**Supplementary Materials to:**

Antidepressant efficacy of administering repetitive transcranial magnetic stimulation (rTMS) with psychological and other non-pharmacological methods: a scoping review and meta-analysis

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**Supplementary Table S1.** Search queries (up-to 10 July 2024).

|  |
| --- |
| PubMed:  (“transcranial magnetic stimulation"[Title/Abstract] OR TMS[Title/Abstract] OR rTMS[Title/Abstract] OR "repetitive transcranial magnetic stimulation"[Title/Abstract] OR "theta burst stimulation"[Title/Abstract] OR TBS[Title/Abstract] OR "intermittent theta burst stimulation"[Title/Abstract] OR iTBS[Title/Abstract] OR "continuous theta burst stimulation"[Title/Abstract] OR cTBS[Title/Abstract] OR "deep transcranial magnetic stimulation"[Title/Abstract] OR dTBS[Title/Abstract]) AND (depression[Title/Abstract] OR depressive[Title/Abstract] OR MDD[Title/Abstract] OR Treatment resistant depression[Title/Abstract] OR TRD[Title/Abstract]) |
| Web of Science; filters set to search titles and abstracts:  (“transcranial magnetic stimulation" OR TMS OR rTMS OR "repetitive transcranial magnetic stimulation" OR "theta burst stimulation" OR TBS OR "intermittent theta burst stimulation" OR iTBS OR "continuous theta burst stimulation" OR cTBS OR "deep transcranial magnetic stimulation" OR dTBS) AND (depression OR depressive OR MDD OR Treatment resistant depression OR TRD) |

## **Supplementary Table S2.** Checklist of the Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR)

| **SECTION** | **ITEM** | **PRISMA-ScR CHECKLIST ITEM** | **REPORTED ON PAGE #** |
| --- | --- | --- | --- |
| **TITLE** | | | |
| Title | 1 | Identify the report as a scoping review. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives. | 3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach. | 4-7 |
| Objectives | 4 | Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives. | 7-8 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number. | 8 |
| Eligibility criteria | 6 | Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale. | 8-9 |
| Information sources\* | 7 | Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed. | 9 |
| Search | 8 | Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated. | Supp. Table 1 |
| Selection of sources of evidence† | 9 | State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review. | 9-10 |
| Data charting process‡ | 10 | Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators. | 9-10 |
| Data items | 11 | List and define all variables for which data were sought and any assumptions and simplifications made. | 10 |
| Critical appraisal of individual sources of evidence§ | 12 | If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate). | n/a |
| Synthesis of results | 13 | Describe the methods of handling and summarizing the data that were charted. | 10-13 |
| **RESULTS** | | | |
| Selection of sources of evidence | 14 | Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram. | 13-14,  Figure 1 |
| Characteristics of sources of evidence | 15 | For each source of evidence, present characteristics for which data were charted and provide the citations. | 14 |
| Critical appraisal within sources of evidence | 16 | If done, present data on critical appraisal of included sources of evidence (see item 12). | n/a |
| Results of individual sources of evidence | 17 | For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives. | 15-24  (Table 1) |
| Synthesis of results | 18 | Summarize and/or present the charting results as they relate to the review questions and objectives. | 25-27 |
| **DISCUSSION** | | | |
| Summary of evidence | 19 | Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups. | 28-32 |
| Limitations | 20 | Discuss the limitations of the scoping review process. | 32-34 |
| Conclusions | 21 | Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps. | 34 |
| **FUNDING** | | | |
| Funding | 22 | Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review. | 35 |

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

\* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O’Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting*.*

§The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

*From:* Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. [doi: 10.7326/M18-0850](http://annals.org/aim/fullarticle/2700389/prisma-extension-scoping-reviews-prisma-scr-checklist-explanation).

