Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis

Julian Mutz,[1] Vijeinika Vipulananthan,[2] Ben Carter,[3] René Hurlemann,[4] Cynthia H Y Fu,[5,6] Allan H Young[2,6]

[1]Social Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, UK

[2]South London and Maudsley Foundation NHS Trust, London, UK

[3]Department of Biostatistics, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

[4]Department of Psychiatry and Division of Medical Psychology, University of Bonn Medical Centre, Bonn, Germany

[5]School of Psychology, College of Applied Health and Communities, University of East London, London, UK

[6]Centre for Affective Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Correspondence to: J Mutz julian.mutz@gmail.com (or @julianmutz on Twitter ORCID 0000-0001-5308-1957)

Additional material is published online only. To view please visit the journal online.

ABSTRACT

OBJECTIVE
To estimate the comparative clinical efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults.

DESIGN
Systematic review with pairwise and network meta-analysis.

DATA SOURCES
Electronic search of Embase, PubMed/Medline, and PsycINFO up to 8 May 2018, supplemented by manual searches of bibliographies of several reviews (published between 2009 and 2018) and included trials.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES
Clinical trials with random allocation to electroconvulsive therapy (ECT), transcranial magnetic stimulation (repetitive (rTMS), accelerated, priming, deep, and synchronised), theta burst stimulation, magnetic seizure therapy, transcranial direct current stimulation (tDCS), or sham therapy.

MAIN OUTCOME MEASURES
Primary outcomes were response (efficacy) and all cause discontinuation (discontinuation of treatment for any reason) (acceptability), presented as odds ratios with 95% confidence intervals. Remission and continuous depression severity scores after treatment were also examined.

RESULTS
113 trials (262 treatment arms) that randomised 6750 patients (mean age 47.9 years; 59% women) with major depressive disorder or bipolar depression met the inclusion criteria. The most studied treatment comparisons were high frequency left rTMS and tDCS versus sham therapy, whereas recent treatments remain understudied. The quality of the evidence was typically of low or unclear risk of bias (94 out of 113 trials, 83%) and the precision of summary estimates for treatment effect varied considerably. In network meta-analysis, 10 out of 18 treatment strategies were associated with higher response compared with sham therapy: bitemporal ECT (summary odds ratio 8.91, 95% confidence interval 2.57 to 30.91), high dose right unilateral ECT (7.27, 1.90 to 27.78), priming transcranial magnetic stimulation (6.02, 2.21 to 16.38), magnetic seizure therapy (5.55, 1.06 to 28.99), bilateral rTMS (4.92, 2.93 to 8.25), bilateral theta burst stimulation (4.44, 1.47 to 13.41), low frequency right rTMS (3.65, 2.13 to 6.24), intermittent theta burst stimulation (3.20, 1.45 to 7.08), high frequency left rTMS (3.17, 2.29 to 4.37), and tDCS (2.65, 1.55 to 4.55). Network meta-analytic estimates of active interventions contrasted with another active treatment indicated that bitemporal ECT and high dose right unilateral ECT were associated with increased response. All treatment strategies were at least as acceptable as sham therapy.

CONCLUSIONS
These findings provide evidence for the consideration of non-surgical brain stimulation techniques as alternative or add-on treatments for adults with major depressive episodes. These findings also highlight important research priorities in the specialty of brain stimulation, such as the need for further well designed randomised controlled trials comparing novel treatments, and sham controlled trials investigating magnetic seizure therapy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Non-surgical brain stimulation techniques, including electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and other treatment modalities have been applied as tertiary treatments for major depressive episodes

Previous network meta-analyses were limited in scope of interventions and included studies that had co-initiated drug treatment, thereby providing narrow insights into the clinical efficacy and acceptability of these treatments

WHAT THIS STUDY ADDS

The findings of this network meta-analysis provide evidence for the consideration of non-surgical brain stimulation techniques as alternative or add-on treatments for adults with major depressive episodes

Treatment protocols with robust evidence and more precision in treatment effect estimates (high frequency left rTMS, low frequency right rTMS, bilateral rTMS, and transcranial direct current stimulation) should be prioritised over novel protocols with a more limited evidence base

Introduction

Major depression is a highly prevalent and debilitating illness with considerable disease burden.[1][2] Its clinical course is often recurrent and can become chronic, with relapse rates of up to 80% within one year of remission.[3] Multiple treatments are available, with drug interventions and psychological therapies being the most commonly prescribed. The effectiveness of these treatments, however, remains limited and less than 50% of patients respond to an initial course of drug treatment.[4] A large number of patients do not tolerate pharmacotherapy because of undesired effects, including sexual dysfunction, weight gain, and insomnia.[5][6] Combination strategies using multiple drugs increase the risk for adverse events and drug

interactions.[7] These factors limit adherence and potentially result in discontinuation of treatment.[8] Similarly, psychological therapies are not effective for every patient and might also be associated with undesired effects.[9]

Non-surgical brain stimulation techniques, including electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) have been applied as tertiary treatments for major depressive episodes. Over the past decade, novel modifications of standard rTMS have been developed to optimise treatment: deep, priming, accelerated, or synchronised transcranial magnetic stimulation, and theta burst stimulation. Clinical trials have also examined the antidepressant efficacy of transcranial direct current stimulation (tDCS) and magnetic seizure therapy (see box 1 and supplementary file section 01).

Previous meta-analyses have examined the clinical efficacy and acceptability of brain stimulation compared with sham therapy[10] or within pairs of active treatments.[11] These approaches provide limited insights into the overall treatment hierarchy because treatment effects are estimated from, and presented for, a subset of relevant treatment comparisons only. Furthermore, the absence of head-to-head clinical trials for some treatment comparisons creates uncertainty for decision makers. Network meta-analysis includes both direct and indirect treatment comparisons[12] in a single analysis, thereby providing more complete insights into the clinical efficacy and acceptability of interventions. It should therefore be regarded as the highest level of evidence in treatment

guidelines.[13] Two network meta-analyses of brain stimulation therapies for major depressive episodes have been published but were limited in scope of included interventions.[14][15] The first meta-analysis provided a comprehensive synthesis of the available evidence for rTMS but did not include ECT, magnetic seizure therapy, or tDCS[14]; moreover, studies that had co-initiated pharmacotherapy were included in the analyses, potentially inflating efficacy estimates of rTMS. The second meta-analysis included trials that compared rTMS with ECT but did not include sham controlled trials or distinguish the various electrode placements or electrical dosages of ECT.[15]

We estimated the efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults participating in randomised clinical trials.
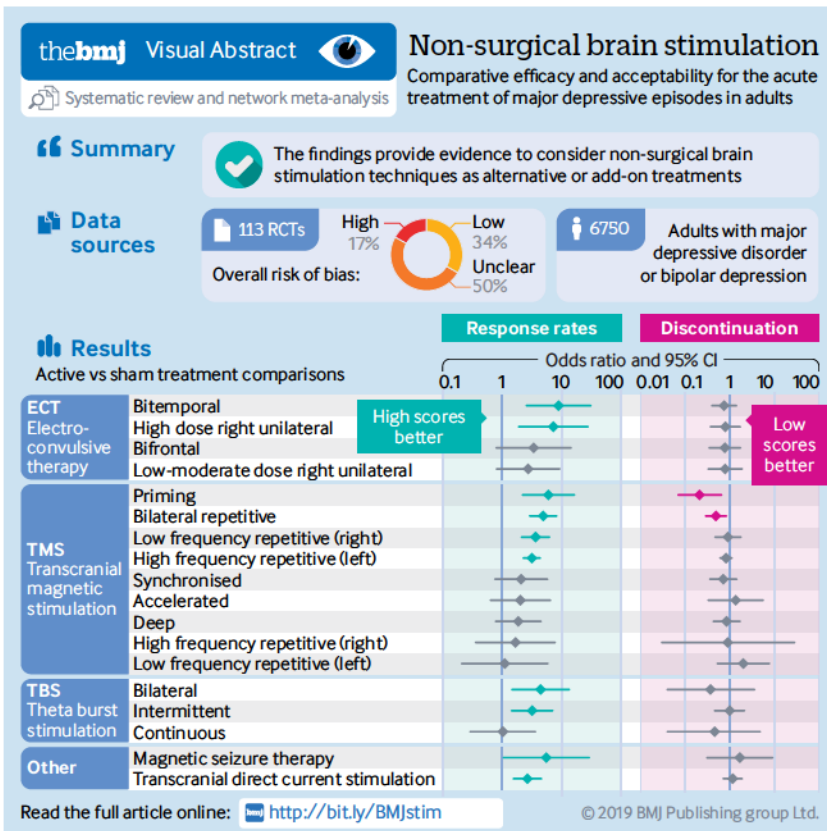
Methods

We followed the PRISMA guidelines for network meta-analysis.[16] The study was conducted between 17 January 2017 and 4 September 2018. No review protocol or registration details are available.

Criteria for considering studies for this review

We included randomised controlled trials with parallel group or crossover designs. Only data from period 1 in crossover trials were analysed to avoid potential carry-over effects. Studies needed to include a clinician administered depression rating scale, the Hamilton Depression Rating Scale,[17] or the Montgomery-Åsberg Depression Rating Scale.[18] We excluded conference abstracts, editorials, reviews, meta-analyses, and case reports or case series, as well as non-English language publications and publications reporting duplicate data.

Participants had to be adults (≥18 years) with a diagnosis of major depressive disorder or bipolar depression according to *Research Diagnostic Criteria, Diagnostic and Statistical Manual of Mental Disorders* (third, fourth, text revision of the fourth, and fifth editions), or *International Classification of Diseases* (ninth and 10th revisions). We excluded other primary diagnoses, trials that recruited patients with a subtype of depression (eg, postpartum depression) or with depression as a secondary diagnosis (eg, fibromyalgia and depression), and animal studies.

