Title: Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: A systematic review and meta-analysis of randomised sham-controlled trials

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Abstract

We examined the efficacy and acceptability of non-invasive brain stimulation in adult unipolar and bipolar depression. Randomised sham-controlled trials of transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS) and theta-burst stimulation (TBS), without co-initiation of another treatment, were included. We analysed effects on response, remission, all-cause discontinuation rates and continuous depression severity measures. Fifty-six studies met our criteria for inclusion (N = 3,058, mean age = 44.96 years, 61.73% female). Response rates demonstrated efficacy of high-frequency rTMS over the left DLPFC (OR = 3.75, 95% CI [2.44; 5.75]), right-sided low-frequency rTMS (OR = 7.44, 95%CI [2.06; 26.83]) bilateral rTMS (OR = 3.68,95%CI [1.66; 8.13]), deep TMS (OR = 1.69, 95%CI [1.003; 2.85]), intermittent TBS (OR = 4.70, 95%CI [1.14; 19.38]) and tDCS (OR = 4.17, 95% CI [2.25; 7.74]); but not for continuous TBS, bilateral TBS or synchronised TMS. There were no differences in all-cause discontinuation rates. The strongest evidence was for high-frequency rTMS over the left DLPFC. Intermittent TBS provides an advance in terms of reduced treatment duration. tDCS is a potential treatment for non-treatment resistant depression. To date, there is not sufficient published data available to draw firm conclusions about the efficacy and acceptability of TBS and sTMS.

Keywords: transcranial magnetic stimulation, theta burst stimulation, transcranial direct current stimulation, depression, meta-analysis, brain stimulation, systematic review

Highlights

- Response, remission, all-cause discontinuation rates and continuous post-treatment depression scores were examined
- Several non-invasive brain stimulation treatments seem efficacious across different outcome metrics
- All-cause discontinuation rates indicate no differences between sham and active treatment

Introduction

Major depression is prevalent[1] and associated with considerable disease burden[2]. Its course is often recurrent and may become chronic with relapse rates within one year of remission ranging from 35% to 80%[3,4]. The most common treatments are pharmacological and psychological therapies. Yet, even with a full course of treatment, at least one third of patients fail to achieve remission[5]. Non-invasive neurostimulation therapies, such as transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES), offer a potential alternative or add-on treatment strategy.

TMS was originally introduced as a tool for investigating and mapping cortical functions and connectivity[6]. TMS utilises intense, rapidly-changing electromagnetic fields generated by a coil of wire near the scalp and allows for a mostly undistorted induction of an electrical current to alter neural activity in relatively focal, superficial areas of the brain. Standard TMS involves single or paired pulses, while repetitive transcranial magnetic stimulation (rTMS) involves the delivery of repeated pulses which enable the prolonged modulation of neural activity. Depending on the stimulation frequency, rTMS can increase or decrease cortical excitability. The prevailing hypothesis is that the aftereffects of high-frequency (usually 10Hz or higher) stimulation are excitatory while those of low-frequency (≤1Hz) stimulation are inhibitory[7].

The rationale for using rTMS to treat depressive illness comes from clinical symptomatology and neuroanatomy as well as neuroimaging studies indicating functional impairments in prefrontal cortical and limbic regions[8]. In 2008, the US Food and Drug Administration (FDA) approved the first rTMS device for the treatment major depressive disorder (MDD) in which there was poor response to at least one pharmacological agent in the current episode[9], and its clinical utilisation has increased since[10].

As stimulation at high frequencies can be uncomfortable during the initial stimulation period, low-frequency rTMS may minimise the occurrence of undesired side effects, namely headaches and scalp discomfort, and may be associated with fewer adverse events, for instance by lowering the risk for developing seizures[11].

Bilateral applications of rTMS have also been developed: simultaneous stimulation over the left and right DLPFC (rDLPFC) or stimulation over one side followed by stimulation of the other side. These applications were hypothesised to be potentially additive or synergistic to reinstate any imbalance in prefrontal neural activity[12]. Moreover, there may be a selective unilateral response and the likelihood for a clinical response may increase by providing both types of stimulation[13].

Technical and methodological efforts to improve the antidepressant efficacy of TMS have led to several alternative treatment protocols. Deep TMS (dTMS) was FDA-approved in 2013, which is able to stimulate larger brain volumes and deeper structures[14] that could be more directly relevant in the pathophysiology of depression (e.g., reward-mediating pathways and areas connected to the subgenual cingulate cortex)[8,15,16].

Another recent modification is theta burst stimulation (TBS)[17], which is a patterned form of TMS pulse delivery that utilises high and low frequencies in the same stimulus train. TBS delivers bursts of three at a high frequency (50Hz) with an inter-burst interval of 5Hz in the theta range at 5Hz. Two different protocols are utilised: continuous theta burst stimulation (cTBS), which delivers 300 or 600 pulses without interruption, and intermittent theta burst stimulation (iTBS), which delivers 30 pulses every 10 seconds for a duration of 190 seconds, totalling 600 pulses[18]. It is suggested that cTBS reduces cortical excitability while iTBS increases it, mimicking the processes of long-term potentiation and long-term depression, respectively[17]. Notably, there is some debate as to whether prolonged stimulation periods reverse the hypothesised effects of TBS[19], while there is also support for a dose-response relationship for iTBS[20].

The main advantages of TBS are its reduced administration time, which is typically less than five minutes as opposed to 20–45 minutes for conventional rTMS, and the lower intensity needed to produce lasting neurophysiological effects as TBS is typically administered at 80% of the resting motor threshold (rMT) and might be more comfortable than stimulation at higher intensities typically used with standard rTMS.

Synchronised TMS refers to magnetic low-field synchronised stimulation (sTMS), a new treatment paradigm that involves rotating spherical rare-earth (neodymium) magnets positioned sagittally along the midline of the scalp, which deliver stimulation synchronised to an individual's alpha frequency[21]. The magnets are positioned to provide a global magnetic field distributed broadly across the midline cortical surface (one magnet over the frontal polar region, one magnet over the top of the head, and one magnet over the parietal region). The rationale for sTMS synchronised to an individual's alpha frequency is the observation that one mechanism of action of rTMS is the entrainment of oscillatory activity to the programmed frequency of stimulation, thereby resetting thalamo-cortical oscillators and restoring normal endogenous oscillatory activity[22]. This modification of TMS may be associated with fewer treatment-emergent adverse and side effects because it does not cause neural depolarisation. It also uses less energy than conventional rTMS as it utilises sinusoidal instead of pulsed magnetic fields, which require less than 1% of the energy needed for conventional rTMS and may thus be less expensive.

Access and costs are among the major impediments to a more widespread use of rTMS, although costs may be lower for TBS and sTMS. A less expensive technique is transcranial electrical stimulation (tES). Its most commonly used protocol, transcranial direct current stimulation (tDCS), was reappraised as a tool in research through the work of Priori et al.[23] and Nitsche and Paulus[24]. tDCS involves the application of a low-amplitude electrical direct current through surface scalp electrodes to superficial areas of the brain. While it does not directly trigger action potentials, it modulates cortical excitability by shifting the neural membrane resting potential and these effects can outlast the electrical stimulation period[25]. The direction of such excitability changes may depend on the polarity of the stimulation: anodal stimulation is hypothesised to cause depolarisation and an increase in neural excitability, whereas cathodal stimulation causes hyperpolarisation and a decrease in cortical excitability[26,27].

The advantages of tDCS compared to TMS include its ease of administration, being much less expensive, its more benign side effect profile, and its portability which could potentially be used in the home environment[28].

We sought to perform a systematic review and meta-analysis of the antidepressant efficacy and acceptability of non-invasive neuromodulation in treating a current depressive episode in unipolar and bipolar depression from randomised sham-controlled trials. The only study to date that evaluated the efficacy of a range of rTMS techniques is Brunoni et al.'s network meta-analysis[29]. However, the analysis had included trials that had co-initiated other treatments (e.g. sleep deprivation and TMS); trials which had not included a sham treatment; had not separated the TBS modifications; and had not included any age-related exclusion criteria. Also, tDCS trials were not included in that meta-analysis. We sought to address these limitations by including only trials with randomised allocation to active or sham treatments, excluding studies which had co-initiated another treatment, and limiting our sample to the adult age range as geriatric depression may impact on efficacy.

Materials and Methods

Search strategy and selection criteria

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[30]. A systematic search of the Embase, Medline, and PsycINFO databases was performed from the first date available to 1st May 2018 (Figure 1). The following search terms were used: (bipolar disorder OR bipolar depression OR major depression OR unipolar depression OR unipolar disorder) AND (transcranial direct current stimulation OR tDCS OR transcranial magnetic stimulation OR TMS OR theta burst stimulation OR TBS OR sTMS OR dTMS), limiting searches to studies in humans and English-language publications. Reference lists of included papers and of recent systematic reviews and meta-analyses (Supplementary Material 1) were screened for further studies. This study has not been previously registered.

Inclusion criteria were: 1) adults aged 18 – 70 years; 2) DSM or ICD diagnosis of MDD or bipolar disorder currently in a major depressive episode; 3) randomised sham-controlled trials, which utilised a parallel-group or cross-over design; 4) clinician-administered depression rating scale, Hamilton Depression Rating Scale (HDRS)[31] or Montgomery-Åsberg Depression Rating Scale (MADRS)[32].

Exclusion criteria were: 1) primary diagnoses other than MDD or bipolar depression; 2) studies limited to a specific subtype of depression (e.g., postpartum depression or vascular depression) or in which a major depressive episode was a secondary diagnosis (e.g., fibromyalgia and major depression); 3) co-initiation of any other form of treatment, such as pharmacotherapy or cognitive control training.

Data analysis

The following sample characteristics were extracted: sex, age, hospitalisation status, whether patients with psychotic symptoms were excluded from the study, diagnosis, treatment strategy, and treatment resistance.

The following treatment-related parameters were extracted. For TMS: type of coil and sham procedure, coil location, stimulation frequency (Hz) for each site, stimulation intensity (percentage of the rMT), total number of pulses delivered, and number of treatment sessions. For TBS: data on the treatment protocol (iTBS, cTBS or bilateral TBS) were also recorded. For tDCS: location of the anode and cathode, electrode size (cm^2), current intensity (mA) and density (mA/cm^2), session duration, number of sessions, and duration of active stimulation in the sham condition.