**Supplementary Table S3.** Studies excluded during full-text screening.

|  |  |  |
| --- | --- | --- |
| **Motivation**  **for Exclusion** | **Study** | **Number**  **of studies** |
| rTMS did not include or was not concurrent with a psychological task or intervention | Adams et al., 2014; Adu et al., 2023; Albuquerque et al., 2018; Arns et al., 2012; Bech et al., 2014; Berlim et al., 2011; Bi et al., 2024; Borckardt et al., 2008; Bovy et al., 2019; Bröcker et al., 2019; Bruno et al., 2021; Charnsil et al., 2012; Chen et al., 2013; Chen et al., 2022a; Chen et al., 2022b; Concerto et al., 2015; Dai et al., 2023; Dan et al., 2023; Del Felice et al., 2016; Deschamps et al., 2016; Deschamps et al., 2018; Di Ponzio et al., 2023; Formánek et al., 2018; Frank et al., 2011; Frick et al., 2021; Fujita & Koga, 2005; Garg et al., 2016; Griffiths et al., 2022; Guinot et al., 2021; Hansen et al., 2004; Hausmann et al., 2004[a]; Hausmann et al., 2004[b]; Hermann et al., 2017; Hoflich et al., 1993; Hu et al., 2022; Huang et al., 2005; Huang et al., 2022a; Huang et al., 2022b; Iliceto et al., 2018; Iznak et al., 2015; Khedr et al., 2014; Kozel et al., 2018; Krstić et al., 2014; Krstić & Ilić, 2014; Kullakçi & Sonkaya, 2021; Langguth et al., 2007; Leblhuber et al., 2019; Leblhuber et al., 2021; Lee et al., 2019; Lee et al., 2016; Leong et al., 2020; Li et al., 2004; Li et al., 2010; Li et al., 2022a; Li et al., 2022b; Li et al., 2022c; Li et al., 2021a; Li et al., 2021b; Li et al., 2023; Lin et al., 2023; Liu et al., 2022; Liu et al., 2024; Majdi et al., 2021; Mansur et al., 2011; Mayer et al., 2021; Mogg et al., 2008; Mollica et al., 2024; Niimi et al., 2020a; Niimi et al., 2020b; Ning et al., 2022; Nongpiur et al., 2011; Norred et al., 2021; Novák et al., 2024;Oh & Kim, 2011; Padberg et al., 2002; Pantazatos et al., 2023; Picarelli et al., 2010; Plewnia et al., 2014; Prasser et al., 2015; Rapinesi et al., 2013; Rapinesi et al., 2016; Reddy et al., 2022; Rich et al., 2016; Richter et al., 2017; Rodriguez et al., 2020; Rossini et al., 2005; Rotharmel et al. 2021; Ryan et al., 2022; Sampson et al., 2011; Sarkhel et al., 2010; Senda et al., 2023; Seo et al., 2016; Schulze et al., 2016; Schutter et al., 2010; Sharma et al., 2020; Shere et al., 2021; Singh et al., 2020; Song et al., 2024; Spronk et al., 2008; Su et al., 2005; Sureshkumar et al., 2014; Tadayonnejad et al., 2022; Taib et al., 2019; Tan et al., 2015; Tang et al., 2022; Tavares et al., 2017; Tavares et al., 2020; Tavarez et al., 2021; Teti Mayer et al., 2021; Tilbor et al., 2024; Tong et al., 2021; Torres et al., 2015; Uygur et al., 2024; Vaithianathan et al., 2022; Verma et al., 2018; Vidya et al., 2022; Wang et al., 2022; Wobrock et al., 2015; Yagci et al., 2014; Yamazako et al., 2022; Yan et al., 2023; Yu et al., 2022; Yuan et al., 2020; Zangen et al., 2021; Zavorotnyy et al., 2020; Zendjidjian et al., 2014; Zhang et al., 2019; Zhang et al., 2020; Zhang et al., 2020; Zhang et al., 2021a; Zhang et al., 2021b | 131 |
| Is protocol, conference paper, book chapter without new data, secondary analysis, or abstract | Abou El-Magd et al., 2020; Adu et al., 2023; Bulteau et al., 2020; Canali et al., 2012; Dalhuisen et al., 2022; Davis et al., 2023; Demitrack et al., 2009; Ekpo et al., 2023; Haque & Malik, 2017; He et al., 2011[b]; Hill et al., 2021; Hu & Lisanby, 2015; Iseger et al., 2018; Jha et al., 2017; Jin et al., 2011; Kujovik et al., 2024; Lee et al., 2014; Lee et al., 2019; Lee et al., 2006; Lee et al., 2009; Leuchter et al., 2014; Leuchter & Hunger, 2016; Maslenikov et al., 2019; Oathes et al., 2022; Stikhina et al., 1999; Tang et al., 2018; Tynan et al., 2023; Uribe et al., 2020; Vaishnavi & Brammer, 2022; Walpoth et al., 2003; Wen et al., 2022 | 31 |
| Depressive symptom severity not assessed | Carmi et al., 2018; Chen et al., 2021; Rabey et al., 2013; Ross et al., 2018; Sokhadze et al., 2014 | 5 |
| rTMS was not applied | Canali et al., 2014; Kaneko et al., 2024; Lissemore et al., 2019; Ross et al., 2024; Salehinejad et al., 2022 | 5 |
| Specialized NIBS protocol (e.g., bilateral protocols or EEG-guided), but not combined with psychological task or intervention | Kavakbasi et al., 2024; Leuchter et al., 2014; Li et al., 2020; McDonald et al., 2006; Price et al., 2010; Robertson & Mortimer, 2022; Sreepada et al., 2020; Zrenner et al., 2020 | 8 |
| Healthy participants recruited only | Dalhuisen et al., 2023; Grosshageur et al., 2024 | 2 |
| Could not retrieve full text | Yin et al., 2022 | 1 |
|  | **Total:** | **183** |