Studies had to include at least two of the following treatments: tDCS, theta burst stimulation, transcranial magnetic stimulation (rTMS, accelerated, priming, deep, or synchronised), ECT, magnetic seizure therapy, or sham therapy. For rTMS, we grouped treatment protocols according to coil location and stimulation frequency: high frequency stimulation of the left dorsolateral prefrontal cortex, high frequency stimulation of the right dorsolateral prefrontal cortex, low frequency stimulation of the right dorsolateral prefrontal cortex, low frequency stimulation of the left dorsolateral prefrontal cortex, and bilateral stimulation of the dorsolateral prefrontal cortex. We grouped theta burst stimulation strategies in a similar

the bmj Visual Abstract
Systematic review and network meta-analysis

Non-surgical brain stimulation
Comparative efficacy and acceptability for the acute treatment of major depressive episodes in adults

Summary — The findings provide evidence to consider non-surgical brain stimulation techniques as alternative or add-on treatments

Data sources — 113 RCTs | Overall risk of bias: High 17%, Low 34%, Unclear 50% | 6750 Adults with major depressive disorder or bipolar depression

Results — Active vs sham treatment comparisons

Read the full article online: http://bit.ly/BMJstim

© 2019 BMJ Publishing group Ltd.

Box 1 Description of treatment strategies

Electroconvulsive therapy
- Electroconvulsive therapy (ECT) involves an electrical current being passed through the brain to induce a generalised seizure. Electrode placement and electrical dosage are the treatment variables most often studied to optimise clinical outcomes
  - *Bitemporal ECT*—electrodes are placed bilaterally over the temporal cortex. This is the most widely studied treatment
  - *Right unilateral ECT*—one electrode placed over the right temporal cortex and one placed on the crown of the head. Treatment is usually delivered at either low to moderate (1-2.5×seizure threshold) or high (4-8×seizure threshold) electrical dosage
  - *Bifrontal ECT*—electrodes placed about 5 cm above the lateral angle of both hemispheres. Treatment targets the frontal cortex

Transcranial magnetic stimulation
- Transcranial magnetic stimulation utilises electromagnetic fields to alter neural activity in relatively focal, superficial areas of the brain
  - *Repetitive transcranial magnetic stimulation (rTMS)*—delivers repeated electromagnetic pulses to induce prolonged modulation of neural activity, typically of the dorsolateral prefrontal cortex. The prevailing hypothesis is that high frequency (>5 Hz) stimulation is excitatory and causes neural depolarisation, whereas low frequency (≤1 Hz) stimulation inhibits neural firing. The most common treatment protocols are:
    - High frequency stimulation of the left dorsolateral prefrontal cortex
    - Low frequency stimulation of the right dorsolateral prefrontal cortex
    - Bilateral stimulation of the dorsolateral prefrontal cortex
  - *Accelerated transcranial magnetic stimulation*—multiple treatment sessions of rTMS administered daily to reduce overall treatment duration
  - *Priming transcranial magnetic stimulation*—preceding low frequency rTMS with a brief period of low intensity high frequency stimulation to enhance the neural response to rTMS
  - *Deep transcranial magnetic stimulation*—a different coil configuration (H coil) that enables larger volumes and deeper structures of the brain to be stimulated
  - *Synchronised transcranial magnetic stimulation*—rotating spherical neodymium magnets are positioned along the midline of the scalp to deliver stimulation synchronised to an individual's α frequency
  - *Theta burst stimulation*—a patterned form of rTMS. Current treatment protocols are:
    - Continuous stimulation of the right dorsolateral prefrontal cortex, which delivers 300 or 600 pulses without interruption
    - Intermittent stimulation of the left dorsolateral prefrontal cortex, which delivers 30 pulses every 10 seconds up to a total of 600 pulses
    - Bilateral stimulation of the dorsolateral prefrontal cortex

Magnetic seizure therapy
- Magnetic seizure therapy utilises magnetic fields to induce a generalised seizure. It is a more focal intervention than ECT and targets the prefrontal cortex

Transcranial electrical stimulation
- Transcranial direct current stimulation (tDCS) involves a low amplitude electrical direct current applied through electrodes on the scalp, targeting superficial areas of the brain. Although tDCS does not trigger action potentials, it modulates cortical excitability by shifting the neural membrane resting potential. Anodal stimulation is hypothesised to cause depolarisation and to increase neural excitability, whereas cathodal stimulation would cause hyperpolarisation and decrease cortical excitability

---

way: intermittent stimulation of the left dorsolateral prefrontal cortex, continuous stimulation of the right dorsolateral prefrontal cortex, and bilateral stimulation of the dorsolateral prefrontal cortex. ECT strategies were grouped according to electrode placement (bitemporal, right unilateral, and bifrontal), and for right unilateral ECT also according to electrical dosage (high and low to moderate). Our decision to group treatment strategies in this way is in line with previous investigations and clinical guidelines and information leaflets (eg, www.nice.org.uk). For multi-arm trials, we combined treatment groups that could not be included individually.[19] Sham controls were merged into one node for the main analysis. Supplementary file section 02 shows the network of potential treatment comparisons. We assumed that any participant receiving one of the treatments included in our review is, in principle, equally likely to be randomised to any other treatment in the network.

We excluded studies examining vagus nerve stimulation or related interventions and trials in which drug or psychological treatments were co-initiated with brain stimulation.

Identification of studies

We carried out an electronic search of Embase, PubMed/Medline, and PsycINFO (accessed via Ovid) for articles published from inception to 8 May 2018. Supplementary file section 03 provides a full description of our search methods. Two authors (JM and VV) independently performed the literature search, screened titles and abstracts, and selected relevant full texts and assessed these for eligibility.

Data extraction

One author (JM) extracted relevant information from eligible trials, and a second author (VV) independently reviewed these data. Discrepancies were resolved by consensus. We used WebPlotDigitizer (https://apps.automeris.io/wpd/) to extract numerical data from figures. In some instances we derived means or standard deviations from individual patient data or standard errors, and categorical data from individual patient data or percentages. Data that could not be retrieved from the original publications were requested from the corresponding authors or searched for in other reviews.

Participant and intervention characteristics

We extracted information on participants' baseline depression severity scores (mean, standard deviation), sex (men or women), age in years (mean, standard deviation, and range), hospital status (outpatient, inpatient, or mixed), whether patients with psychotic symptoms were excluded from the trial (yes or no), diagnosis (major depressive disorder, bipolar depression, or mixed), treatment strategy (monotherapy, add-on therapy, or mixed), and whether patients were considered treatment resistant (yes, no, or mixed).

For ECT we extracted data on electrical dosage (multiples of seizure threshold) and electrode placement. For rTMS we extracted data on coil location and stimulation frequency (in hertz). Similar data were extracted for theta burst stimulation, also including the treatment strategy (intermittent, continuous, or bilateral).

Study design and outcomes

We also extracted data on crossover design (yes or no); version of Hamilton Depression Rating Scale; response and remission criteria; the number of patients randomised, meeting response and remission criteria at primary treatment endpoint, discontinuing treatment for any reason, and analysed; and post-treatment depression severity scores (final score mean and standard deviation).

Risk of bias assessment

We used the Cochrane tool for assessing risk of bias in randomised trials[20] to evaluate each study. Potential sources of bias include random sequence generation, allocation concealment, blinding of participants and staff, blinding of outcome assessors, incomplete outcome data, and selective reporting. Each trial received a study level score of low, high, or unclear risk of bias for each domain. Two authors (JM and VV) independently conducted this assessment, and discrepancies were resolved by consensus.

Data synthesis

To estimate effect sizes for categorical and continuous outcomes, we computed odds ratios (Mantel-Haenszel method) and standardised mean differences (Hedge's g) with 95% confidence intervals (DerSimonian-Laird method), respectively. The primary outcome measure of efficacy was response, defined in most trials as a 50% or greater reduction in depressive symptoms at primary treatment endpoint. Remission was our secondary outcome measure of efficacy, according to the criteria used in each trial (eg, Hamilton Depression Rating Scale score ≤7 at primary treatment endpoint). Continuous depression severity scores after treatment constituted our tertiary efficacy outcome measure. Our primary outcome measure of acceptability was all cause discontinuation (discontinuation of treatment for any reason). If trials reported data on both the Hamilton Depression Rating Scale and the Montgomery-Åsberg Depression Rating Scale, we selected the Hamilton Depression Rating Scale data for analyses to facilitate comparability between trials. When multiple versions of the Hamilton Depression Rating Scale existed, we used the original 17 item scale for analysis. We preferred data based on the intention-to-treat sample (ie, number of participants randomised) or modified intention-to-treat sample (ie, number of participants who attended at least one treatment session) over data based on completers for all analyses.

Pairwise meta-analysis

We conducted frequentist random effects (DerSimonian-Laird estimator[21]) meta-analyses for all direct treatment comparisons, allowing for heterogeneity in treatment effects between studies. Pairwise analyses were conducted using the "meta" package (version 4.9-4)[22] in RStudio 1.0.143.

The proportion of the total variance within each pairwise comparison that is due to between study heterogeneity was estimated using the I^2 statistic.[23] We also report the heterogeneity variance τ^2 (DerSimonian-Laird estimator) for each pairwise comparison as a measure of heterogeneity that is independent of sample size.

Network meta-analysis

To visualise network geometry and node connectivity, we produced network plots for each outcome.[24] Network meta-analyses were fit within a frequentist framework using a multivariate random effects (restricted maximum likelihood estimation) meta-analysis model[25 26] that accounts for the correlations between effect sizes in trials with more than two groups.

We assumed network consistency and a common heterogeneity parameter across all treatment contrasts. For all treatment comparisons we present summary odds ratios or standardised mean differences and 95% confidence intervals that account for uncertainty in variance estimates[27] in league tables. We also present summary treatment effects with 95% confidence intervals and 95% prediction intervals[24] for all sham comparisons in forest plots. To obtain treatment hierarchies, we used a parametric bootstrap procedure with 10 000 resamples to compute ranking probabilities for all ranks and outcomes.[26] Mean rankings as well as Surface Under the Cumulative Ranking curve (SUCRA) values were computed for each treatment. Network meta-analyses were conducted using the "mvmeta"[28 29] and "network"[30] packages in Stata SE 15.0.