The primary outcome measure was clinical response, defined as a ≥ 50% reduction in symptom scores at the primary study endpoint. Remission rates were the secondary outcome measure based on the definition provided by each study. If response or remission rates were reported for both HDRS and MADRS, data for the HDRS were selected to facilitate comparability between trials. If data for multiple versions of the HDRS were reported, the original 17-item version was selected. We also extracted baseline and post-treatment depression severity scores; the latter constituted our tertiary outcome measure. If available, the intention-to-treat (ITT) or modified intention-to-treat (mITT) data were preferred over data based only on completers. For cross-over trials, only data from the initial randomisation were used to avoid carry-over effects. Data presented in figures were extracted with

WebPlotDigitizer (http://arohatgi.info/WebPlotDigitizer/app/). All-cause discontinuation rates were recorded separately for active and sham groups and were treated as a primary outcome measure of acceptability.

Data that could not be directly retrieved from the original publications were requested from the authors or searched for in previous systematic reviews and meta-analyses. For trials with more than two groups that could not be included as separate treatment comparisons, we combined groups to create single pair-wise comparisons.

For dichotomous outcome data, odds ratios (Mantel-Haenszel method) were used as an index of effect size. We also computed Hedge's *g* to estimate the effect sizes for continuous post-treatment depression scores. A random-effects model was chosen as it was assumed that the underlying true effect size would vary between studies. A random-effects model provides wider confidence intervals than a fixed-effects model if there is significant heterogeneity among studies and thus tends to be more conservative in estimating summary effect sizes.

Contour-enhanced funnel plots[33] were visually inspected to assess whether potential funnel asymmetry is likely to be due to statistical significance-based publication bias.

Heterogeneity between studies was assessed with the Q_T statistic, which estimates whether the variance of effect sizes is greater than what would be expected due to sampling error. A p value smaller than .01 provides an indication for significant heterogeneity[34]. The I^2 statistic was computed for each analysis to provide a descriptive measure of inconsistency across the results of individual trials included in our analyses. It provides an indication of what percentage of the observed variance in effect sizes reflects real differences in effect sizes as opposed to sampling error. Higgins et al.[35] suggested that 25%, 50%, and 75% represent little, moderate, and high heterogeneity, respectively.

Where sufficient data were available, we conducted subgroup analyses to examine potential differences in antidepressant efficacy by clinical and study characteristics including diagnosis, whether the trial excluded patients with psychotic symptoms, hospitalization status and treatment resistance.

Analyses were conducted using the 'meta' package[36] for RStudio (Version 0.98.932) and STATA (Version 13.1; StataCorp, 2013) was used for data processing.

The Cochrane tool for assessing risk of bias in randomised trials[37] was used to evaluate included studies. Each trial received a score of low, high, or unclear risk of bias for each of the potential sources of bias. Two raters independently conducted the assessment of risk of bias.

Results

Overview

Fifty-six RCTs, consisting of 131 treatment arms met our criteria for inclusion (Figure 1, Supplementary Material 2). Overall, 66 treatment comparisons were included, total $N = 3{,}058$ patients (mean age = 44.96 years, 61.73% female) of whom $n = 1{,}598$ were randomised to active and $n = 1{,}460$ to sham treatments (Tables 1-4).

Visual inspection of the contour-enhanced funnel plots did not suggest small study effects (Figure 2; Supplementary Material 3). However, due to the small number of studies for treatment modalities other than left-sided high-frequency rTMS and tDCS, these need to be interpreted with caution. The results of our risk of bias assessment are presented in Supplementary Material 4.

Response and remission rates

Sixty-two comparisons of experimental and sham treatment arms met the inclusion criteria for the meta-analysis of response rates (Table 5; Figure 3), and 50 treatment comparisons for the meta-analysis of remission rates (Table 6; Figure 4).

High-frequency rTMS over the left DLPFC (lDLPFC) was associated with improved rates of response as well as remission in comparison with sham treatment. The odds ratio of response was OR = 3.75 compared to sham (k = 32, 95% CI [2.44; 5.75]). There was little evidence that the heterogeneity between trials exceeded that expected by chance (I^2 = 26.1%; Q_{31}= 41.96, p = .09). Sensitivity analyses suggested similar effect sizes in trials that had recruited patients with unipolar depression only and those that had recruited both patients with unipolar and bipolar depression (Supplementary Figure 3a).Only one pilot study[38] had recruited patients with bipolar depression only, but provided no support for antidepressant efficacy (OR = 1.14, 95% CI [0.21; 6.37]). Response rates were greater in trials that (i) excluded patients with psychotic features, (ii) recruited outpatients only, and (iii) recruited either treatment resistant patients only or both treatment resistant patients and those that were not treatment resistant (Supplementary Figures 3b-3d).

The odds of achieving remission were over twice that of sham (k = 26, OR = 2.51, 95% CI [1.62; 3.89]). There was no evidence for significant heterogeneity (I^2 = 1.4%; Q_{25} = 22.35, p = .44). Sensitivity analyses for remission rates were in line with those for response rates, although we did not find left-sided high-frequency rTMS to be effective in samples that had recruited both treatment resistant and non-treatment resistant patients (Supplementary Figures 6a-6d).

Low-frequency rTMS over the rDLPFC was also associated with significantly greater response and remission rates than sham stimulation. There was a sevenfold improvement in response rates compared to sham (k = 3, OR= 7.44 (95% CI [2.06; 26.83]), with no indication for significant heterogeneity between trials (I^2 = 0.0%; Q_2= 1.59, p = .45). No sensitivity analyses were conducted due to the small number of treatment comparisons.

The odds of remission were greater than those of sham (k = 2, OR = 14.10 (95% CI [2.79; 71.42]). Heterogeneity between trials was not greater than expected due to sampling error (I^2 = 0.0%; Q_1 = 0.50, p = .48). No sensitivity analyses were conducted due to the small number of treatment comparisons.

Low-frequency rTMS over the lDLPFC was not associated with any significant improvements in rates of response or remission. There were no significant differences in response rates compared to sham (k = 3, OR = 1.41, 95% CI [0.15; 12.88]). The heterogeneity between trials did not exceed that expected by chance (I^2 = 0.0%; Q_2 = 0.14, p = .93), and no sensitivity analyses were conducted due to the small number of treatment comparisons. There were no significant differences in remission rates compared to sham (k = 3, OR = 0.86, 95% CI [0.08; 9.11]). The variance in effect sizes between trials was no greater than expected due to sampling error (I^2 = 0.0%; Q_2 = 0.03, p = .98). No sensitivity analyses were conducted due to the small number of treatment comparisons.

Bilateral rTMS was associated with significant improvement in response but not remission rates compared to sham. There was a significant improvement in response rates compared to sham (k = 6, OR = 3.68 (95% CI [1.66; 8.13]), and the variance in effect sizes between trials did not exceed that expected due to sampling error (I^2 = 0.0%; Q_5 = 3.45, p = .63). Sensitivity analyses suggested subgroup differences according to whether trials had excluded psychotic patients or had recruited patients with diagnosis of MDD only, bipolar depression only, or both MDD and bipolar depression (Supplementary Figures 4a,4b).We found no evidence for a significant improvement in rates of remission associated with bilateral TMS compared to sham (k = 5, OR = 3.05, 95% CI [0.87; 10.67]). There was no evidence for significant heterogeneity between trials (I^2 = 10.7%; Q_4 = 4.48, p = .34), and sensitivity analyses suggested no differences according to any patient characteristics tested (Supplementary Figures 7a,7b).

There were significant improvements in both response and remission rates for dTMS compared to sham. The response rates were marginally higher while statistically significant for dTMS relative to sham (k =2, OR = 1.69, 95% CI [1.003; 2.85]). The variance in effect sizes between trials did not exceed that expected due to sampling error (I^2 = 0.0%; Q_1 = 0.97, p = .33). No sensitivity analyses were conducted due to the small number of treatment comparisons. The remission rates were greater for dTMS compared to sham (k = 2, OR = 2.24, 95% CI [1.24; 4.06]). There was no evidence for significant heterogeneity between trials (I^2 = 0.0%; Q_1 = 0.02, p = 0.88), and no sensitivity analyses were conducted due to the small number of treatment comparisons.

Neither response nor remission rates for sTMS were significantly higher than for sham. There was no evidence for increased response rates compared to sham (k = 2, OR = 2.71, 95% CI [0.44; 16.86]). There was significant heterogeneity between these two studies (I^2 = 75.9%; Q_1= 4.15, p = .04). No sensitivity analyses were conducted due to the small number of treatment comparisons. There were also no significant improvements in remission rates for sTMS compared to sham (k= 2, OR = 2.51 (95% CI [0.23; 26.76]). There was evidence for significant heterogeneity between the two studies though (I^2 = 75.7%; Q_1 = 4.12, p = .04). No sensitivity analyses were conducted due to the small number of treatment comparisons.

iTBS over the lDLPFC was associated with a fivefold improvement in response rates compared to sham (k = 2, OR = 4.70 (95% CI [1.14; 19.38]). The heterogeneity between trials did not exceed that expected by chance (I^2 = 0.0%; Q_1 = 0.02, p = .89). No sensitivity analyses were conducted due to the small number of treatment comparisons. For only one trial[39] was data on remission rates for iTBS available, with no evidence for antidepressant efficacy compared to sham.

Neither cTBS over the rDLPFC nor bilateral TBS were statistically different from sham in terms of response rates (k = 1, OR = 1.63, 95% CI [0.23; 11.46] and k = 2, OR = 4.28, 95% CI [0.54; 34.27]). For bilateral TBS there was evidence that the variance in effect sizes between studies was greater than what would be expected due to sampling error (I^2 = 65.7%; Q_1 = 2.91, p = .09). No sensitivity analyses were conducted due to the small number of treatment comparisons. The only trial of bilateral TBS for which remission rates were available[40] found no evidence for its antidepressant efficacy compared to sham. No remission rates were available for cTBS.

tDCS was associated with significant improvement in both response and remission rates in comparison to sham stimulation. There was a significant improvement in response rates relative to sham (k = 9, OR = 4.17, 95% CI [2.25; 7.74]). There was little evidence for significant heterogeneity between studies (I^2 = 26.2%; Q_8 = 10.83, p = .21) and sensitivity analyses suggested tDCS to be effective only in patients with non-treatment resistant depression and in trials that had recruited patients with both treatment resistant and non-treatment resistant depression (Supplementary Figure 5).