### *References by Motivation for Exclusion*

***rTMS did not include or was not concurrent with a psychological task or intervention***

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***Healthy participants recruited only***

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## **Supplementary Table S4:** Stability of Pharmacological Treatments by Study

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Stable** | **Not Stable** | **Not Mentioned / Unclear** | **Relevant Quote from Each Study** |
| Barbini2021 | x |  |  | *All patients were on a stable and equivalent dose of antide- pressants for at least 4 weeks; were administered stable and equivalent doses of short-acting benzodiazepine hypnotics. BD patients were under stable dosage of lithium for at least 6 months (range 0.6–0.8 mEq/L).* |
| Bentwich2011 | x |  |  | *Exclusion criteria  - Patients with a history of epilepsy, severe agitation, lack of cooperation, unstable medical conditions, alcoholism and/or drug abuse, or regular use of ben- zodiazepines or other hypnotics (up until 2 weeks before the beginning of the study) were excluded from the study* |
| Caloc'h2023 |  |  | x |  |
| Cavallero2021 |  | x |  | *It was recommended that patients be maintained on their psychotropic medication regimen throughout their courses of TMS. Many of these patients also continued in ongoing psychotherapy with their community clinicians during their course of TMS and participation in this study. [...] The MT was established at the beginning of a treatment course and rechecked as needed to address tolerability or if there were changes to medications.* |
| Donse2018 |  |  | x |  |
| Duan2023 | x |  |  | *Patients taking 5-hydroxytryptamine reuptake inhibitors (SSRIs) were permitted to participate if the drug had been taken for at least three months before the commencement of the study and the dosage had remained steady for the preceding 60 days.* |
| Eichhammer2002 | x |  |  | *Antidepressant pharmacotherapy was kept stable for at least one week prior to the begin of the study and remained unchanged during the study period* |
| Fryml2019 | x |  |  | *Exclusion criteria included prior or current psychosis, substantial substance abuse, prior head trauma, seizures, metal in or near their head, unstable medical comorbidities, or currently taking medications known to lower seizure threshold (eg, methylphenidate, bupropion) or benzodiaze- pines (may block activation of the anxiety circuit during exposure therapy). Patients enrolled as subjects in the trial were allowed to remain on their current medications but were required to be fixed and stable for the 2-month trial.* |
| Isserles2011 | x |  |  | *Patients were enrolled after a period of at least 4 weeks of stable antidepressant treatment. During the study no change was made in antidepressant treatment and only limited use of hypnotic or anxiolytic medication was allowed (up to of 2 mg/day lorazepam or equivalent) for treatment-emergent insomnia or anxiety.* |
| Kreuzer2012 | x |  |  | *Another potential confounding factor may have been the concomitant antidepressant medication, which was kept stable for at least 1 week before conduction of SD and rTMS treatment. However, as most antidepressants exert their mood elevating effects after 2 or even more weeks of intake, medication effects may have influenced study results. A longer period of stable medication may have been desirable, but would have made patient recruitment under inpatient conditions extremely difficult.* |
| Li2016 | x |  |  | *To minimize medication effects, a wash-out period was requested so that all the recruited subjects were free from all medication for at least 1 week before the experiment. None of the recruited patient used fluoxetine, so the predefined wash-out period could assure that neurocognitive and functional neuro-electrical signals were not influenced by the concurrent use of medications* |
| ManiaKaur2019 |  |  | x |  |
| Martinotti2022 |  | x |  | *They were asked to avoid alcohol and caffeine consumption in the 12 h preceding TMS administration but to continue taking their regular doses of prescribed medications unless otherwise instructed by a physician […] participants continued to use psychoactive medications during the study, which could have had a confounding effect on our outcome measure and may have limited rTMS efficacy. It should be noted, however, that a recent review by the authors did not find effects of psychotropics on cortical excitability (Martinotti et al., 2019)  Previous pharmacological treatments were continued as prescribed.* |
| Neacsiu2018 | x |  |  | *participants were medically cleared by a psychiatrist to receive treatment with rTMS. Four participants were not cur- rently taking any psychotropic medications. One participant was on a stable dose of levomilnacipran for depression and was taking clonazepam as needed for anxiety* |
| Osuch2009 | x |  |  | *They were on constant levels of antidepressant and/or benzodiazepine medications. A medication-free condition was avoided to reduce the risk of a confounding period of potential symptom exacerba- tion, with clinical deterioration that could have prohibited study participation.* |
| Ross2023 | x |  |  | *Participants were either not taking antidepressant medication or were able to continue their prescribed, stable (same dosage for previous 4 weeks prior to enrollment) dose at enrollment through the study period* |
| Russo2018 |  |  | x |  |
| Thierree2022 |  | x |  | *Randomization was stratified on the use of selective-serotonin reuptake inhibitors (SSRI) at inclusion* |
| VanDerwerker2018 | x |  |  | *Inclusion criteria […] not taking antidepressant medication or able to continue the currently prescribed dose throughout the study* |
| Vedeniapin2010 | x |  |  | *Her current medication was tranylcyprimine 30 mg daily. The medication and the dose were not changed over a period of the last 6 months before beginning this TMS course* |