We assessed the transitivity assumption by comparing the distribution or frequency of potential effect modifiers across treatment comparisons: continuous (depression severity at baseline, age, percentage of women) and categorical (treatment resistance, diagnosis, hospital status, exclusion of participants with psychotic features, and treatment strategy). Finally, we assessed the efficacy of the different sham interventions as additional proof of transitivity by computing pre-post treatment changes in continuous depression severity score (Hedge's g) for transcranial magnetic stimulation sham therapy, tDCS sham therapy, and ECT sham therapy. Considering that

the ECT sham controlled trials were substantially older than the rTMS and tDCS sham controlled trials, and because the discussion is ongoing that placebo effects in antidepressant trials could have increased over time,[31] [32] we investigated whether there is evidence of an association between date of publication and sham efficacy in our data.

Assuming equivalence of direct and indirect evidence (ie, consistency) in network meta-analyses might lead to inaccurate conclusions when there is evidence for statistically significant inconsistency.[26] Hence we assessed the assumption of consistency by fitting a design-by-treatment interaction model,[25] [26] which accounts for loop and design inconsistencies and provides a global Wald test to evaluate inconsistency in the entire network.

To estimate absolute differences between direct and indirect evidence we also computed inconsistency factors and 95% confidence intervals for each closed triangular and quadratic loop within treatment networks. We used a method of moments estimator of loop specific heterogeneity, assuming a common heterogeneity parameter for all comparisons within the same loop.[24] [33]

Sensitivity analysis
We conducted several sensitivity analyses to assess the robustness of our findings for response and all cause discontinuation rates, by excluding trials that examined tDCS, excluding trials that examined ECT or magnetic seizure therapy, and excluding trials with high overall risk of bias.

Small study effects
To evaluate the presence of small study effects we visually inspected comparison adjusted funnel plots for each outcome.[24] We produced funnel plots for all comparisons concerning active treatment versus sham therapy.

Patient and public involvement
The initial draft of this paper was reviewed by a patient editor at *The BMJ*. No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results
Overall, 113 randomised controlled trials (262 treatment arms) met our inclusion criteria (fig 1 and supplementary file section 04). Section 05 of the supplementary file provides the full citations of the included trials and section 06 provides details of the excluded trials and reasons for exclusion.

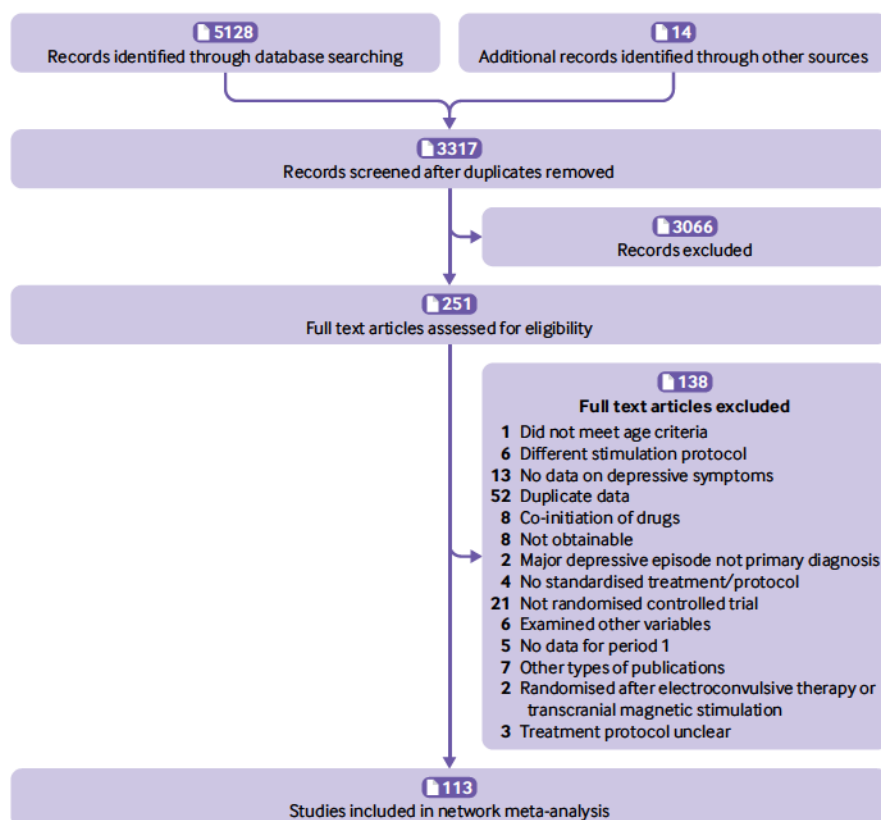Overall, 6750 participants (mean age 47.9 years) were randomised to treatment. Fifty nine per cent

Fig 1 | PRISMA flow diagram

(n=3545) were women. The median study sample size was 40 participants (range 6-414). The most common treatment comparisons, which made a large contribution to each network estimation, were high frequency left rTMS versus sham therapy, bilateral rTMS versus sham therapy, bitemporal ECT versus high dose right unilateral ECT, and tDCS versus sham therapy (see supplementary file section 07). More recent treatment modalities (eg, accelerated transcranial magnetic stimulation, priming transcranial magnetic stimulation, bilateral theta burst stimulation, and continuous theta burst stimulation) as well as sham controlled ECT trials were represented by a small number of treatment comparisons, reflecting novelty and the ethical challenges of administering sham ECT. Section 08 in the supplementary file presents the risk of bias assessment. Briefly, 34% of the included trials were considered low risk, 50% unclear risk, and 17% high risk.

Most trials (81%) recruited only patients with treatment resistant depression, typically defined as a minimum of two failed drug treatments, 13% recruited patients with treatment resistant depression and non-treatment resistant depression, and the remaining 6% recruited patients with non-treatment resistant depression. Overall, 59% of the studies excluded patients with psychotic features. Forty nine per cent recruited patients with major depressive disorder only. For the trials that recruited patients with major depressive disorder and bipolar depression (46%), few patients had a diagnosis of bipolar depression. Regarding hospital status, 49% of trials recruited outpatients only, 29% inpatients only, and 22% both outpatients and inpatients. In 63% of the studies, brain stimulation was an add-on treatment to stable drug treatment in most, if not all, patients (see supplementary file sections 04 and 09). Baseline depression severity, percentage of women, and age were similar across most treatment comparisons (see supplementary file section 09). Moreover, changes in continuous depression severity score of the different sham interventions pre-post treatment were medium to large (transcranial magnetic stimulation sham therapy: standardised mean difference 0.83, 95% confidence interval 0.66 to 1.00, τ^2=0.21, I^2=66%; tDCS sham therapy: 0.97, 0.72 to 1.22, τ^2=0.06, I^2=41%; and ECT sham therapy: 0.66, 0.17 to 1.15; see supplementary file section 10) with no evidence for subgroup differences between sham groups ($Q_{(2)}$=1.51, P=0.47). We also did not find evidence of an association between sham efficacy and date of publication ($F_{(1,62)}$=3.30, P=0.07; see supplementary file section 11). As such, the assumption of transitivity is likely to hold in our data.

Pairwise meta-analysis

Supplementary file section 12 presents the results of the pairwise meta-analysis and heterogeneity estimates. Briefly, bitemporal ECT, high frequency left rTMS, low frequency right rTMS, tDCS, and deep transcranial magnetic stimulation were more efficacious than sham therapy across all outcomes (response: summary odds ratio 1.69 (minimum) to 5.50 (maximum); remission: 2.24 to 5.54; continuous post-treatment depression severity: standardised mean difference −0.29 to −0.77). Bilateral rTMS was more efficacious than sham therapy for response (4.93, 95% confidence interval 2.78 to 8.75; τ^2=0; I^2=0%, 95% confidence interval 0% to 41.2%) and remission (4.67, 1.84 to 11.84; τ^2=0; I^2=0%, 0% to 70.2%), whereas intermittent theta burst stimulation was more efficacious than sham therapy for response (4.25, 1.22 to 14.84; τ^2=0; I^2=0%, 0% to 0%). There were few differences between active treatments. Most notably, bitemporal ECT was more efficacious than low to moderate dose right unilateral ECT across all outcomes (response: 3.87, 2.26 to 6.64; τ^2=0; I^2=0%, 0% to 76.6%; remission: 6.67, 1.87 to 23.71; post-treatment depression severity: standardised mean difference −0.88, −1.28 to −0.49; τ^2=0; I^2=0%, 0% to 73.4%). We found no differences between active treatments and sham therapy for all cause discontinuation.

Network meta-analysis

Figure 2 shows the results of the network meta-analysis for the primary outcome of efficacy (response) and acceptability (all cause discontinuation). Response rates were available for 208 treatment arms (5962 participants) including all 18 active interventions and sham therapy (fig 3).

The results of the network meta-analysis indicate that bitemporal ECT (summary odds ratio 8.91, 95% confidence interval 2.57 to 30.91), high dose right unilateral ECT (7.27, 1.90 to 27.78), priming transcranial magnetic stimulation (6.02, 2.21 to 16.38), magnetic seizure therapy (5.55, 1.06 to 28.99), bilateral rTMS (4.92, 2.93 to 8.25), bilateral theta burst stimulation (4.44, 1.47 to 13.41), low frequency right rTMS (3.65, 2.13 to 6.24), intermittent theta burst stimulation (3.20, 1.45 to 7.08), high frequency left rTMS (3.17, 2.29 to 4.37), and tDCS (2.65, 1.55 to 4.55) were more efficacious than sham therapy (fig 4).

In the comparisons between two active treatments, bitemporal ECT was associated with higher response than bifrontal ECT, low to moderate dose right unilateral ECT, low frequency left rTMS, continuous theta burst stimulation, and deep transcranial magnetic stimulation. High dose right unilateral ECT was associated with higher response than low to moderate dose right unilateral ECT and continuous theta burst stimulation. Priming transcranial magnetic stimulation and bilateral rTMS were associated with higher response than continuous theta burst stimulation. We did not find statistical evidence to suggest any other differences between active treatments (fig 2).