The analysis of remission rates showed a statistically significant advantage of tDCS compared to sham (k = 8, OR = 2.88, 95% CI [1.65; 5.04]). There was no indication for significant heterogeneity between trials (I^2 = 0.0%; Q_7 = 6.32, p = .50), and sensitivity analyses found that only trials that had recruited patients with both treatment resistant and non-treatment resistant depression provided evidence for antidepressant efficacy (Supplementary Figure 8).

Effects on continuous measures

Forty-six treatment comparisons reported post-intervention continuous depression scores. There was evidence for the antidepressant efficacy of high-frequency rTMS over the lDLPFC compared to sham (k = 29, Hedge's g = -0.72, 95% CI [-0.99; -0.46]), dTMS compared to sham (k = 2, Hedge's g = -0.29, 95% CI [-0.55; -0.03]), and tDCS compared to sham (k = 7, Hedge's g = -0.76, 95% CI [-1.31; -0.21]). There was evidence for significant heterogeneity between trials for several treatment modalities (Table 7; Figure 5).

Acceptability

Sixty-four treatment comparisons were available for all-cause discontinuation rates. There were no significant differences in drop-out rates for any treatment modalities (Table 8; Figure 6).

Discussion

The present systematic review and meta-analysis examined the efficacy and acceptability of non-invasive brain stimulation techniques for a current depressive episode in unipolar and bipolar depression. We sought to investigate the efficacy of the brain stimulation techniques without the potential confound of co-initiation of another treatment and in trials which had included randomised allocation to a sham stimulation treatment arm in order to account for potential placebo effects.

The largest evidence base to date is for high-frequency rTMS over the lDLPFC which is associated with 3.75 times greater odds of response than sham stimulation as well as odds of remission that are 2.52 times greater than sham. These findings are consistent with previous systematic reviews and meta-analyses[41] and have led to the consensus review and treatment guideline by the *Clinical TMS Society* for daily high-frequency rTMS over the lDLPFC for the treatment of medication-resistant or medication-intolerant depressive episodes[42].

Additional support for treatment efficacy was revealed for low-frequency rTMS over the rDLPFC, which was associated with improved rates of response as well as remission. Bilateral rTMS was associated with higher rates of response but not remission. It is unclear whether any advantages of bilateral rTMS compared to left-sided high-frequency or right-sided low-frequency rTMS would be due to the treatment protocol. As bilateral stimulation delivers a greater number of pulses than unilateral stimulation, unless the number of treatment sessions or the treatment duration are adjusted for accordingly, it is difficult to reliably assess whether the difference in stimulation protocol (bilateral vs. unilateral stimulation) or the difference in the number of stimuli delivered leads to differences in clinical effects[43].

To date, no studies have directly compared dTMS and standard rTMS protocols. In an exploratory meta-analysis of nine open-label trials, including a total of 150 patients, Kedzior et al.[44] provided evidence for the antidepressant efficacy of dTMS. The present meta-analysis found that dTMS was associated with 1.69 times greater odds of response and 2.24 greater odds of remission than sham which were statistically significant. While the open-label trials included in Kedzior et al.'s analysis may have overestimated the true efficacy of dTMS, we provide initial support for the clinical efficacy of dTMS that was greater than for sham treatment but less than for high-frequency rTMS over the lDLPFC, low-frequency rTMS over the rDLPFC or bilateral rTMS.

The meta-analytic estimates did not indicate significant treatment effects associated with low-frequency rTMS over the lDLPFC or with sTMS. However, these have been trialled in onlythree[45-47] and twostudies[21,48], respectively. Specific treatment effects of TMS that depend on side and frequency of stimulation have been proposed but it may be possible that low-frequency rTMS over the lDLPFC has a marginal effect in at least a small number of patients[47]. Leuchter et al.[48] found sTMS to only be effective when administered at the individual's alpha frequency and with a minimum of 80% treatment adherence, suggesting a dose-response relationship.

With theta burst stimulation, the duration of each treatment session is reduced to a few minutes. Our meta-analysis did demonstrate almost five times greater odds of response compared to sham for iTBS over the lDLPFC. However, this estimate is based on two trials only. One trial had examined remission rates as well[39], reporting remission rates of 0% for sham and 9.1% for active stimulation. The meta-analytic estimates for cTBS and the bilateral modification of TBS did not show any advantage over sham in terms of response rates. The only trial that reported remission rates for bilateral TBS did not provide evidence for its antidepressant efficacy either and no data were available to evaluate remission rates following cTBS.

Transcranial direct current stimulation is a form of neurostimulation that offers greater portability and lower costs relative to TMS. The meta-analysis revealed significant improvements in response and remission rates following tDCS treatment in comparison to sham, which was 4.17 times greater for response rates and 2.88 times greater for remission rates. We have been able to identify the effects of tDCS without potential confounds of co-initiation of another treatment, revealing significantly greater odds of response as well as remission[49]. The clinical efficacy of tDCS is evident also in the non-treatment resistant form of depression, in contrast to most rTMS trials, suggesting that tDCS is a potential initial therapeutic option for depression.

The finding that there were no differences in terms of drop-out rates at study end between the active treatment and sham conditions for any treatment modality suggests that non-invasive brain stimulation is generally well tolerated by patients. We chose all-cause discontinuation rates based on the intention-to-treat sample, representing the most conservative estimate of treatment acceptability.

We chose response and remission rates as our main outcome measures, which are commonly used in the medical sciences and arguably constitute clinically-useful estimates of the antidepressant efficacy of treatment. However, the dichotomisation of outcome data has received criticism because it is known to produce a loss of signal and might inflate Type I error rates, for example an individual who has a 49% reduction in their depressive severity scores would not be included in the clinical response rate while a 51% reduction would be included in the response rate[50]. To address these limitations, we had also analysed continuous depression severity scores. However, outcome data were not reported for each trial, and some missing data could not be obtained. Studies have also suggested that the antidepressant efficacy of active stimulation may separate from sham only after multiple weeks of treatment, for both rTMS[9] and cTBS[51]. We had examined the acute antidepressant effects at primary study endpoint, and we cannot estimate the long-term effects.

A significant number of TMS studies used active magnetic stimulation with the coil being angulated at 45 or 90 degrees to the scalp surface as sham condition. Because differences in coil orientation may produce considerably different sensations on the scalp and coil angulation might still produce a limited degree of intracortical activity[52], ensuring a valid control condition constitutes a methodological challenge. One study placed an inactive coil on the patient's head while discharging an active coil at least one meter away in order to mimic the auditory effects of rTMS[53].

A more recent approach is to use a specifically designed sham coil that does not generate a magnetic field but is visually and auditorily indistinguishable from an active coil. A meta-analysis by Berlim et al.[54] found no significant differences between the number of patients who correctly guessed their treatment allocation when comparing active high-frequency left-sided or bilateral rTMS and sham. There were also no significant differences between studies that utilised angulated coils and sham coils. Blinding integrity is less of a methodological hurdle for sTMS trials because neither active stimulation nor sham procedure produce any physical sensation, they look identical, and are comparable in terms of acoustic artefacts. Only few of the more recent modifications of TMS reported on the adequacy of their blinding procedure. Given that cross-over designs are particularly prone to unblinding after cross-over, we included only data corresponding to the initial randomisation in our analyses.

For tDCS, the sham condition typically involves delivering active stimulation for up to 30 seconds, which mimics the initial somatic sensations without inducing a therapeutic effect. However, the adequacy of blinding of tDCS sham has also been called into question[55].

The clinical trials had enrolled patients based on a diagnostic assessment of clinical symptoms rather than underlying brain pathology. The potential for biological heterogeneity might mask the clinical efficacy of non-invasive brain stimulation in some trials but could not be assessed in the present analysis. We implemented reasonably strict inclusion criteria to limit the influence of a range of potential confounders, for example we excluded RCTs that co-initiated treatment with medication. However, potential effects of specific medications on the clinical efficacy of brain stimulation could not be adequately controlled for as patients often had a large number of heterogeneous treatments prior to enrolling, which might have distorted the clinical effects of brain stimulation.

Finally, compared to the network meta-analysis (NMA) on TMS[29], we were not able to compare the active treatments. In the NMA priming rTMS seemed most effective. However, the two RCTs that used this treatment modality compared it with another active stimulation and could not be included in the present meta-analysis.

Conclusion

The present systematic review and meta-analysis supports the efficacy and acceptability of non-invasive brain stimulation techniques in adult unipolar and bipolar depression. The strongest evidence was for high-frequency rTMS over the lDLPFC, followed by low-frequency rTMS over the rDLPFC and bilateral rTMS. Intermittent TBS provides a potential advance in terms of reduced treatment duration and the meta-analysis did find support for improved rates of response. tDCS is a potential treatment for non-resistant depression which has demonstrated efficacy in terms of response as well as remission. All the trials included in the present meta-analysis had included randomised allocation to a sham treatment arm and we had excluded trials in which there was co-initiation of another treatment. Some of the more recent treatment modalities though require additional trials and more direct comparisons between different treatment modalities are warranted.

Authorship contributions

C.H.Y.F. and J.M. conceived the project; J.M. performed the systematic literature search with supervision by C.H.Y.F; J.M. extracted and analysed the data; D.R.E. reviewed the quality of the extracted data; J.M. wrote the initial draft; C.H.Y.F. critically revised each draft, including interpretation of the data; A.R.B. critically revised the paper. All authors read and approved the final version of this paper. J.M is the guarantor.

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Supplementary material

Supplementary information is available online.

Figure 1

Caption: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of literature search.

Figure 2

Caption: Contour-enhanced funnel plot of all RCTs included in the meta-analysis of response rates.

Legend: rTMS (black); tDCS (navy); TBS (red); dTMS (yellow): sTMS (pink).