# **Supplementary Text**

## **Supplementary Text 1.** ***Effect sizes based on change scores of within-group and between-group comparisons***

Most included studies measured depression severity with standardized scales to assess the effects of active or sham combinations of rTMS with psychological method (e.g., psychotherapy, bright light therapy, psychophysical tasks), and reported the baseline and immediate endpoint means, standard deviations, and sample sizes.

To compute effect sizes, we used custom scripts written in Python (version 3.11.5) with NumPy and panda libraries in a Jupyter Notebook environment. We computed standardized mean differences of change scores for individual study comparisons:

|  |  |
| --- | --- |
|  | [Equation 1] |

Where is standardized mean difference (Cohen’s d), is the average change score for the active group and is the average change score for the control group (or for within-group comparisons, the baseline average change scores is subtracted from the endpoint average change scores), and is the pooled standard deviation of the change scores from both groups (or just one group for within-group comparisons) (Higgins et al., 2019). We then converted this estimate to Hedges’ g to correct for potential bias due to small sample sizes (Hedges et al., 1981):

|  |  |
| --- | --- |
| ) | [Equation 2] |

Where *J* is the bias correction factor, and *df* is the degrees of freedom, which equals n-1 for within-group comparisons and n1+n2-2 for between group comparisons (Hedges et al., 1981).

### *Controlled Effect Sizes*

This extracted data was used to compute the standardize mean differences (SMDs) of change scores for two groups being compared (e.g., active combination treatments – sham combination treatments). Below is pseudocode of the equations ran in custom python scripts; used after importing *numpy* and *pandas* libraries.

|  |
| --- |
| Function name: “calculate\_controlledEffectSizes”  Required input:  active\_premeans, active\_preSD, active\_postmeans, active\_postSD, active\_n  sham\_premeans, sham\_preSD, sham\_postmeans, sham\_postSD, sham\_n  prepost\_r  Mean score changes:  ChangeScore\_active = active\_postmeans - active\_premeans  ChangeScore\_sham = sham\_postmeans - sham\_premeans    Difference in mean score changes:  ChangeScore\_diff = ChangeScore\_active - ChangeScore\_sham  Standard deviations of the above mean score changes:  SD\_ChangeScore\_active = sqrt(active\_preSD^2 + active\_postSD^2 - 2 \* prepost\_r \* active\_preSD \* active\_postSD)  SD\_ChangeScore\_active = sqrt(sham\_preSD^2 + sham\_postSD^2 - 2 \* prepost\_r \* sham\_preSD \* sham\_postSD)  Pooled standard deviation of the changes:  pooled\_SD = sqrt(((active\_n - 1) \* SDChange\_active^2 + (sham\_n - 1) \* SDChange\_sham^2) / (active\_n + sham\_n - 2))  Standardized difference in means (Cohen’s d):  SMD = ChangeScore\_diff / pooled\_SD  Standard error of the standardized difference:  SMD\_SE = sqrt(1 / active\_n + 1 / sham\_n + SMD ^2 / (2 \* (active\_n + sham\_n)))    Return effect size (SMD = Cohen’s d) and its standard error. |