All cause discontinuation rates were available for 227 treatment arms (6362 participants), including all 18 active interventions and sham therapy (fig 5).

The results of the network meta-analysis suggest that priming transcranial magnetic stimulation was more acceptable than low frequency left rTMS (summary odds ratio 0.11, 95% confidence interval

All cause discontinuation (upper triangle) / **Response** (lower triangle)

	tDCS	sTMS	pTMS	iTBS	dTMS	cTBS	blTBS	aTMS	MST	LMRUL ECT	LFR rTMS	LFL rTMS	HRUL ECT	HFR rTMS	HFL rTMS	BT ECT	BL rTMS	BF ECT	SHM
tDCS		1.62 (0.70 to 3.78)	5.46 (1.63 to 18.31)	1.17 (0.47 to 2.91)	1.37 (0.59 to 3.20)	2.55 (0.23 to 28.01)	3.12 (0.31 to 31.59)	0.86 (0.19 to 3.83)	0.69 (0.12 to 4.03)	1.48 (0.54 to 4.06)	1.28 (0.56 to 2.92)	0.58 (0.14 to 2.41)	1.47 (0.59 to 3.6)	1.30 (0.04 to 42.23)	1.41 (0.80 to 2.51)	1.56 (0.70 to 3.45)	2.38 (1.15 to 4.94)	1.50 (0.59 to 3.82)	1.17 (0.72 to 1.91)
sTMS	1.27 (0.41 to 3.95)		3.37 (0.92 to 12.38)	0.72 (0.26 to 2.03)	0.85 (0.32 to 2.24)	1.57 (0.14 to 18.13)	1.93 (0.18 to 20.47)	0.53 (0.11 to 2.55)	0.43 (0.07 to 2.65)	0.91 (0.30 to 2.79)	0.79 (0.30 to 2.05)	0.36 (0.08 to 1.61)	0.91 (0.32 to 2.54)	0.80 (0.02 to 26.93)	0.87 (0.41 to 1.84)	0.96 (0.38 to 2.44)	1.47 (0.61 to 3.52)	0.92 (0.32 to 2.65)	0.72 (0.36 to 1.44)
pTMS	0.44 (0.14 to 1.36)	0.35 (0.08 to 1.43)		0.21 (0.06 to 0.81)	0.25 (0.07 to 0.92)	0.47 (0.04 to 6.19)	0.57 (0.05 to 6.85)	0.16 (0.03 to 0.93)	0.13 (0.02 to 0.95)	0.27 (0.07 to 1.11)	0.23 (0.08 to 0.72)	0.11 (0.02 to 0.59)	0.27 (0.07 to 1.02)	0.24 (0.01 to 8.84)	0.26 (0.08 to 0.79)	0.28 (0.08 to 1.01)	0.44 (0.16 to 1.16)	0.27 (0.07 to 1.06)	0.21 (0.07 to 0.65)
iTBS	0.83 (0.32 to 2.16)	0.65 (0.18 to 2.37)	1.88 (0.54 to 6.57)		1.17 (0.42 to 3.28)	2.17 (0.19 to 24.42)	2.66 (0.26 to 27.58)	0.73 (0.15 to 3.49)	0.59 (0.09 to 3.71)	1.26 (0.40 to 3.95)	1.09 (0.41 to 2.92)	0.49 (0.11 to 2.27)	1.25 (0.44 to 3.58)	1.10 (0.03 to 37.38)	1.20 (0.59 to 2.47)	1.33 (0.51 to 3.44)	2.03 (0.82 to 5.05)	1.28 (0.44 to 3.73)	1.00 (0.46 to 2.14)
dTMS	1.42 (0.51 to 3.95)	1.12 (0.29 to 4.25)	3.22 (0.85 to 12.11)	1.71 (0.53 to 5.58)		1.86 (0.16 to 21.41)	2.27 (0.21 to 24.18)	0.63 (0.13 to 3.01)	0.50 (0.08 to 3.13)	1.08 (0.35 to 3.29)	0.93 (0.36 to 2.42)	0.42 (0.09 to 1.90)	1.07 (0.38 to 3.01)	0.94 (0.03 to 31.80)	1.03 (0.49 to 2.18)	1.13 (0.45 to 2.88)	1.74 (0.72 to 4.16)	1.09 (0.38 to 3.13)	0.85 (0.43 to 1.70)
cTBS	2.58 (0.66 to 10.06)	2.03 (0.41 to 10.18)	5.84 (1.19 to 28.61)	3.11 (0.80 to 12.08)	1.82 (0.39 to 8.37)		1.23 (0.06 to 24.03)	0.34 (0.02 to 5.18)	0.27 (0.02 to 4.89)	0.58 (0.05 to 7.11)	0.50 (0.04 to 5.72)	0.23 (0.02 to 3.38)	0.58 (0.05 to 6.79)	0.51 (0.01 to 32.89)	0.55 (0.05 to 5.86)	0.61 (0.05 to 6.91)	0.93 (0.08 to 10.30)	0.59 (0.05 to 6.98)	0.46 (0.04 to 4.80)
blTBS	0.60 (0.17 to 2.04)	0.47 (0.11 to 2.11)	1.35 (0.32 to 5.71)	0.72 (0.21 to 2.45)	0.42 (0.10 to 1.72)	0.23 (0.05 to 1.02)		0.27 (0.02 to 3.93)	0.22 (0.01 to 3.72)	0.47 (0.04 to 5.35)	0.41 (0.04 to 4.23)	0.19 (0.01 to 2.56)	0.47 (0.04 to 5.11)	0.42 (0.01 to 25.60)	0.45 (0.05 to 4.39)	0.50 (0.05 to 5.19)	0.76 (0.08 to 7.52)	0.48 (0.04 to 5.25)	0.37 (0.04 to 3.60)
aTMS	1.31 (0.36 to 4.69)	1.03 (0.22 to 4.80)	2.96 (0.66 to 13.40)	1.58 (0.40 to 6.20)	0.92 (0.22 to 3.94)	0.51 (0.09 to 2.77)	2.19 (0.45 to 10.71)		0.81 (0.09 to 7.19)	1.73 (0.33 to 8.96)	1.49 (0.32 to 6.98)	0.67 (0.10 to 4.67)	1.71 (0.35 to 8.36)	1.51 (0.04 to 62.09)	1.65 (0.41 to 6.60)	1.81 (0.40 to 8.32)	2.78 (0.62 to 12.41)	1.74 (0.35 to 8.64)	1.36 (0.33 to 5.60)
MST	0.48 (0.08 to 2.72)	0.38 (0.05 to 2.63)	1.08 (0.16 to 7.41)	0.58 (0.09 to 3.54)	0.34 (0.05 to 2.19)	0.19 (0.02 to 1.47)	0.80 (0.11 to 5.81)	0.37 (0.05 to 2.69)		2.14 (0.42 to 10.78)	1.85 (0.30 to 11.27)	0.84 (0.10 to 7.18)	2.12 (0.44 to 10.26)	1.87 (0.04 to 86.69)	2.04 (0.37 to 11.10)	2.25 (0.44 to 11.37)	3.44 (0.55 to 20.15)	2.16 (0.43 to 10.88)	1.69 (0.31 to 9.16)
LMRUL ECT	0.97 (0.25 to 3.68)	0.76 (0.16 to 3.74)	2.19 (0.46 to 10.50)	1.17 (0.28 to 4.88)	0.68 (0.15 to 3.07)	0.38 (0.07 to 2.14)	1.62 (0.31 to 8.33)	0.74 (0.14 to 3.87)	2.02 (0.64 to 6.36)		0.86 (0.29 to 2.57)	0.39 (0.08 to 1.93)	0.99 (0.43 to 2.31)	0.87 (0.02 to 30.58)	0.95 (0.39 to 2.33)	1.05 (0.47 to 2.33)	1.61 (0.58 to 4.47)	1.01 (0.46 to 2.22)	0.79 (0.33 to 1.90)
LFR rTMS	0.73 (0.34 to 1.55)	0.57 (0.18 to 1.80)	1.65 (0.62 to 4.42)	0.88 (0.35 to 2.21)	0.51 (0.18 to 1.43)	0.28 (0.07 to 1.09)	1.22 (0.37 to 4.03)	0.56 (0.16 to 1.94)	1.52 (0.27 to 8.51)	0.75 (0.20 to 2.79)		0.45 (0.11 to 1.95)	1.15 (0.42 to 3.13)	1.01 (0.03 to 33.81)	1.10 (0.56 to 2.19)	1.22 (0.50 to 2.99)	1.86 (0.99 to 3.49)	1.17 (0.42 to 3.26)	0.91 (0.47 to 1.77)
LFL rTMS	2.39 (0.42 to 13.77)	1.89 (0.27 to 13.26)	5.42 (0.79 to 37.15)	2.89 (0.46 to 17.99)	1.69 (0.32 to 11.08)	0.93 (0.12 to 7.43)	4.00 (0.55 to 29.34)	1.83 (0.24 to 13.67)	5.00 (0.48 to 51.70)	2.47 (0.32 to 19.25)	3.29 (0.59 to 18.32)		2.54 (0.55 to 11.82)	2.24 (0.06 to 90.30)	2.44 (0.63 to 9.45)	2.69 (0.62 to 11.72)	4.12 (0.99 to 17.17)	2.59 (0.55 to 12.21)	2.02 (0.53 to 7.73)
HRUL ECT	0.36 (0.09 to 1.55)	0.29 (0.05 to 1.55)	0.83 (0.16 to 4.36)	0.44 (0.09 to 2.04)	0.26 (0.05 to 1.28)	0.14 (0.02 to 0.88)	0.61 (0.11 to 3.44)	0.28 (0.05 to 1.60)	0.76 (0.22 to 2.63)	0.38 (0.18 to 0.78)	0.50 (0.12 to 2.08)	0.15 (0.02 to 1.28)		0.88 (0.03 to 29.99)	0.96 (0.44 to 2.08)	1.06 (0.61 to 1.83)	1.62 (0.64 to 4.09)	1.02 (0.60 to 1.73)	0.80 (0.37 to 1.72)
HFR rTMS	1.58 (0.31 to 7.97)	1.24 (0.20 to 7.79)	3.58 (0.58 to 22.00)	1.90 (0.35 to 10.48)	1.11 (0.19 to 6.48)	0.61 (0.09 to 4.40)	2.64 (0.40 to 17.31)	1.21 (0.18 to 8.06)	3.30 (0.35 to 30.98)	1.63 (0.23 to 11.38)	2.17 (0.44 to 10.81)	0.66 (0.07 to 6.27)	4.32 (0.57 to 32.63)		1.09 (0.03 to 34.34)	1.20 (0.04 to 39.79)	1.84 (0.06 to 60.14)	1.16 (0.03 to 39.61)	0.90 (0.03 to 28.44)
HFL rTMS	0.84 (0.45 to 1.56)	0.66 (0.23 to 1.91)	1.90 (0.69 to 5.22)	1.01 (0.46 to 2.20)	0.59 (0.23 to 1.50)	0.33 (0.09 to 1.17)	1.40 (0.45 to 4.33)	0.64 (0.21 to 1.99)	1.75 (0.34 to 9.11)	0.87 (0.26 to 2.91)	1.15 (0.67 to 1.98)	0.35 (0.07 to 1.86)	2.30 (0.60 to 8.75)	0.53 (0.11 to 2.46)		1.10 (0.58 to 2.08)	1.69 (0.95 to 2.99)	1.06 (0.47 to 2.37)	0.83 (0.61 to 1.12)
BT ECT	0.30 (0.08 to 1.15)	0.23 (0.05 to 1.17)	0.67 (0.14 to 3.28)	0.36 (0.08 to 1.53)	0.21 (0.05 to 0.96)	0.12 (0.02 to 0.67)	0.50 (0.10 to 2.61)	0.23 (0.04 to 1.21)	0.62 (0.18 to 2.14)	0.31 (0.17 to 0.57)	0.41 (0.11 to 1.55)	0.12 (0.02 to 0.98)	0.82 (0.45 to 1.49)	0.19 (0.03 to 1.34)	0.36 (0.10 to 1.23)		1.53 (0.68 to 3.45)	0.96 (0.53 to 1.73)	0.75 (0.40 to 1.41)
BL rTMS	0.54 (0.26 to 1.13)	0.43 (0.14 to 1.32)	1.22 (0.49 to 3.05)	0.65 (0.26 to 1.62)	0.38 (0.14 to 1.05)	0.21 (0.06 to 0.79)	0.90 (0.29 to 2.83)	0.41 (0.12 to 1.44)	1.13 (0.20 to 6.30)	0.56 (0.15 to 2.07)	0.74 (0.41 to 1.35)	0.23 (0.04 to 1.27)	1.48 (0.36 to 6.14)	0.34 (0.07 to 1.70)	0.64 (0.37 to 1.11)	1.81 (0.48 to 6.87)		0.63 (0.24 to 1.63)	0.49 (0.29 to 0.84)
BF ECT	0.78 (0.17 to 3.65)	0.62 (0.11 to 3.60)	1.77 (0.31 to 10.14)	0.94 (0.19 to 4.79)	0.55 (0.10 to 2.98)	0.30 (0.05 to 2.04)	1.31 (0.21 to 7.99)	0.60 (0.10 to 3.71)	1.63 (0.41 to 6.44)	0.81 (0.36 to 1.82)	1.07 (0.23 to 4.92)	0.33 (0.04 to 2.93)	2.14 (0.83 to 5.53)	0.50 (0.06 to 4.01)	0.93 (0.22 to 3.93)	2.62 (1.03 to 6.71)	1.45 (0.32 to 6.63)		0.78 (0.35 to 1.74)
SHM	2.65 (1.55 to 4.55)	2.09 (0.76 to 5.77)	6.02 (2.21 to 16.38)	3.20 (1.45 to 7.08)	1.87 (0.78 to 4.49)	1.03 (0.29 to 3.60)	4.44 (1.47 to 13.41)	2.03 (0.64 to 6.48)	5.55 (1.06 to 28.99)	2.74 (0.81 to 9.31)	3.65 (2.13 to 6.24)	1.11 (0.21 to 5.87)	7.27 (1.90 to 27.78)	1.68 (0.36 to 7.77)	3.17 (2.29 to 4.37)	8.91 (2.57 to 30.91)	4.92 (2.93 to 8.25)	3.40 (0.80 to 14.41)	