Figure 3

Caption: Forest plot of response rates.

Figure 4

Caption: Forest plot of remission rates.

Figure 5

Caption: Forest plot of post-treatment continuous depression scores.

Figure 6

Caption: Forest plot of all-cause discontinuation rates.

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Table 1

Treatment characteristics: TMS studies

Authors	Location	Frequency (Hz)		% rMT	Total pulses	Sessions	Treatment strategy	Active group	Sham group
HF-L		Left	Right						
Anderson et al., 2007	LDLPFC	10	-	110[a]	12,000	12	Mixed	Figure-of-eight	Sham-coil
Avery et al., 2006	LDLPFC	10	-	110[b]	24,000	15	Mixed	Figure-of-eight	90°
Avery et al., 1999	LDLPFC	10	-	80	NR	10	Mixed	NR	45°
Baeken et al., 2013[*]	LDLPFC	20	-	110	31,200	20	Monotherapy	Figure-of-eight	90°
Bakim et al., 2012[1]	LDLPFC	20	-	80; 100	24,000	30	Augmentation	Figure-of-eight	45°
Berman et al., 2000	LDLPFC	20	-	80	NR	10	Monotherapy	Figure-of-eight	30-45°
Bortolomasi et al., 2007	LDLPFC	20	-	90	4,000	5	Mixed	Circular	90°
Boutros et al., 2002	LDLPFC	20	-	80	8,000	10	Mixed	Figure-of-eight	90°
Chen et al., 2013	LDLPFC	20	-	90	NR	10	Augmentation	Figure-of-eight	90°
Concerto et al., 2015	LDLPFC	10	-	120	60,000	20	Augmentation	Figure-of-eight	45°
Eschweiler et al., 2000[*]	LDLPFC	10	-	90	NR	5	Augmentation	Figure-of-eight	90°

Fitzgerald et al., 2012 (1)	LDLPFC	10	-	120	NR	15	Mixed	Figure-of-eight	45°
Fitzgerald et al., 2003 (1)	LDLPFC	10	-	100	10,000	10	Augmentation	Figure-of-eight	45°
Garcia-Toro et al., 2001	LDLPFC	20	-	90	NR	10	Augmentation	Figure-of-eight	90°
George et al., 2010	LDLPFC	10	-	120	45,000	15	Monotherapy	Figure-of-eight	Sham-coil
George et al., 2000[2]	LDLPFC	5; 20[c]	-	100[d]	16,000	10	Monotherapy	Figure-of-eight	45°
George et al., 1997[*]	LDLPFC	20	-	80	8000	10	Mixed	Figure-of-eight	45°
Hansen et al., 2004	LDLPFC	10	-	90	30,000	15	Augmentation	Figure-of-eight	90°
Hernández-Ribas et al., 2013	LDLPFC	15	-	100	22,500	15	Augmentation	Figure-of-eight	90°
Holtzheimer et al., 2004	LDLPFC	10	-	110	16,000	10	Monotherapy	Figure-of-eight	45°[e]
Jakob et al., 2008 (1)	LDLPFC	20	-	100	20,000	10	Mixed	Figure-of-eight	Sham-coil
Jakob et al., 2008 (2)	LDLPFC	50	-	100	20,000	10	Mixed	Figure-of-eight	Sham-coil
Kimbrell et al., 1999[*]	LDLPFC	20	-	80	8,000	10	Monotherapy	Figure-of-eight	45°
Kreuzer et al., 2015	LDLPFC	10	-	110	30,000	15	Augmentation	Figure-of-eight	Sham-coil
Lingeswaran et al., 2011	LDLPFC	10	-	100	NR	12	NR	Figure-of-eight	90°
Loo et al., 1999[*]	LDLPFC	10	-	110	NR	10	Mixed	Figure-of-eight	90°

Nahas et al., 2003	LDLPFC	5	-	110	16,000	10	Monotherapy	Figure-of-eight	45°
O'Reardon et al., 2007	LDLPFC	10	-	120[g]	60,000	20	Monotherapy	Figure-of-eight	Sham-coil
Paillère-Martinot et al., 2010	LDLPFC	10	-	90	16,000	10	Augmentation	Figure-of-eight	Sham-coil
Speer et al., 2014	LDLPFC	20	-	110	24,000	15	Monotherapy	Figure-of-eight	45°
Su et al., 2005[3]	LDLPFC	5; 20	-	100	16,000	10	Augmentation	Figure-of-eight	90°
Taylor et al., 2018	LDLPFC	10	-	120[g]	60,000	20	Mixed	Figure-of-eight	Sham-coil
Theleritis et al., 2017 (1)	LDLPFC	20	-	100	24,000	15	Mixed	Figure-of-eight	90°
Theleritis et al., 2017 (2)	LDLPFC	20	-	100	48,000	30[f]	Mixed	Figure-of-eight	90°
Zheng et al., 2010	LDLPFC	15	-	110[g]	60,000	20	Augmentation	Figure-of-eight	90°
LF-R									
Fitzgerald et al., 2003 (2)	RDLPFC	-	1	100	3,000	10	Augmentation	Figure-of-eight	45°
Januel et al., 2006	RDLPFC	-	1	90	1,920	16	Monotherapy	Figure-of-eight	Sham-coil
Pallanti et al., 2010 (1)	RDLPFC	-	1	110	6,300	15	Augmentation	Figure-of-eight	Sham-coil
LF-L									
Kimbrell et al., 1999[*]	LDLPFC	1	-	80	8,000	10	Monotherapy	Figure-of-eight	45°

Padberg et al., 1999	LDLPFC	0.3	-	90	1,250	5	Mixed	Figure-of-eight	90°
Speer et al., 2014	LDLPFC	1	-	110	24,000	15	Monotherapy	Figure-of-eight	45°
BL									
Fitzgerald et al., 2006	DLPFC	10	1	110(R); 100(L)	7,200	10	Mixed	Figure-of-eight	45°
Fitzgerald et al., 2016	DLPFC	10	1	110	40,000	20	Mixed	Figure-of-eight	45°
Fitzgerald et al., 2012 (2)	DLPFC	10	1	120	NR	15	Mixed	Figure-of-eight	45°
McDonald et al., 2006[4]	DLPFC	10	1	110	16,000	10	Monotherapy	Figure-of-eight	90°
Pallanti et al., 2010 (2)	DLPFC	10	1	110(R); 100(L)	21,300	15	Augmentation	Figure-of-eight	Sham-coil
Prasser et al., 2015 (1)	DLPFC	10	1	110	30,000	15	Augmentation	Figure-of-eight	Sham-coil
iTBS									
Duprat et al., 2016[*]	LDLPFC	50	-	110	32,400	20[i]	Monotherapy	Figure-of-eight	Sham-coil
Li et al., 2014 (1)	LDLPFC	50	-	80[j]	18,000	10	Mixed	Figure-of-eight	90°
cTBS									
Li et al., 2014 (2)	RDLPFC	50	-	80[j]	18,000	10	Mixed	Figure-of-eight	90°
BLTBS									

Li et al., 2014 (3)	DLPFC	50	50	80[j]	36,000	10	Mixed	Figure-of-eight	90°
Prasser et al., 2015 (2)	DLPFC	50	50	80	36,000	15	Augmentation	Figure-of-eight	Sham-coil
dTMS									
Levkovitz et al., 2015	LDLPFC	18	-	120[h]	39,600	20	Monotherapy	H1	Sham-coil
Tavares et al., 2017	LDLPFC	18	-	120	39,600	20	Augmentation	H1	Sham-coil
sTMS									
Jin et al., 2014[5]	Midline	IAF; 8-13		-	-	20	Augmentation	sTMS	NMRS
Leuchter et al., 2015	Midline	IAF		-	-	30	Monotherapy	sTMS	NMRS

Note. Numbers in parentheses behind authors indicate that multiple active treatment arms of the same study are reported. Hz = hertz; rMT = resting motor threshold; LDLPFC = left dorsolateral prefrontal cortex; RDLPFC = right dorsolateral prefrontal cortex; TMS = transcranial magnetic stimulation; HF-L = high-frequency, left-sided repetitive transcranial magnetic stimulation; LF-R = low-frequency, right-sided repetitive transcranial magnetic stimulation; BL = bilateral repetitive transcranial magnetic stimulation; iTBS = intermittent theta burst stimulation; cTBS = continuous theta burst stimulation; BLTBS = bilateral theta burst stimulation; dTMS = deep transcranial magnetic stimulation; sTMS = synchronised transcranial magnetic stimulation; IAF = individual alpha frequency; NMRS = non-magnetic rotating shaft; NR = not reported. [*]Cross-over design. [1-5]Two active treatment groups were combined. [a]Two patients received active stimulation at 100% rMT. [b]Stimulation delivered at estimated prefrontal threshold. [c]During the 5th session, stimulation was delivered for 2min at 10Hz. [d]During the 5th session, stimulation was delivered for 2min at 60% rMT. [e]Two patients received sham treatment with the coil angulated at 90°. [f]Received treatment twice daily. [g]During the first week, 110% rMT could be used for tolerability. [h]During the first three treatment session, rMT could be titrated from 100% to 120%. [i]Received treatment five times daily. [j]Stimulation delivered at active motor threshold.