These SMDs were then converted to Hedges’ g with the correction factor:

|  |
| --- |
| Function name: “SMD\_to\_g”  Required input:  SMD, SMD\_SE, active\_n, sham\_n    Degrees of freedom and correction factor (J):  df = active\_n + sham\_n - 2  J = 1 - (3 / (4 \* df - 1))  Hedges’ g and its standard error:  g = SMD \* J  g\_SE = SMD\_SE \* J    Return corrected effect size (Hedges’ g) and its standard error. |

### *Uncontrolled Effect Sizes*

Effect sizes of active combinations of rTMS with psychological methods were also pooled.

|  |
| --- |
| Function name: “calculate\_wg\_hedgesg” # “wg” dis-abbreviates to ‘within group’  Required input:  baseline\_mean, baseline\_sd, endpoint\_mean, endpoint\_sd, prepost\_r, n  Within-group mean differences  wg\_diff = endpoint\_mean - baseline\_mean  wg\_diff\_sd = sqrt(baseline\_sd ^2 + endpoint\_sd ^2 - 2 \* prepost\_r \* baseline\_sd \* endpoint\_sd)  wg\_diff\_se = wg\_diff\_sd / sqrt(n)    Standardized mean difference (SMD)  wg\_SMD = wg\_diff / (wg\_diff\_sd / sqrt(2 \* (1 - prepost\_r)))  wg\_SMD\_se = sqrt((1 / n) + (wg\_SMD^2 / (2 \* n))) \* sqrt(2 \* (1 - prepost\_r))    Corrected SMD (g)  df = n - 1  j = 1 - (3 / (4 \* df - 1))  wg\_g = wg\_SMD \* j  wg\_g\_SE = wg\_SMD\_se \* j    Return corrected effect size (Hedges' g) and its standard error. |

### *Special Cases*

Few included studies did not provide means or standard deviations, or reported SMDs. These were handled case-by-case.

Two included studies (Osuch et al., 2009, J Anxiety Disord; Ross et al., 2023, Top Stroke Rehabil) provided the within-group SMD (Cohen’s d) of their findings. The correction factor was applied to SMD to estimate Hedges’ g.

|  |
| --- |
| Corrected SMD (g)  df = n - 1  j = 1 - (3 / (4 \* df - 1))  g = SMD \* j  g\_SE = SMD\_se \* j    Return corrected effect size (Hedges' g) and its standard error. |

One included study (Fryml et al., 2019, J ECT) reported the interaction F-statistic of time x treatment. We used the sample sizes for each group and the reported F-statistic to compute the SMD and its standard error, which was subsequently converted to Hedges’ g, as above.

|  |
| --- |
| SMD = sqrt(F \* ((n1 + n2) / (n1 \* n2)))  SMD\_se = sqrt((1 / n1) + (1 / n2) + (SMD^2 / (2 \* (n1 + n2)))) |

## **Supplementary Text 2. *Meta-analysis results of depression change scores across disorders***

Pooled study effects were substantially heterogeneous (Q(df = 3) = 46.00, p < 0.01, I² = 90.22%). Leave-one-out sensitivity tests indicated a poor reliability of the estimate, with g ranging between -0.32 to +0.44 (each iteration remained non-significant). The funnel plot appeared symmetric, indicating unlikely publication bias.

**Supplementary Figure 1.** Four studies compared groups receiving [active rTMS + active PSYC] versus [active rTMS + sham PSYC]. The figures below show the forest and funnel plots for this analysis and discussed in the main text.

## **Supplementary Text 3: *Secondary meta-analysis: left DLPFC treatment for depressive disorders***

**Supplementary Figure 2.** Within-group comparisons of [active rTMS + active PSYC] at endpoint minus baseline change scores included 14 studies (16 datasets) where the left DLPFC of patients with depressive conditions was targeted. The figures below show the forest and funnel plots for this analysis and discussed in the main text.

