (616169)

14 (placebo or sham).ab,ti,kf. (313435)

15 trial.ti. (243668)

16 (groups or (control* adj3 group*)).ab. (2447849)

17 ((control* or trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kf,hw. (42076)

18 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,kf. (182695)

19 double-blind method/ or random allocation/ or single-blind method/ (290621)

20 or/8-19 (3536103)

21 exp animals/ not humans.sh. (4861143)

22 20 not 21 (2994077)

23 7 and 22 (71)

****

CONTRIBUTIONS OF AUTHORS

RB drafted the initial version of the protocol. All authors contributed to the development of the protocol and agreed on the final text.

DECLARATIONS OF INTEREST

RB: no known conflict of interest.
KC: no known conflict of interest.
KJ: is the NIHR Network Support Fellow for the Cochrane Acute and Emergency Care Network, and previously for the Cochrane Mental Health and Neuroscience Network (2019 to 2021).
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