Fig 2 | Network meta-analysis of response and all cause discontinuation rates. Effect sizes represent summary odds ratios and 95% confidence intervals. For the lower triangle (response rates) and upper triangle (all cause discontinuation rates), values less than 1 favour the treatment in the corresponding row, whereas values greater than 1 favour the treatment in the corresponding column. aTMS=accelerated transcranial magnetic stimulation; BF ECT=bifrontal electroconvulsive therapy (ECT); BL rTMS=bilateral repetitive transcranial magnetic stimulation; blTBS=bilateral theta burst stimulation; BT ECT=bitemporal ECT; cTBS=continuous theta burst stimulation; dTMS=deep transcranial magnetic stimulation; HFL rTMS=high frequency left repetitive transcranial magnetic stimulation; HFR rTMS=high frequency right repetitive transcranial magnetic stimulation; HRUL ECT=high dose right unilateral ECT; iTBS=intermittent theta burst stimulation; LFL rTMS=low frequency left repetitive transcranial magnetic stimulation; LFR rTMS=low frequency right repetitive transcranial magnetic stimulation; LMRUL ECT=low to moderate dose right unilateral ECT; MST=magnetic seizure therapy; pTMS=priming transcranial magnetic stimulation; SHM=sham therapy; sTMS=synchronised transcranial magnetic stimulation; tDCS=transcranial direct current stimulation

0.02 to 0.59), magnetic seizure therapy (0.13, 0.02 to 0.95), accelerated transcranial magnetic stimulation (0.16, 0.03 to 0.93), tDCS (0.18, 0.05 to 0.61), low frequency right rTMS (0.23, 0.08 to 0.72), deep transcranial magnetic stimulation (0.25, 0.07 to 0.92), high frequency left rTMS (0.26, 0.08 to 0.79), and sham (0.21, 0.07 to 0.65). Moreover, bilateral rTMS was associated with fewer drop-outs than tDCS and sham (fig 2). All treatments were at least as acceptable as sham therapy (fig 6).

Supplementary file sections 13-15 show the findings for the secondary and tertiary efficacy measures (remission and continuous post-treatment depression severity scores, respectively).

Ranking probabilities
Supplementary file section 16 presents the ranking probabilities, ranking plots, mean ranks, and SUCRA values for all outcomes. The treatment protocols with the highest probabilities of being the most efficacious in terms of response were bitemporal ECT (37%) and priming transcranial magnetic stimulation (19%), whereas low frequency left rTMS and continuous theta burst stimulation (30% each) were least efficacious. Bitemporal ECT and high dose right unilateral ECT had the highest mean ranks (2.6 and 4.0, respectively) and sham and continuous theta burst stimulation had the lowest mean ranks (17.4 and 16.5, respectively). For all cause discontinuation, priming transcranial magnetic stimulation (42%) and bilateral theta burst stimulation (23%) had the highest probabilities of being best accepted, whereas low frequency left rTMS (28%) and high frequency right rTMS (24%) had similar probabilities of being least accepted. Priming transcranial magnetic stimulation and bilateral rTMS had the highest mean ranks (2.1 and 4.7, respectively) and low frequency left rTMS and magnetic seizure therapy had the lowest mean ranks (16.2 and 14.8, respectively).
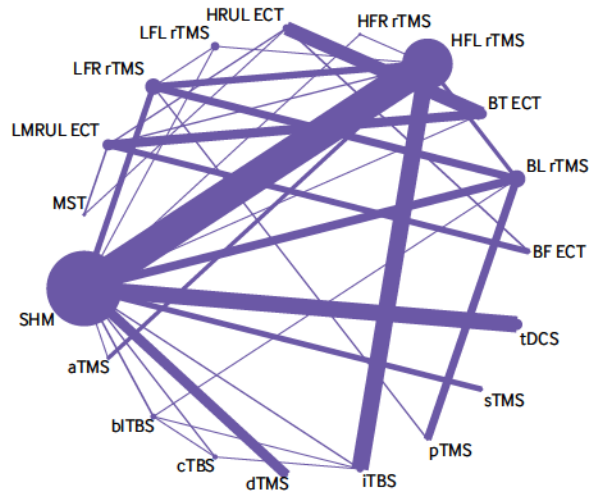
Fig 3 | Network plot of available treatment comparisons for response rates. Size of node is proportional to number of patients randomised to each treatment. Line width is proportional to number of randomised controlled trials comparing each pair of treatments. aTMS=accelerated transcranial magnetic stimulation; BF ECT=bifrontal electroconvulsive therapy (ECT); BL rTMS=bilateral repetitive transcranial magnetic stimulation; blTBS=bilateral theta burst stimulation; BT ECT=bitemporal ECT; cTBS=continuous theta burst stimulation; dTMS=deep transcranial magnetic stimulation; HFL rTMS=high frequency left repetitive transcranial magnetic stimulation; HFR rTMS=high frequency right repetitive transcranial magnetic stimulation; HRUL ECT=high dose right unilateral ECT; iTBS=intermittent theta burst stimulation; LFL rTMS=low frequency left repetitive transcranial magnetic stimulation; LFR rTMS=low frequency right repetitive transcranial magnetic stimulation; LMRUL ECT=low to moderate dose right unilateral ECT; MST=magnetic seizure therapy; pTMS=priming transcranial magnetic stimulation; SHM=sham therapy; sTMS=synchronised transcranial magnetic stimulation; tDCS=transcranial direct current stimulation

Inconsistency

Fitting the design-by-treatment interaction model provided no evidence for statistically significant inconsistency for response, remission, and all cause discontinuation (global Wald tests: P=0.42 to 0.99). However, we found some evidence for inconsistency in the post-treatment depression severity network (global Wald test: P=0.09). Supplementary file section 17 presents inconsistency plots for each outcome. For our primary outcome measure of efficacy (response), we found evidence for inconsistency in 3/21 (14%) loops, whereas there was no evidence for inconsistency for all cause discontinuation. These estimates were, however, of moderate uncertainty, and we cannot exclude the possibility that the actual number of inconsistent loops is higher than those that we report.