Table 2

Sample characteristics: TMS studies

Authors	Number of participants (female)		Age		Diagnosis	HDRS / MADRS		Excluded psychosis	Status	Treatment resistance
	Active	Sham	Active	Sham		Active	Sham			
HF-L										
Anderson et al., 2007[1]	13 (7)	16 (9)	48.0 (8.0)	46.0 (12.0)	MDD	26.7 (3.6)[M]	27.7 (7.1)[M]	No	Outpatient	Mixed
Avery et al., 2006[2]	35 (21)	33 (16)	44.3 (10.3)	44.2 (9.7)	MDD	23.5 (3.9)[a]	23.5 (2.9)[a]	Yes	NR	TRD
Avery et al., 1999	4 (4)	2 (1)	44.3 (10.1)	45.0 (7.1)	Mixed	21.3 (6.7)[b]	19.5 (8.1)[b]	Yes	Outpatient	TRD
Baeken et al., 2013	9 (7)	11 (5)	51.8 (12.1)	47.3 (13.7)	MDD	24.8 (7.1)[a]	26.5 (8.7)[a]	Yes	Mixed	TRD
Bakim et al., 2012[3]	23 (20)	12 (11)	40.8 (10.0)	44.4 (10.2)	MDD	23.6 (3.6)[a]	25.6 (3.8)[a]	Yes	Outpatient	TRD
Berman et al., 2000[2]	10 (2)	10 (4)	45.2 (9.5)	39.4 (10.8)	Mixed	37.1 (9.7)[c]	37.3 (8.5)[c]	No	Mixed	TRD
Bortolomasi et al., 2007	12 (7)	7 (4)	NR	NR	Mixed	25.17 (7.84)[d]	21.57 (2.15)[d]	No	Inpatient	TRD
Boutros et al., 2002[6]	12 (4)	9 (1)	49.5 (8.0)	52.0 (7.0)	MDD	34.4 (10.1)[c]	31.7 (4.9)[c]	No	Outpatient	TRD

Chen et al., 2013	10 (7)	10 (4)	44.1 (4.4)	47.3 (3.5)	MDD	23.5 (1.9)[a]	24.9 (1.9)[a]	No	Inpatient	TRD
Concerto et al., 2015	15 (6)	15 (7)	51.0 (6.5)	53.0 (6.7)	MDD	22.0 (21.0; 24.0)[b]	21.0 (20.0; 22.0)[b]	Yes	Outpatient	TRD
Eschweiler et al., 2000	5 (NR)	5 (NR)	NR	NR	MDD	27.4 (4.6)[b]	20.2 (3.8)[b]	No	NR	non-TRD
Fitzgerald et al., 2012 (1)[2]	24 (15)	20 (8)	43.4 (12.7)	44.9 (15.7)	MDD	23.7 (3.8)[a]	22.8 (2.1)[a]	No	NR	TRD
Fitzgerald et al., 2003 (1)	20 (8)	20 (11)	42.2 (9.8)	49.2 (14.2)	Mixed	36.1 (7.5)[M]	35.7 (8.1)[M]	No	Outpatient	TRD
Garcia-Toro et al., 2001	17 (7)	18 (8)	51.5 (15.9)	50.0 (11.0)	MDD	27.1 (6.7)[b]	25.6 (4.9)[b]	No	NR	TRD
George et al., 2010[2]	92 (58)	98 (50)	47.7 (10.6)	46.5 (12.3)	MDD	26.3 (5.0)[d]	26.5 (4.8)[d]	Yes	Outpatient	TRD
George et al., 2000[4]	20 (13)	10 (6)	42.4 (10.5)	48.5 (8.0)	Mixed	28.2 (5.9)[b]	23.8 (4.1)[b]	Yes	Outpatient	Mixed
George et al., 1997	7 (6)	5 (5)	42.4 (15.5)	41.0 (8.3)	Mixed	30.0 (4.0)[b]	26.0 (3.0)[b]	Yes	Outpatient	non-TRD
Hansen et al., 2004[6]	6 (2)	7 (2)	42.5 (38; 58)[13]	46 (44; 62)[13]	Mixed	26.5 (21.5; 27.6)[a]	23.8 (19.4; 28.0)[a]	No	Inpatient	NR
Hernández-Ribas et al., 2013	10 (8)	11 (8)	42.6 (5.6)	50.1 (8.1)	Mixed	19.7 (3.8)[b]	16.6 (2.4)[b]	Yes	Outpatient	TRD
Holtzheimer et al., 2004	7 (4)	8 (3)	40.4 (8.5)	45.4 (4.9)	MDD	22.7 (5.3)[a]	20.8 (6.3)[a]	Yes	Outpatient	TRD
Jakob 2008 (1)	12 (6)	12 (5)	NR	NR	MDD	27.2 (NR)[a]	23.9 (NR)[a]	NR	NR	NR

Jakob 2008 (2)	12 (7)	12 (5)	NR	NR	MDD	24.1 (NR)[a]	23.9 (NR)[a]	NR	NR	NR
Kimbrell et al., 1999	5 (2)	3 (1)	40.2 (15.1)	43.7 (19.1)	Mixed	25.0 (6.6)[b]	24.3 (6.8)[b]	No	Mixed	TRD
Kreuzer et al., 2015	15 (8)	12 (8)	46.1 (9.5)	43.8 (10.5)	Mixed	22.3 (4.7)[b]	22.3 (4.7)[b]	No	Inpatient	NR
Lingeswaran et al., 2011	9 (6)	14 (8)	34 (10.5)	37.2 (11.8)	MDD	22.8 (3.7)[a]	22.0 (3.1)[a]	Yes	Mixed	NR
Loo et al., 1999	9 (NR)	9 (NR)	45.7 (14.7)	50.9 (14.7)	Mixed	21.5 (NR)[a]	25.1 (NR)[a]	No	Mixed	TRD
Nahas et al., 2003	11 (7)	12 (7)	42.4 (7.3)	43.4 (9.3)[11]	BD[12]	32.5 (4.3)[e]	32.8 (7.6)[e]	NA	Outpatient	NR
O'Reardon et al., 2007[6]	155 (86)	146 (74)	47.9 (11.0)	48.7 (10.6)	MDD	22.6 (3.3)[a]	22.9 (3.5)[a]	Yes	Outpatient	TRD
Paillère-Martinot et al., 2010	18 (11)	14 (10)	48.2 (7.8)	46.6 (10.3)	Mixed	26.0 (6.4)[b]	25.9 (6.7)[b]	Yes	Inpatient	TRD
Speer et al., 2014[2]	8 (5)	8 (11)	41.3 (14.5)	44.9 (9.1)	Mixed	35.8 (10.6)[e]	24.0 (4.6)[e]	No	Mixed	TRD
Su et al., 2005[5]	20 (15)	10 (7)	43.4 (11.3)	42.6 (11.0)	Mixed	24.9 (6.4)[b]	22.7 (4.7)[b]	Yes	NR	TRD
Taylor et al., 2018	16 (11)	16 (10)	46.9 (10.7)	44.13 (11.1)	MDD	16 (3.9)[a]	13.1 (2.3)[a]	Yes	Outpatient	TRD
Theleritis et al., 2017 (1)[6]	26 (15)	20 (10)	39.1 (10.1)	38.0 (9.9)	MDD	30.6 (3.2)[a]	29.4 (3.2)[a]	Yes	Outpatient	TRD
Theleritis et al., 2017 (2)[6]	26 (11)	24 (10)	38.9 (13.9)	39.4 (8.9)	MDD	29.7 (4.6)[a]	30.3 (3.6)[a]	Yes	Outpatient	TRD

Zheng et al., 2010	19 (7)	15 (5)	26.9 (6.2)	26.7 (4.3)	MDD	24.6 (3.0)[a]	24.6 (2.8)[a]	Yes	NR	TRD
LF-R										
Fitzgerald et al., 2003 (2)	20 (7)	20 (11)	45.6 (11.5)	49.2 (14.2)	Mixed	37.7 (8.4)[M]	35.7 (8.1)[M]	No	Outpatient	TRD
Januel et al., 2006[2]	11 (9)	16 (12)	38.6 (11.2)	37.2 (11.7)	MDD	21.7 (3.5)[a]	22.5 (2.7)[a]	Yes	Inpatient	non-TRD
Pallanti et al., 2010 (1)	20 (12)	20 (12)	51.2 (12.5)	47.9 (9.1)	MDD	28.0 (5.9)[a]	29.1 (3.5)[a]	Yes	Outpatient	TRD
LF-L										
Kimbrell et al., 1999 (2)[2]	5 (4)	3 (1)	44 (15.92)	43.67 (19.14)	Mixed	34.4 (7.99)[b]	24.33 (6.81)[b]	No	Mixed	TRD
Padberg et al., 1999	6 (5)	6 (4)	46.7 (14.7)	43.3 (11.6)	MDD	26.7 (9.4)[b]	22.2 (8.8)[b]	NR	NR	TRD
Speer et al., 2014	8 (5)	8 (3)	39.6 (9)	44.9 (9.1)	Mixed	28.6 (7.6)[e]	24 (4.6)[e]	No	Mixed	TRD
BL										
Fitzgerald et al., 2006[2]	25 (15)	25 (16)	46.8 (10.7)	43.7 (10.2)	Mixed	22.5 (7.4)[a]	19.8 (4.4)[a]	No	Outpatient	TRD
Fitzgerald et al., 2016[7]	23 (13)	23 (13)	46.3 (12.6)	49.7 (11.0)	BD	23.2 (4.0)[a]	23.0 (5.1)[a]	NA	Outpatient	TRD
Fitzgerald et al., 2012 (2)[2]	22 (14)	20 (8)	40.5 (15.5)	44.9 (15.7)	MDD	24.3 (3.6)[a]	22.8 (2.1)[a]	No	NR	TRD

McDonald et al., 2006[8]	50 (27)	12 (5)	NR	NR	Mixed	26.4 (1.38)[b]	27.33 (2.86)[b]	Yes	Outpatient	TRD
Pallanti et al., 2010 (2)	20 (11)	20 (12)	47.6 (12.3)	47.9 (9.1)	MDD	28.8 (6.0)[a]	29.1 (3.5)[a]	Yes	Outpatient	TRD
Prasser et al., 2015 (1)	17 (8)	17 (9)	50.4 (9.9)	42.6 (12.4)	Mixed	25.0 (4.4)[b]	25.3 (5.4)[b]	No	Mixed	Mixed
iTBS										
Duprat et al., 2016	22 (16)	25 (17)	40.09 (11.45)	43.16 (12.15)	MDD	21.14 (4.99)[a]	21.52 (6.21)[a]	Yes	Mixed	TRD
Li et al., 2014 (1)	15 (8)	15 (11)	42.4 (NR)	46.9 (NR)	MDD	23.1 (3.9)[a]	23.8 (3.2)[a]	Yes	NR	TRD
cTBS										
Li et al., 2014 (2)	15 (10)	15 (11)	49.2 (NR)	46.9 (NR)	MDD	24.3 (5.5)[a]	23.8 (3.2)[a]	Yes	NR	TRD
BLTBS										
Li et al., 2014 (3)	15 (11)	15 (11)	42.5 (NR)	46.9 (NR)	MDD	25.4 (5.1)[a]	23.8 (3.2)[a]	Yes	NR	TRD
Prasser et al., 2015 (2)	20 (10)	17 (9)	48.2 (10.9)	42.6 (12.4)	Mixed	27.4 (6.5)[b]	25.3 (5.4)[b]	No	Mixed	Mixed
dTMS										
Levkovitz et al..2015[6]	101 (48)	111 (53)	45.1 (11.7)	47.6 (11.6)	MDD	23.5 (4.3)[b]	23.4 (3.7)[b]	Yes	Outpatient	TRD