**Supplementary Figure 3.** Five studies compared [active rTMS + active PSYC] versus [sham rTMS + active PSYC] and targeted the left DLPFC of patients with depressive conditions.

## **Supplementary Text 4: *Power analysis methods and results***

To estimate the sample size needed to obtain sufficient power (β=0.80, given ⍺=0.05) to investigate the hypothesis that combining rTMS with PSYC is a superior treatment (compared to sham conditions), we used the results of representative studies in simulation-based power analyses. The extracted results were the average change scores per group. The simulated analysis was basic and reflects published work (Li et al., 2016, Cerebral Cortex): a one-way ANOVA with four groups (both active treatments group, active rTMS with sham PSYC, sham rTMS with active PSYC, and both sham treatments group); the dependent variable was change scores randomly sampled from a normal distribution with mean and standard deviation imputed from efficacy data reported in included studies. If the ANOVA was significant, Tukey's Honest Significant Difference (HSD) post hoc test was conducted to compare pairwise differences among treatment groups, while controlling for multiple comparisons within a simulation. The custom Python script counted the frequency that "both active" group was significantly better than the other groups, reflecting the definition of power and investigating the research hypothesis that active combinations were significantly better than all other treatments.

Simulations assumed a set of sample sizes ranging from 4 (one patient per group) to 240 (60 patients per group), with 10,000 iterations for each sample size. This analysis assumes a normal distribution of change scores and independence among observations. Power was formulated as follows, representing the probability of correctly rejecting the null hypothesis when it is false:

|  |  |
| --- | --- |
|  | [Equation 3] |

Average change scores reported by Li et al. (2016) were imputed for the following groups: [active rTMS + active PSYC], [active rTMS + sham PSYC], and [sham rTMS + active PSYC]. Li et al.’s study was selected as these authors included two active comparators and their findings supported the hypothesis that combining rTMS with PSYC improved antidepressant efficacy over either alone. However, Li et al. did not include a [sham rTMS + sham PSYC] group; we imputed average change scores for this group from Duan et al. (2023), as these authors used the same standardized assessment (17-item Hamilton Depression Rating Scale), treated patients diagnosed with MDD, and combined sham rTMS with a control for active PSYC.

Results are shown in **Supplementary Figure 4**. This large difference in sample size requirement for sufficient power is due to the small difference in average change scores between the [active rTMS + active PSYC] and [active rTMS + sham PSYC] groups

**Supplementary Figure 4.** Curve with Circle-Shaped Points. Power analysis for testing the hypothesis that [active rTMS + active PSYC] was significantly better than [sham rTMS + active PSYC] and [sham rTMS + sham PSYC], but not compared to [active rTMS + sham PSYC]. The figure below also shows the threshold to achieve 80% power; the table below the figure shows values corresponding to specific sample sizes. Alpha is 0.05. Curve with Square-Shaped Points. Power analysis for testing the hypothesis that the both active treatment is better than all active and sham comparators (including [active rTMS + sham PSYC]).

The following table shows the results in **Supplementary Figure 4**.

|  |  |  |  |
| --- | --- | --- | --- |
| **Sample Size for Both active - both sham** | **Power (%) (Both active - both sham)** | **Sample Size for Both active - [active rTMS + sham PSYC]** | **Power (%) (Both active - [active rTMS + sham PSYC])** |
| 4 | 10.05 | 4 | 1.95 |
| 8 | 30.12 | 20 | 7.63 |
| 12 | 50.54 | 80 | 29.74 |
| 16 | 69.87 | 140 | 51.38 |
| 20 | 81.88 | 200 | 69.16 |
| 24 | 89.85 | 260 | 81.93 |
| 32 | 97.25 | 320 | 89.74 |
| 40 | 99.34 |  |  |

## **Supplementary Text 5: *Major Depressive Disorder (MDD) Focused Analysis***

The number of studies that strictly recruited patients with MDD was low, allowing for a meta-analysis of nine uncontrolled trials: [active rTMS + active PSYC] endpoint versus baseline scores.

**Supplementary Figure 5.** Within-group comparisons of [active rTMS + active PSYC] at endpoint minus baseline change scores included 9 studies where patients were diagnosed with major depressive disorder (MDD) and without comorbidities. The figures show the forest and funnel plots for these results. The effect size is large and significantly therapeutic, comparable to the transdiagnostic meta-analysis in Supplementary Figure 4.