Sensitivity analysis

Supplementary file section 18 presents the results of the sensitivity analyses. Excluding trials that investigated tDCS did not materially change our results and overall conclusions. Similarly, removing magnetic seizure therapy and ECT from the network meta-analysis had little impact on the other treatment effect estimates. When trials with high overall risk of bias were excluded, efficacy and acceptability estimates had to be computed separately for two network components. We did not find statistical evidence that intermittent theta burst stimulation was associated with higher

response than sham therapy, and treatment effects of ECT and magnetic seizure therapy compared with sham therapy could not be estimated. Finally, high dose right unilateral ECT was associated with higher response than bifrontal ECT.

Small study effects

Overall, we found no strong evidence of small study effects across outcomes, except that small trials of tDCS were more likely to find large response rates and that two trials of high frequency left rTMS and one trial of tDCS found larger efficacy estimates for continuous depression severity scores after treatment (see supplementary file section 19).

Discussion

This systematic review and network meta-analysis of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults included data from 113 clinical trials including 6750 patients with major depressive disorder or bipolar depression who were randomised to 18 distinct treatment protocols or sham therapy. The quality of the evidence was typically of low or unclear risk of bias (94 out of 113 trials; 83%). The precision of summary treatment effect estimates varied considerably, with higher levels of uncertainty for novel treatment protocols or those for which there were only few or no sham controlled trials available.

Principal findings and comparison with other studies

Our findings provide further clarification about the antidepressant efficacy of different electroconvulsive therapy (ECT) protocols. Previous comparative analyses did not consistently favour bitemporal ECT or right unilateral ECT, and it has been suggested that right unilateral ECT needs to be delivered at multiples of seizure threshold to be effective.[34 35] Trials that used electrical dosages at or just above seizure threshold might have underestimated treatment effects. Our findings support this view. We found no evidence of differences in efficacy between high dose right unilateral ECT and bitemporal ECT across outcomes, whereas low to moderate dose right unilateral ECT was less efficacious than bitemporal ECT across outcomes in pairwise meta-analyses, was associated with lower response rates than bitemporal ECT and high dose right unilateral ECT in network meta-analysis and failed to separate from sham therapy.

Two trials[36 37] evaluated the antidepressant efficacy of magnetic seizure therapy compared with moderate dose right unilateral ECT, and one trial[38] compared magnetic seizure therapy with high dose right unilateral ECT. Although we found no evidence of differences between treatments in pairwise meta-analysis, the network meta-analysis of response provides preliminary evidence in favour of magnetic seizure therapy compared with sham therapy. This estimate is, however, accompanied by a high level of uncertainty and relies on indirect evidence only. As
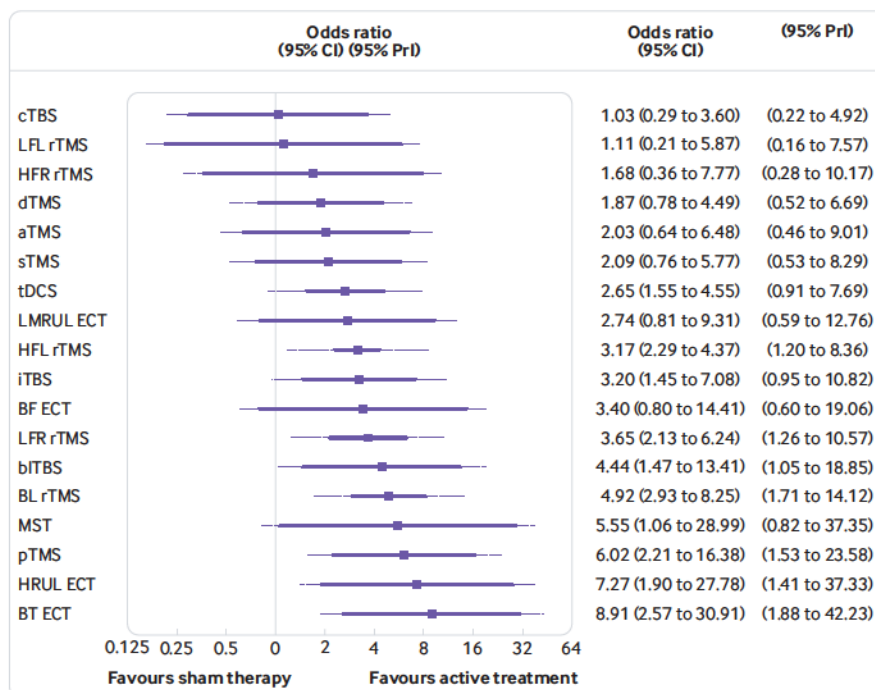
	Odds ratio (95% CI) (95% PrI)	Odds ratio (95% CI)	(95% PrI)
cTBS		1.03 (0.29 to 3.60)	(0.22 to 4.92)
LFL rTMS		1.11 (0.21 to 5.87)	(0.16 to 7.57)
HFR rTMS		1.68 (0.36 to 7.77)	(0.28 to 10.17)
dTMS		1.87 (0.78 to 4.49)	(0.52 to 6.69)
aTMS		2.03 (0.64 to 6.48)	(0.46 to 9.01)
sTMS		2.09 (0.76 to 5.77)	(0.53 to 8.29)
tDCS		2.65 (1.55 to 4.55)	(0.91 to 7.69)
LMRUL ECT		2.74 (0.81 to 9.31)	(0.59 to 12.76)
HFL rTMS		3.17 (2.29 to 4.37)	(1.20 to 8.36)
iTBS		3.20 (1.45 to 7.08)	(0.95 to 10.82)
BF ECT		3.40 (0.80 to 14.41)	(0.60 to 19.06)
LFR rTMS		3.65 (2.13 to 6.24)	(1.26 to 10.57)
bITBS		4.44 (1.47 to 13.41)	(1.05 to 18.85)
BL rTMS		4.92 (2.93 to 8.25)	(1.71 to 14.12)
MST		5.55 (1.06 to 28.99)	(0.82 to 37.35)
pTMS		6.02 (2.21 to 16.38)	(1.53 to 23.58)
HRUL ECT		7.27 (1.90 to 27.78)	(1.41 to 37.33)
BT ECT		8.91 (2.57 to 30.91)	(1.88 to 42.23)

0.125 0.25 0.5 0 1 2 4 8 16 32 64
Favours sham therapy   Favours active treatment

Fig 4 | Forest plot of active versus sham treatment comparisons for response rates. Effect sizes represent summary odds ratios with 95% confidence intervals and 95% prediction intervals estimates from network meta-analysis. aTMS=accelerated transcranial magnetic stimulation; BF ECT=bifrontal electroconvulsive therapy (ECT); BL rTMS=bilateral repetitive transcranial magnetic stimulation; bITBS=bilateral theta burst stimulation; BT ECT=bitemporal ECT; cTBS=continuous theta burst stimulation; dTMS=deep transcranial magnetic stimulation; HFL rTMS=high frequency left repetitive transcranial magnetic stimulation; HFR rTMS=high frequency right repetitive transcranial magnetic stimulation; HRUL ECT=high dose right unilateral ECT; iTBS=intermittent theta burst stimulation; LFL rTMS=low frequency left repetitive transcranial magnetic stimulation; LFR rTMS=low frequency right repetitive transcranial magnetic stimulation; LMRUL ECT=low to moderate dose right unilateral ECT; MST=magnetic seizure therapy; pTMS=priming transcranial magnetic stimulation; sTMS=synchronised transcranial magnetic stimulation; tDCS=transcranial direct current stimulation

such, a sham controlled trial is needed to confirm this finding.

Consistent with previous analyses,[14 39-42] our results provide evidence for the antidepressant efficacy of high frequency left and low frequency right repetitive transcranial magnetic stimulation (rTMS). The efficacy of bilateral rTMS is comparable to both high frequency left and low frequency right rTMS,[11] with little evidence for additional benefit of bilateral compared with unilateral stimulation. Overall, the treatment effect estimates of these protocols are more precise than those of most other treatment protocols included in our review. The finding that neither low frequency left nor high frequency right rTMS were more efficacious than sham therapy lends support to the view that the antidepressant effects of rTMS depend on specific stimulation frequency and coil location.