Tavares et al., 2017[6]	25 (17)	25 (18)	43.5 (12)	41.2 (8.9)	BD	25.32 (3.76)[a]	25.8 (5.25)[a]	NA	Outpatient	TRD
sTMS										
Jin et al., 2014[6,9,10]	29 (16)	16 (9)	42.5 (15.0)	46.3 (12.7)	MDD	21.3 (4.0)[a]	19.4 (4.1)[a]	No	Outpatient	non-TRD
Leuchter et al., 2015	59 (NR)	61 (NR)	46.7 (11.2)	45.7 (12.6)	MDD	21.8 (3.8)[a]	21.2 (2.9)[a]	Yes	Mixed	Mixed

Note. Mean ages are reported in years with standard deviation in parentheses for each of the active and sham treatment arms. The mean Hamilton Depression Rating Scale (HDRS) score at baseline is reported for each study with standard deviation in parentheses (except for Concerto et al., 2015 and Hansen et al., 2004 for which median, first quartile, and third quartile are reported). The Montgomery-Åsberg Depression Rating Scale (MADRS) score, denoted with superscript [M], is reported when the HDRS was not recorded. Means and standard deviations are rounded to the first figure after the decimal. Status refers to whether patients were outpatients, inpatients in a hospital admission, or whether there were both outpatients and inpatients (mixed). TMS = transcranial magnetic stimulation; HF-L = high-frequency left-sided repetitive transcranial magnetic stimulation; LF-R = low-frequency right-sided repetitive transcranial magnetic stimulation; BL = bilateral repetitive transcranial magnetic stimulation; iTBS = intermittent theta burst stimulation; cTBS = continuous theta burst stimulation; BLTBS = bilateral theta burst stimulation; dTMS = deep transcranial magnetic stimulation; sTMS = synchronised transcranial magnetic stimulation; NR = not reported; NA = not applicable; MDD = major depressive disorder; BD = bipolar depression; TRD = treatment resistant depression. [1]MADRS based on the intention-to-treat sample who received ≥ 1 session of active stimulation. [2]Numbers are based on the intention-to-treat sample. [3,4,5,8,9]Two active treatment groups were combined. [6]Numbers based on the intention-to-treat sample who received ≥ 1 session of active stimulation. [7]HDRS based on the intention-to-treat sample. [10]Age based on the intention-to-treat sample who received ≥ 1 session of active stimulation. [11]Age based on 11 patients. [12]Two patients had mixed features. [13]Indicates Median and IQR. [a]HDRS-17. [b]HDRS-21. [c]HDRS-25. [d]HDRS-24. [e]HDRS-28.

Table 3

Treatment characteristics: tDCS studies

Authors	Location		Electrode size	Current strength	Current density	Session duration	Number of sessions	Treatment strategy	Sham stimulation
	Anode	Cathode/Reference							
Fregni et al., 2006a	F3	FP2	35cm^2	1mA	0.028	20min	5	Monotherapy	05sec
Fregni et al., 2006b	F3	FP2	35cm^2	1mA	0.028	20min	5	Monotherapy	05sec
Boggio et al., 2008[1]	F3	FP2; Midline	35cm^2	2mA	0.057	20min	10	Monotherapy	30sec
Loo et al., 2010	pF3	F8	35cm^2	1mA	0.028	20min	5	Mixed	30sec
Blumberger et al., 2012	F3	F4	35cm^2	2mA	0.057	20min	15	Mixed	30sec
Brunoni et al., 2013[2]	F3	F4	25cm^2	2mA	0.080	30min	12	Monotherapy	60sec
Salehinejad et al., 2015	F3	F4	35cm^2	2mA	0.057	20min	22	Monotherapy	30sec
Salehinejad et al., 2017	F3	F4	35cm^2	2mA	0.057	30min	10	Monotherapy	30sec
Brunoni et al., 2017[2]	F3	F4	25cm^2	2mA	0.080	30min	10	Monotherapy	30sec
Sampaio-Junior et al., 2017	F3[3]	F4[3]	25cm^2	2mA	0.080	30min	12	Augmentation	30sec

Note. Electrode locations are reported according to the EEG 10/20 system. Current densities are reported in mA/cm^2. Sham stimulation indicates the duration of time that current was applied for giving an initial sensation of tDCS on the scalp. tDCS = transcranial direct current stimulation. [1]Two sham treatment groups were combined.[2]Patients in sham group also received an oral placebo tablet.[3]Omnilateral electrode system.

Table 4

Sample characteristics: tDCS studies

Authors	Number of participants (female)		Age		Diagnosis	HDRS		Excluded psychosis	Status	Treatment resistance
	Active	Sham	Active	Sham		Active	Sham			
Fregni et al., 2006a	5 (NR)	5 (NR)	NR	NR	MDD	NR	NR	NR	NR	NR
Fregni et al., 2006b	9 (5)	9 (6)	47.6 (10.4)	45.3 (9.3)	MDD	23,6 (5,0)	25,9 (4,3)	Yes[a]	Outpatient	NR
Boggio et al., 2008[1]	21 (14)	19 (13)	51.6 (7.7)	46.4 (7.1)	MDD	21,1 (4,4)[b]	21,8 (4,8)[b]	Yes	NR	Mixed
Loo et al., 2010[2]	20 (11)	20 (11)	49.0 (10.0)	45.6 (12.5)	MDD	18,3 (5,8)[c]	17,3 (4,7)[c]	Yes[a]	Outpatient	Mixed
Blumberger et al., 2012[3,6]	13 (10)	11 (10)	45.3 (11.6)	49.7 (9.4)	MDD	24,9 (3,1)[c]	24,1 (2,9)[c]	Yes	Outpatient	TRD
Brunoni et al., 2013[4]	30 (21)	30 (20)	41.0 (12.0)	46.4 (14.0)	MDD	21,0 (3,8)[c]	22,0 (4,2)[c]	Yes	Outpatient	Mixed
Salehinejad et al., 2015	15 (8)	15 (9)	28.7 (5.87)	27.9 (5.84)	MDD	24.7 (3.05)[d]	22.8 (2.06)[d]	Yes	Outpatient	TRD
Salehinejad et al., 2017	12 (7)	12 (8)	26.8 (7.1)	25.5 (4.6)	MDD	24,6 (2,6)[d]	22,6 (1,9)[d]	Yes	Outpatient	non-TRD
Brunoni et al., 2017[5,6,7]	91 (64)	60 (41)	44 (11.19)	40.88 (12.87)	MDD	21.93 (3.89)[c]	22.7 (4.27)[c]	Yes	Outpatient	Mixed

Sampaio-Junior et al., 2017[8]	30 (16)	29 (24)	46.2 (11.8)	45.7 (10.3)	BD	23.1 (3.9)	23.5 (4.7)	NA	Outpatient	Mixed

Note. Mean ages are reported in years with standard deviation in parentheses for each of the active and sham treatment arms. The mean Hamilton Depression Rating Scale (HDRS) score at baseline is reported for each study with standard deviation in parentheses. Means and standard deviations are rounded to the first figure after the decimal. Status refers to whether patients were outpatients, inpatients in a hospital admission, or whether there were both outpatients and inpatients (mixed). tDCS = transcranial direct current stimulation; MDD = major depressive disorder; TRD = treatment resistant depression; NR = not reported; NA = not applicable. [1]Two sham treatment groups were combined. [2,3,4,7,8]Numbers are based on the intention-to-treat sample.[5]Numbers based on participants of age ≤ 70 years.[6]Patients in sham group also received an oral placebo tablet. [a]Excluded "other psychiatric disorders." [b]HDRS-21. [c]HDRS-17. [d]HDRS-24.

Table 5

Random-Effects Meta-Analysis of Response Rates

Treatment Modality	*k*	Odds Ratio	95% Confidence Interval		Q	I^2
HF-L	32	**3.75**	**2.44**	**5.75**	41.96	26.1%
LF-R	3	**7.44**	**2.06**	**26.83**	1.59	0.0%
LF-L	3	1.41	0.15	12.88	0.14	0.0%
BL	6	**3.68**	**1.66**	**8.13**	3.45	0.0%
cTBS*	1	1.63	0.23	11.46	-	-
iTBS	2	**4.70**	**1.14**	**19.38**	0.02	0.0%
blTBS	2	4.28	0.54	34.27	2.91	65.7%
dTMS	2	**1.69**	**1.003**	**2.85**	0.97	0.0%
sTMS	2	2.71	0.44	16.86	4.15	75.9%
tDCS	9	**4.17**	**2.25**	**7.74**	10.83	26.2%

Note. HF-L = high-frequency, left-sided repetitive transcranial magnetic stimulation; LF-R = low-frequency, right-sided repetitive transcranial magnetic stimulation; LF-L = low-frequency, left-sided repetitive transcranial magnetic stimulation; BL = bilateral repetitive transcranial magnetic stimulation; dTMS = deep transcranial magnetic stimulation; cTBS = continuous theta burst stimulation; iTBS = intermittent theta burst stimulation; blTBS = bilateral theta burst stimulation; sTMS = synchronised transcranial magnetic stimulation; tDCS = transcranial magnetic stimulation. *inverse variance method used.