We found limited evidence in support of the more recent treatment modalities. Compared with sham therapy, intermittent theta burst stimulation and priming transcranial magnetic stimulation were associated with improved response and remission in network meta-analysis, whereas bilateral theta burst stimulation was associated with higher response. However, when only data from pairwise direct comparisons were considered, the evidence in favour of intermittent theta burst stimulation compared with sham therapy was limited to higher response. For deep transcranial magnetic stimulation we found evidence of antidepressant efficacy across outcome measures in pairwise analyses but not in network meta-analysis. As the direct evidence is based on data from only two randomised controlled trials,[43 44] further investigations are warranted. We found no evidence suggesting that continuous theta burst stimulation, accelerated transcranial magnetic stimulation, or synchronised transcranial magnetic stimulation are effective treatments for major depressive episodes. These findings need to be treated with caution, however, owing to the limited number of included studies, which is also reflected in the high levels of uncertainty accompanying these effect size estimates. Finally, although previous meta-analyses of the antidepressant efficacy of transcranial direct current stimulation (tDCS) yielded inconsistent results,[10 45-49] we found tDCS to be efficacious across outcomes in both pairwise and network meta-analyses. Given that tDCS tends to be a less expensive treatment than transcranial magnetic stimulation, ECT, or psychotherapy, this finding is particularly relevant for policy makers who might consider tDCS as a clinical therapy outside the research setting.
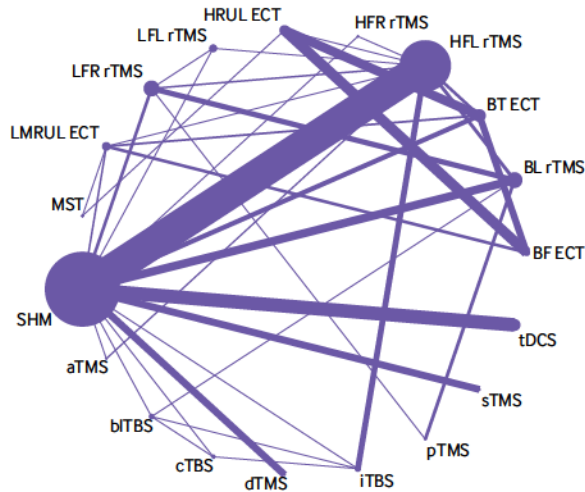
Fig 5 | Network plot of available treatment comparisons for all cause discontinuation rates. Size of node is proportional to number of patients randomised to each treatment. Line width is proportional to number of randomised controlled trials comparing each pair of treatments. aTMS=accelerated transcranial magnetic stimulation; BF ECT=bifrontal electroconvulsive therapy (ECT); BL rTMS=bilateral repetitive transcranial magnetic stimulation; bITBS=bilateral theta burst stimulation; BT ECT=bitemporal ECT; cTBS=continuous theta burst stimulation; dTMS=deep transcranial magnetic stimulation; HFL rTMS=high frequency left repetitive transcranial magnetic stimulation; HFR rTMS=high frequency right repetitive transcranial magnetic stimulation; HRUL ECT=high dose right unilateral ECT; iTBS=intermittent theta burst stimulation; LFL rTMS=low frequency left repetitive transcranial magnetic stimulation; LFR rTMS=low frequency right repetitive transcranial magnetic stimulation; LMRUL ECT=low to moderate dose right unilateral ECT; MST=magnetic seizure therapy; pTMS=priming transcranial magnetic stimulation; SHM=sham therapy; sTMS=synchronised transcranial magnetic stimulation; tDCS=transcranial direct current stimulation

We found little evidence for differences in all cause discontinuation between active treatments and sham therapy. The notable exception was priming transcranial magnetic stimulation for which lower drop-out rates were reported. However, we did not examine specific undesired and adverse effects in this review; and future research will systematically evaluate specific cognitive and adverse effects.[50]

Limitations of this study

The limitations of this study were that most included studies exhibited unclear risk of bias, particularly for random sequence generation and allocation concealment. Overall risk of bias was deemed high in 19 trials (17%). In a sensitivity analysis excluding these trials, we found that intermittent theta burst stimulation was no longer associated with higher response than sham therapy. Moreover, high dose right unilateral ECT was associated with higher response than bifrontal ECT. Treatment effects of ECT protocols and magnetic seizure therapy versus sham therapy could not be estimated.

We found some evidence for statistical heterogeneity within pairwise comparisons, and a small number of loops in our network meta-analysis of response suggested inconsistency between direct and indirect sources of evidence. For most treatment comparisons these estimates suggest that heterogeneity might not be important. To facilitate interpretation of our results taking the magnitude of heterogeneity into account, we presented predictive intervals for all sham comparisons. For magnetic seizure therapy, intermittent theta burst stimulation, and tDCS the estimates from a future trial might suggest that these treatment protocols are no more efficacious than sham therapy.

Although several randomised controlled trials have compared different rTMS or different ECT protocols, few trials have compared novel brain stimulation techniques with ECT protocols. A conceivable explanation is that rTMS and related interventions require no anaesthetic but a higher level of cooperation from the patient, whereas ECT can be prescribed to patients who are more severely depressed. However, most trials that were included in our analyses were conducted after multiple drug treatments had failed, and most participant characteristics did not materially differ between treatment comparisons.

To deal with potential concerns about lack of transitivity, we conducted several sensitivity analyses. Firstly, we excluded trials that examined tDCS, because this therapy is a less invasive treatment protocol, particularly compared with ECT, and because several trials of tDCS recruited participants who were on average younger and less treatment resistant. Excluding these studies did not materially change our results. Secondly, we excluded magnetic seizure therapy and ECT because these treatment modalities involve anaesthetic agents being administered and sedation, and they are generally considered more invasive treatment protocols. A small number of treatment comparisons involving ECT were also characterised by higher baseline depression severity. Removing magnetic seizure therapy and ECT from the network meta-analysis had little impact on the other efficacy and acceptability estimates. To assess whether transcranial magnetic stimulation, tDCS, and ECT sham nodes could be merged, we assessed the efficacy of each sham therapy and found no evidence of between group differences. We also did not find evidence of an association between year of publication and response to sham therapy. Data on pre-post treatment continuous depression severity scores, however, were only available for one trial of sham ECT,[51] which limits the conclusions that can be drawn from these findings.

Finally, we focused on the acute antidepressant effects at primary study endpoint, so our conclusions might not apply to the long term effects of non-surgical brain stimulation. Continuation and maintenance treatment will need to be reviewed separately. Important treatment related characteristics such as dosage and duration of treatment will also need to be systematically investigated in future research.

Policy implications

We anticipate our findings to have implications for clinical decision making and research in that they will inform clinicians, patients, and healthcare providers on the relative merits of multiple non-surgical brain
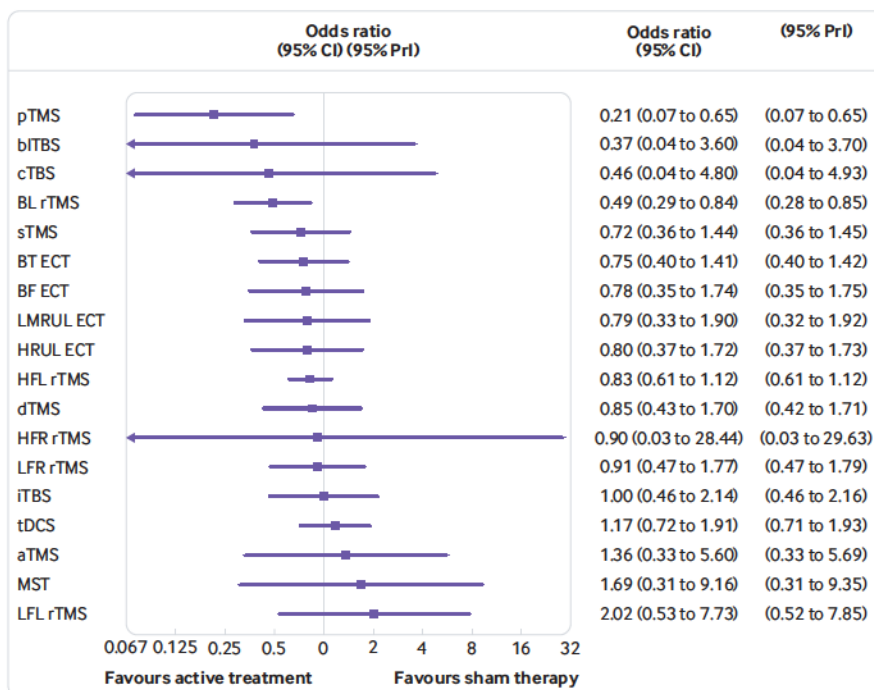
Fig 6 | Forest plot of active versus sham treatment comparisons for all cause discontinuation rates. Effect sizes represent summary odds ratios with 95% confidence intervals and 95% prediction intervals estimates from network meta-analysis. aTMS=accelerated transcranial magnetic stimulation; BF ECT=bifrontal electroconvulsive therapy (ECT); BL rTMS=bilateral repetitive transcranial magnetic stimulation; blTBS=bilateral theta burst stimulation; BT ECT=bitemporal ECT; cTBS=continuous theta burst stimulation; dTMS=deep transcranial magnetic stimulation; HFL rTMS=high frequency left repetitive transcranial magnetic stimulation; HFR rTMS=high frequency right repetitive transcranial magnetic stimulation; HRUL ECT=high dose right unilateral ECT; iTBS=intermittent theta burst stimulation; LFL rTMS=low frequency left repetitive transcranial magnetic stimulation; LFR rTMS=low frequency right repetitive transcranial magnetic stimulation; LMRUL ECT=low to moderate dose right unilateral ECT; MST=magnetic seizure therapy; pTMS=priming transcranial magnetic stimulation; sTMS=synchronised transcranial magnetic stimulation; tDCS=transcranial direct current stimulation

stimulation techniques. Personalising clinically effective treatments without major risk of adverse effects for treatment resistant depression remains an unmet need. The magnitude of effects of drug or psychological treatments range from moderate to small.[52][53] The present findings are comparable and suggest additional benefits of limited risk of adverse effects. Moreover, the findings are relevant to policy makers involved in regulating medical devices and developing treatment guidelines. Although guidelines do support the use of non-surgical brain stimulation, these treatments tend to be applied in clinical practice too little and too late.[54][55] Although ECT is sometimes considered for severe forms of depression, our review suggests that other treatment protocols with robust evidence and more precision in treatment effect estimates (high frequency left rTMS, low frequency right rTMS, bilateral rTMS, and tDCS) should be prioritised over novel protocols with a more limited evidence base. This should be promoted by policy changes, including quality improvement and audit. These should be considered alongside cost effectiveness. Finally, this review highlights important research priorities in the specialty of brain stimulation—for example, the need to conduct further well designed randomised controlled trials comparing novel treatment modalities, and sham controlled trials investigating magnetic seizure therapy.

Conclusion

We found that there is evidence for the consideration of non-surgical brain stimulation techniques as alternative or add-on treatments for adults with major depressive episodes. Our findings also highlight important research priorities in the specialty of brain stimulation, such as the need to conduct further randomised controlled trials for novel treatment protocols.