Table 6

Random-Effects Meta-Analysis of Remission Rates

Treatment Modality	*k*	Odds Ratio	95% Confidence Interval		Q	I^2
HF-L	26	**2.52**	**1.62**	**3.89**	25.35	1.4%
LF-R	2	**14.10**	**2.79**	**71.42**	0.50	0.0%
LF-L	3	0.86	0.08	9.11	0.03	0.0%
BL	5	**3.05**	**0.87**	**10.67**	4.48	10.7%
cTBS	-	-	-	-	-	-
iTBS*	1	6.22	0.28	136.90	-	-
blTBS*	1	1.32	0.19	9.02	-	-
dTMS	2	**2.24**	**1.24**	**4.06**	0.02	0.0%
sTMS	2	2.51	0.23	26.76	4.12	75.7%
tDCS	8	**2.88**	**1.65**	**5.04**	6.32	0.0%

Note. HF-L = high-frequency, left-sided repetitive transcranial magnetic stimulation; LF-R = low-frequency, right-sided repetitive transcranial magnetic stimulation; LF-L = low-frequency, left-sided repetitive transcranial magnetic stimulation; BL = bilateral repetitive transcranial magnetic stimulation; dTMS = deep transcranial magnetic stimulation; cTBS = continuous theta burst stimulation; iTBS = intermittent theta burst stimulation; blTBS = bilateral theta burst stimulation; sTMS = synchronised transcranial magnetic stimulation; tDCS = transcranial magnetic stimulation. *inverse variance method used.

Table 7

Random-Effects Meta-Analysis of Continuous Treatment Effects

Treatment Modality	*k*	*g*	95% Confidence Interval		Q	I^2
HF-L	29	**-0.72**	**-0.99**	**-0.46**	102.67	72.7%
LF-R	2	-0.77	-1.64	0.09	2.72	63.3%
LF-L	2	-0.33	-1.18	0.51	0.76	0.0%
BL	4	-0.07	-0.38	0.25	0.25	0.0%
cTBS	-	-	-	-	-	-
iTBS	1	-0.44	-1.02	0.14	0.00	-
blTBS	1	-0.03	-0.65	0.56	-	-
dTMS	2	**-0.29**	**-0.55**	**-0.03**	0.75	0.0%
sTMS	2	-0.55	-1.13	0.02	3.24	69.1%
tDCS	7	**-0.76**	**-1.31**	**-0.21**	33.68	82.2%

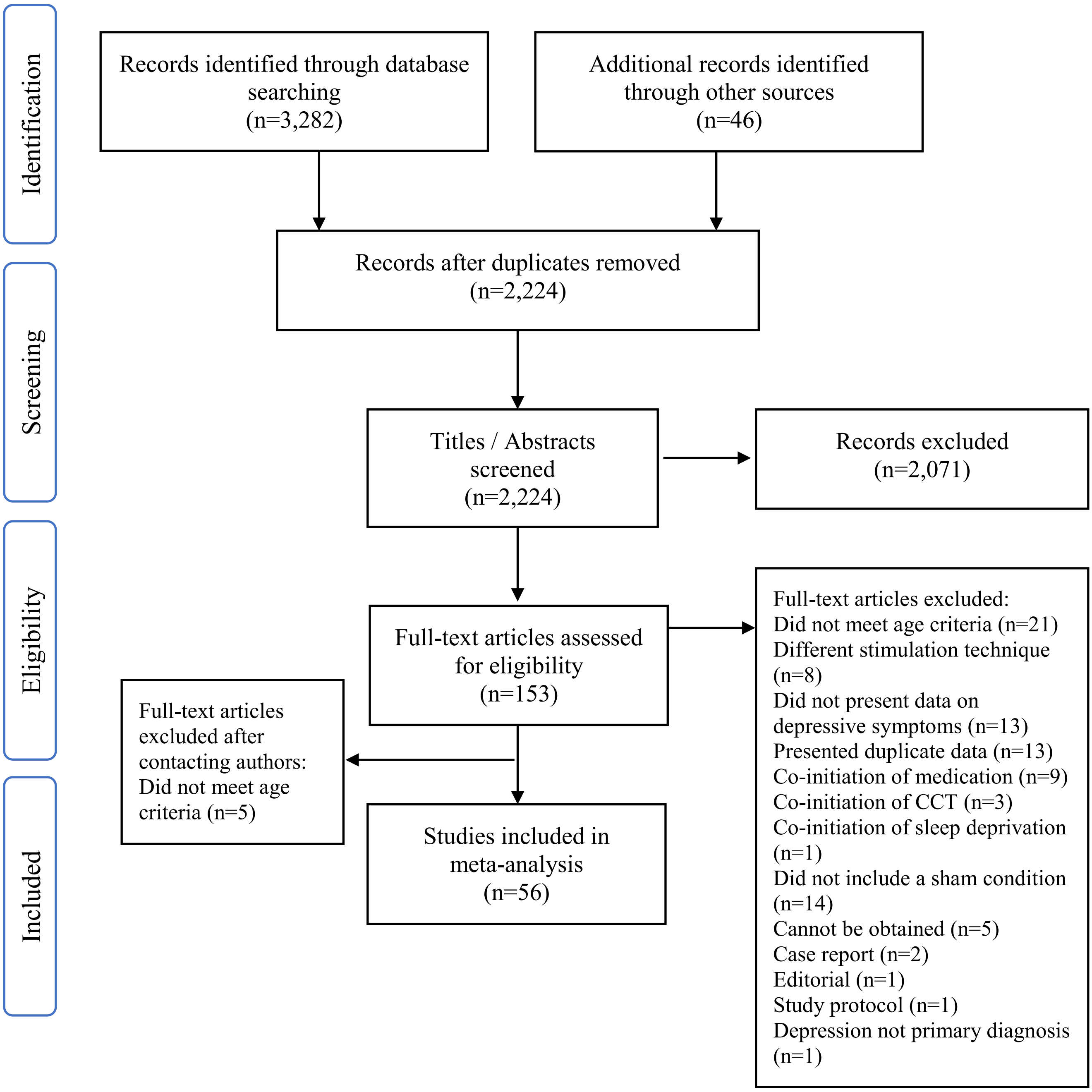
Note. HF-L = high-frequency, left-sided repetitive transcranial magnetic stimulation; LF-R = low-frequency, right-sided repetitive transcranial magnetic stimulation; LF-L = low-frequency, left-sided repetitive transcranial magnetic stimulation; BL = bilateral repetitive transcranial magnetic stimulation; dTMS = deep transcranial magnetic stimulation; cTBS = continuous theta burst stimulation; iTBS = intermittent theta burst stimulation; blTBS = bilateral theta burst stimulation; sTMS = synchronised transcranial magnetic stimulation; tDCS = transcranial direct current stimulation. *inverse variance method used.

Table 8

Random-Effects Meta-Analysis of All-cause Discontinuation Rates

Treatment Modality	*k*	Odds Ratio	95% Confidence Interval		Q	I^2
HF-L	35	0.86	0.60	1.23	14.58	0.0%
LF-R	3	0.48	0.12	1.99	0.35	0.0%
LF-L	3	0.84	0.11	6.73	0.71	0.0%
BL	6	0.90	0.33	2.43	3.03	0.0%
cTBS*	1	1.00	0.02	53.66	-	-
iTBS	2	1.06	0.06	17.66	0.00	0.0%
BLTBS	2	0.47	0.04	5.88	0.23	0.0%
dTMS	2	1.03	0.32	3.36	2.10	52.3%
sTMS	2	0.72	0.36	1.44	0.32	0.0%
tDCS	10	1.34	0.71	2.52	6.66	0.0%