1 Kessler RC, Berglund P, Demler O, et al, National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 2003;289:3095-105. doi:10.1001/jama.289.23.3095

2 Murray CJ, Barber RM, Foreman KJ, et al, GBD 2013 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. *Lancet* 2015;386:2145-91. doi:10.1016/S0140-6736(15)61340-X

3 Fekadu A, Wooderson SC, Markopoulo K, Donaldson C, Papadopoulos A, Cleare AJ. What happens to patients with treatment-resistant depression? A systematic review of medium to long term outcome studies. *J Affect Disord* 2009;116:4-11. doi:10.1016/j.jad.2008.10.014

4 Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006;163:1905-17. doi:10.1176/ajp.2006.163.11.1905

5 Kikuchi T, Suzuki T, Uchida H, Watanabe K, Mimura M. Association between antidepressant side effects and functional impairment in patients with major depressive disorders. *Psychiatry Res* 2013;210:127-33. doi:10.1016/j.psychres.2013.05.007

6 Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. *J Clin Psychiatry* 2010;71:1259-72. doi:10.4088/JCP.09r05346blu

7 Papakostas GI. Tolerability of modern antidepressants. *J Clin Psychiatry* 2008;69(Suppl E1):8-13.

8 Velligan DI, Weiden PJ, Sajatovic M, et al, Expert Consensus Panel on Adherence Problems in Serious and Persistent Mental Illness. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. *J Clin Psychiatry* 2009;70(Suppl 4):1-46, quiz 47-8. doi:10.4088/JCP.7090su1cj

9 Scott J, Young AH. Psychotherapies should be assessed for both benefit and harm. *Br J Psychiatry* 2016;208:208-9. doi:10.1192/bjp.bp.115.169060

10 Mutz J, Edgcumbe DR, Brunoni AR, Fu CHY. 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. *Neurosci Biobehav Rev* 2018;92:291-303. doi:10.1016/j.neubiorev.2018.05.015

11 Chen JJ, Liu Z, Zhu D, et al. Bilateral vs. unilateral repetitive transcranial magnetic stimulation in treating major depression: a meta-analysis of randomized controlled trials. *Psychiatry Res* 2014;219:51-7. doi:10.1016/j.psychres.2014.05.010

12 Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012;3:80-97. doi:10.1002/jrsm.1037

13 Leucht S, Chaimani A, Cipriani AS, Davis JM, Furukawa TA, Salanti G. Network meta-analyses should be the highest level of evidence in treatment guidelines. *Eur Arch Psychiatry Clin Neurosci* 2016;266:477-80. doi:10.1007/s00406-016-0715-4

14 Brunoni AR, Chaimani A, Moffa AH, et al. Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: A systematic review with network meta-analysis. *JAMA Psychiatry* 2017;74:143-52. doi:10.1001/jamapsychiatry.2016.3644

15 Chen JJ, Zhao LB, Liu YY, Fan SH, Xie P. Comparative efficacy and acceptability of electroconvulsive therapy versus repetitive transcranial magnetic stimulation for major depression: A systematic review and multiple-treatments meta-analysis. *Behav Brain Res* 2017;320:30-6. doi:10.1016/j.bbr.2016.11.028

16 Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777-84. doi:10.7326/M14-2385

17 Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62. doi:10.1136/jnnp.23.1.56

18 Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382-9. doi:10.1192/bjp.134.4.382

19 Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* The Cochrane Collaboration, 2011: 33-49.

20 Higgins JP, Altman DG, Gøtzsche PC, et al, Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928. doi:10.1136/bmj.d5928

21 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88. doi:10.1016/0197-2456(86)90046-2

22 Schwarzer G. Meta: An R package for meta-analysis. *R News* 2007;7:40-5.

23 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60. doi:10.1136/bmj.327.7414.557

24 Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One* 2013;8:e76654. doi:10.1371/journal.pone.0076654

25 Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012;3:98-110. doi:10.1002/jrsm.1044

26 White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods* 2012;3:111-25. doi:10.1002/jrsm.1045

27 Jackson D, Riley RD. A refined method for multivariate meta-analysis and meta-regression. *Stat Med* 2014;33:541-54. doi:10.1002/sim.5957

28 White IR. Multivariate random-effects meta-analysis. *Stata J* 2009;9:40. doi:10.1177/1536867X0900900103

29 White IR. Multivariate random-effects meta-regression: updates to mvmeta. *Stata J* 2011;11:255. doi:10.1177/1536867X1101100206

30 Liu Y, Wang W, Zhang AB, Bai X, Zhang S. Epley and Semont maneuvers for posterior canal benign paroxysmal positional vertigo: A network meta-analysis. *Laryngoscope* 2016;126:951-5. doi:10.1002/lary.25688

31 Furukawa TA, Cipriani A, Atkinson LZ, et al. Placebo response rates in antidepressant trials: a systematic review of published and unpublished double-blind randomised controlled studies. *Lancet Psychiatry* 2016;3:1059-66.

32 Khan A, Fahl Mar K, Faucett J, Khan Schilling S, Brown WA. Has the rising placebo response impacted antidepressant clinical trial

outcome? Data from the US Food and Drug Administration 1987-2013. *World Psychiatry* 2017;16:181-92. doi:10.1002/wps.20421

33 Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;50:683-91. doi:10.1016/S0895-4356(97)00049-8

34 Sackeim HA, Prudic J, Devanand DP, et al. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *N Engl J Med* 1993;328:839-46. doi:10.1056/NEJM199303253281204

35 McCall WV, Reboussin DM, Weiner RD, Sackeim HA. Titrated moderately suprathreshold vs fixed high-dose right unilateral electroconvulsive therapy: acute antidepressant and cognitive effects. *Arch Gen Psychiatry* 2000;57:438-44. doi:10.1001/archpsyc.57.5.438

36 Fitzgerald PB, Hoy KE, Elliot D, et al. A pilot study of the comparative efficacy of 100 Hz magnetic seizure therapy and electroconvulsive therapy in persistent depression. *Depress Anxiety* 2018;35:393-401. doi:10.1002/da.22715

37 Kayser S, Bewernick BH, Grubert C, Hadrysiewicz BL, Axmacher N, Schlaepfer TE. Antidepressant effects, of magnetic seizure therapy and electroconvulsive therapy, in treatment-resistant depression. *J Psychiatr Res* 2011;45:569-76. doi:10.1016/j.jpsychires.2010.09.008

38 Kayser S, Bewernick BH, Soehle M, et al. Degree of Postictal Suppression Depends on Seizure Induction Time in Magnetic Seizure Therapy and Electroconvulsive Therapy. *J ECT* 2017;33:167-75. doi:10.1097/YCT.0000000000000425

39 Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. *Psychol Med* 2009;39:65-75. doi:10.1017/S0033291708003462

40 Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Psychol Med* 2014;44:225-39. doi:10.1017/S0033291713000512

41 Lepping P, Schönfeldt-Lecuona C, Sambhi RS, et al. A systematic review of the clinical relevance of repetitive transcranial magnetic stimulation. *Acta Psychiatr Scand* 2014;130:326-41. doi:10.1111/acps.12276

42 Berlim MT, Van den Eynde F, Jeff Daskalakis Z. Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary major depression: a meta-analysis of randomized, double-blind and sham-controlled trials. *Neuropsychopharmacology* 2013;38:543-51. doi:10.1038/npp.2012.237

43 Levkovitz Y, Isserles M, Padberg F, et al. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. *World Psychiatry* 2015;14:64-73. doi:10.1002/wps.20199

44 Tavares DF, Myczkowski ML, Alberto RL, et al. Treatment of Bipolar Depression with Deep TMS: Results from a Double-Blind, Randomized, Parallel Group, Sham-Controlled Clinical Trial. *Neuropsychopharmacology* 2017;42:2593-601.

45 Berlim MT, Van den Eynde F, Daskalakis ZJ. Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *J Psychiatr Res* 2013;47:1-7. doi:10.1016/j.jpsychires.2012.09.025

46 Kalu UG, Sexton CE, Loo CK, Ebmeier KP. Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. *Psychol Med* 2012;42:1791-800. doi:10.1017/S0033291711003059

47 Shiozawa P, Fregni F, Benseñor IM, et al. Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. *Int J Neuropsychopharmacol* 2014;17:1443-52. doi:10.1017/S1461145714000418

48 Meron D, Hedger N, Garner M, Baldwin DS. Transcranial direct current stimulation (tDCS) in the treatment of depression: Systematic review and meta-analysis of efficacy and tolerability. *Neurosci Biobehav Rev* 2015;57:46-62. doi:10.1016/j.neubiorev.2015.07.012

49 Brunoni AR, Moffa AH, Fregni F, et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. *Br J Psychiatry* 2016;208:522-31. doi:10.1192/bjp.bp.115.164715

50 Kiebs M, Hurlemann R, Mutz J. Cognitive effects of non-surgical brain stimulation for major depressive disorder: protocol for a systematic review and meta-analysis. *BMJ Open* 2019;9:e023796. doi:10.1136/bmjopen-2018-023796

51 Brandon S, Cowley P, McDonald C, Neville P, Palmer R, Wellstood-Eason S. Electroconvulsive therapy: results in depressive illness from the Leicestershire trial. *Br Med J (Clin Res Ed)* 1984;288:22-5. doi:10.1136/bmj.288.6410.22

52 Trivedi MH, Rush AJ, Wisniewski SR, et al, STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* 2006;163:28-40. doi:10.1176/appi.ajp.163.1.28

53 van Bronswijk S, Moopen N, Beijers L, Ruhe HG, Peeters F. Effectiveness of psychotherapy for treatment-resistant depression: a meta-analysis and meta-regression. *Psychol Med* 2018;49:1-14.

54 Kellner CH, Geduldig ET, Knapp RG, et al. More data on speed of remission with ECT in geriatric depression. *Br J Psychiatry* 2015;206:167.

55 Heijnen WT, Birkenhäger TK, Wierdsma AI, van den Broek WW. Antidepressant pharmacotherapy failure and response to subsequent electroconvulsive therapy: a meta-analysis. *J Clin Psychopharmacol* 2010;30:616-9.

Supplementary information: Additional material (sections 01-19)