Note. HF-L = high-frequency, left-sided repetitive transcranial magnetic stimulation; LF-R = low-frequency, right-sided repetitive transcranial magnetic stimulation; LF-L = low-frequency, left-sided repetitive transcranial magnetic stimulation; BL = bilateral repetitive transcranial magnetic stimulation; dTMS = deep transcranial magnetic stimulation; cTBS = continuous theta burst stimulation; iTBS = intermittent theta burst stimulation; blTBS = bilateral theta burst stimulation; sTMS = synchronised transcranial magnetic stimulation; tDCS = transcranial direct current stimulation. *inverse variance method used.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Records excluded (n=2,071)
Full-text articles assessed for eligibility (n=153)
Full-text articles excluded:
Did not meet age criteria (n=21)
Different stimulation technique (n=8)
Did not present data on depressive symptoms (n=13)
Presented duplicate data (n=13)
Co-initiation of medication (n=9)
Co-initiation of CCT (n=3)
Co-initiation of sleep deprivation (n=1)
Did not include a sham condition (n=14)
Cannot be obtained (n=5)
Case report (n=2)
Editorial (n=1)
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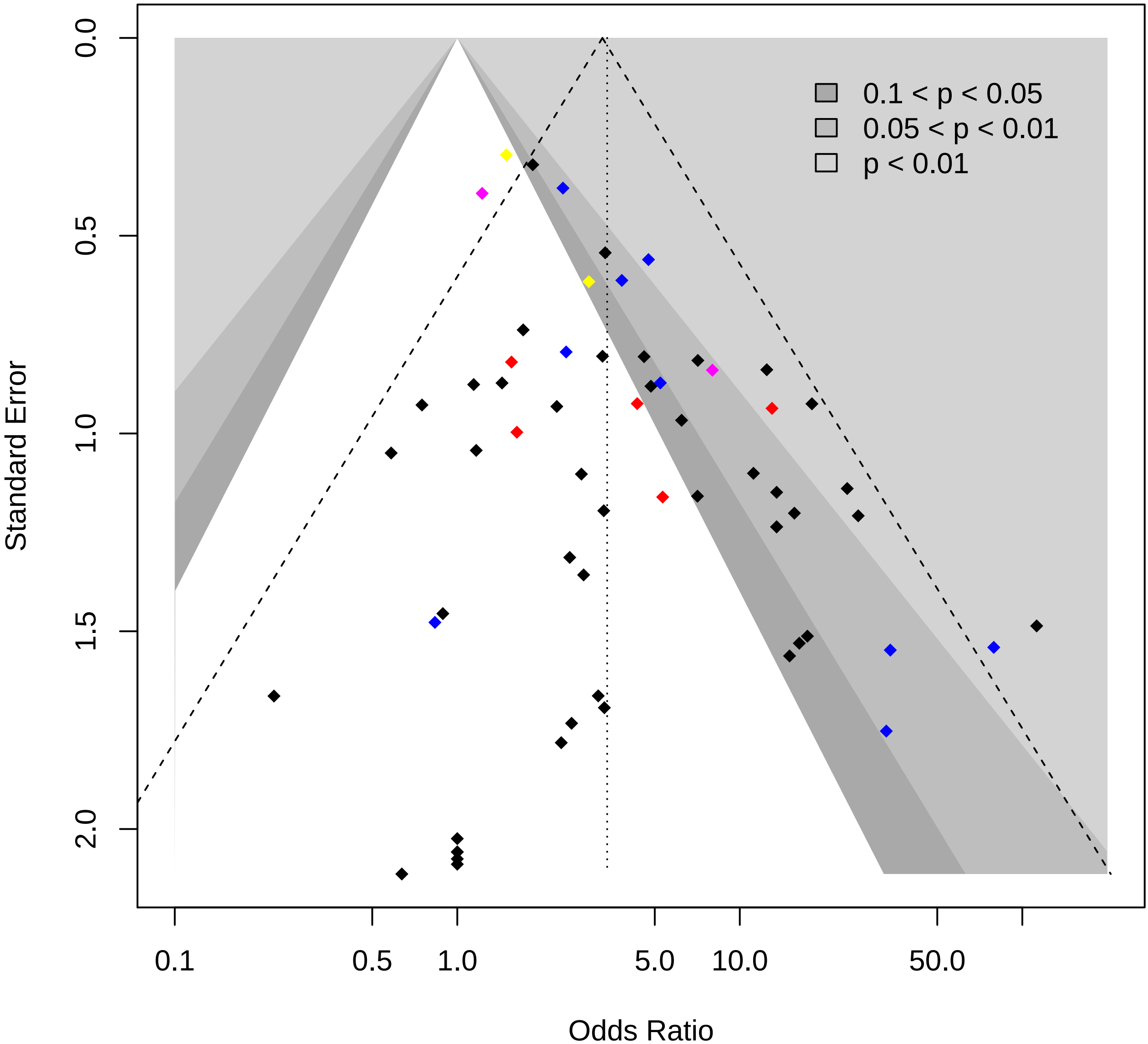
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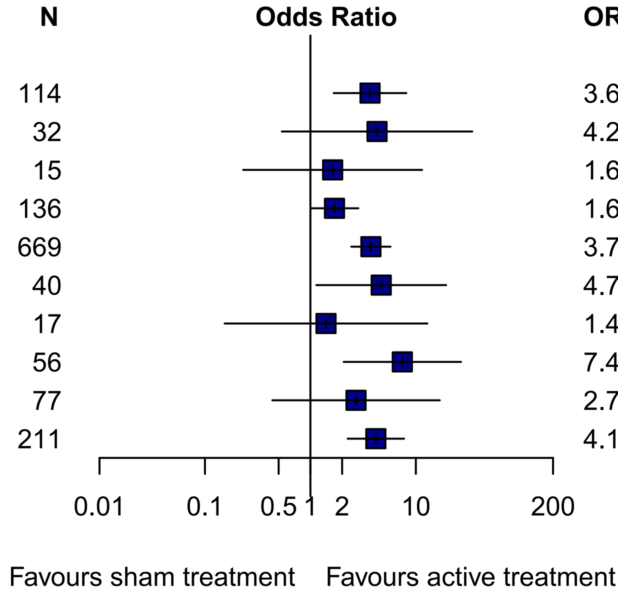
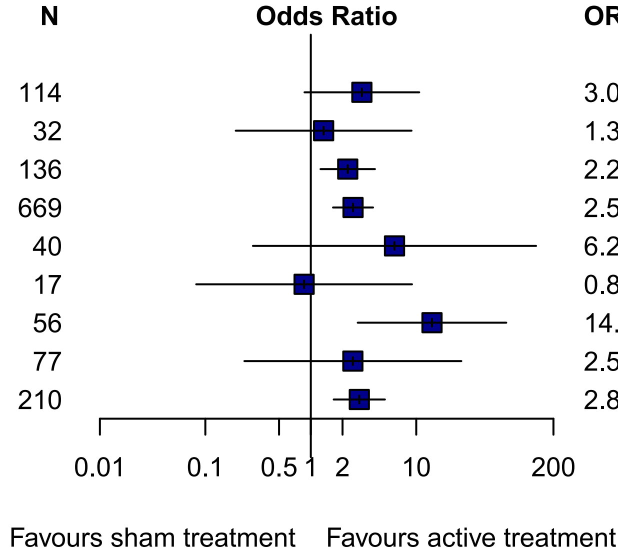
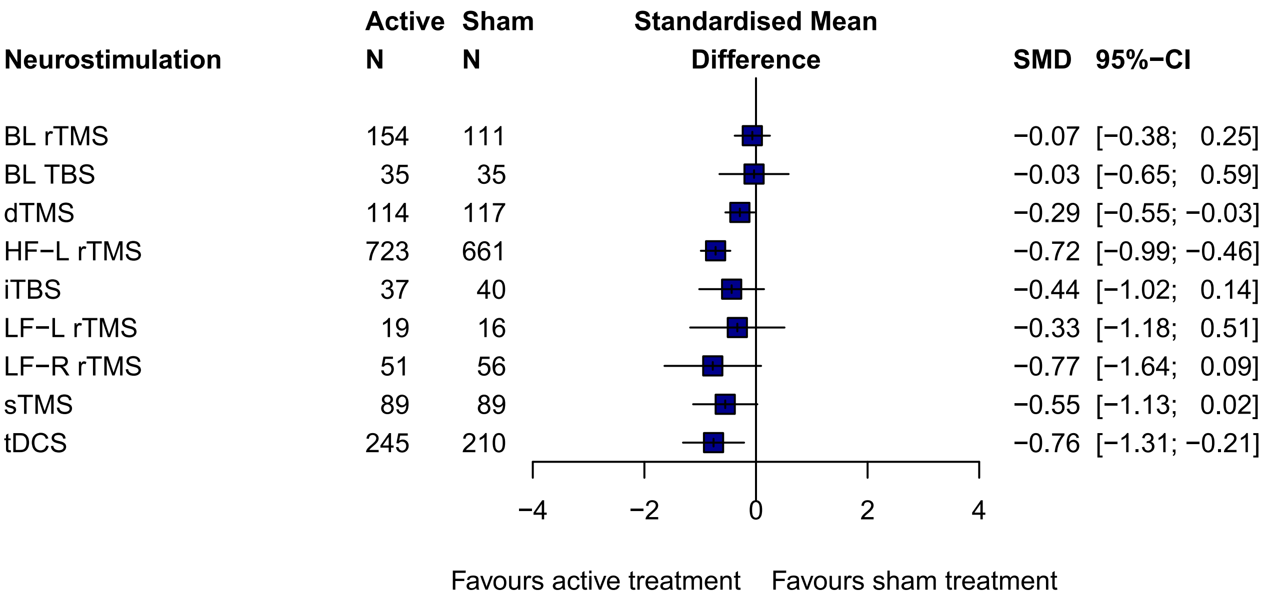
0.5
1.0
5.0
10.0
50.0
Odds Ratio

	Active		Sham			
Neurostimulation	**n**	**N**	**n**	**N**	**OR**	**95%−CI**
BL rTMS	38	154	10	114	3.68	[1.66; 8.13]
BL TBS	15	35	5	32	4.28	[0.54; 34.27]
cTBS	3	15	2	15	1.62	[0.23; 11.46]
dTMS	49	126	37	136	1.69	[1.00; 2.85]
HF−L rTMS	222	734	70	669	3.75	[2.44; 5.75]
iTBS	10	37	3	40	4.70	[1.14; 19.38]
LF−L rTMS	1	19	0	17	1.41	[0.15; 12.88]
LF−R rTMS	15	51	3	56	7.44	[2.06; 26.83]
sTMS	36	89	20	77	2.71	[0.44; 16.86]
tDCS	105	246	32	211	4.17	[2.25; 7.74]



Neurostimulation	Active n	Active N	Sham n	Sham N	OR	95%−CI
BL rTMS	19	154	3	114	3.05	[0.87; 10.67]
BL TBS	3	35	2	32	1.32	[0.19; 9.02]
dTMS	38	126	22	136	2.24	[1.24; 4.06]
HF−L rTMS	107	734	30	669	2.52	[1.62; 3.89]
iTBS	2	37	0	40	6.22	[0.28; 136.90]
LF−L rTMS	0	19	0	17	0.86	[0.08; 9.11]
LF−R rTMS	13	51	2	56	14.10	[2.79; 71.42]
sTMS	21	89	11	77	2.51	[0.23; 26.76]
tDCS	62	245	19	210	2.88	[1.65; 5.04]




Neurostimulation
Active N
Sham N
Standardised Mean Difference
SMD
95%−CI
BL rTMS 154 111 −0.07 [−0.38; 0.25]
BL TBS 35 35 −0.03 [−0.65; 0.59]
dTMS 114 117 −0.29 [−0.55; −0.03]
HF−L rTMS 723 661 −0.72 [−0.99; −0.46]
iTBS 37 40 −0.44 [−1.02; 0.14]
LF−L rTMS 19 16 −0.33 [−1.18; 0.51]
LF−R rTMS 51 56 −0.77 [−1.64; 0.09]
sTMS 89 89 −0.55 [−1.13; 0.02]
tDCS 245 210 −0.76 [−1.31; −0.21]
−4
−2
0
2
4
Favours active treatment
Favours sham treatment

Neurostimulation	Active n	Active N	Sham n	Sham N	OR	95%−CI
BL rTMS	8	158	9	118	0.90	[0.33; 2.43]
BL TBS	0	35	1	33	0.47	[0.04; 5.88]
cTBS	0	15	0	15	1.00	[0.02; 53.66]
dTMS	18	137	22	148	1.03	[0.32; 3.36]
HF−L rTMS	60	764	69	705	0.86	[0.60; 1.23]
iTBS	0	37	0	40	1.06	[0.06; 17.66]
LF−L rTMS	1	19	1	17	0.84	[0.11; 6.73]
LF−R rTMS	3	51	8	56	0.48	[0.12; 2.00]
sTMS	18	136	22	118	0.72	[0.36; 1.44]
tDCS	32	246	19	210	1.34	[0.71; 2.52]