

BRAIN STIMULATION DEPRESSION META-ANALYSIS

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

4
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28 **Abstract**

29 We examined the efficacy and acceptability of non-invasive brain stimulation in adult
30 unipolar and bipolar depression. Randomised sham-controlled trials of transcranial direct
31 current stimulation (tDCS), transcranial magnetic stimulation (TMS) and theta-burst
32 stimulation (TBS), without co-initiation of another treatment, were included. We analysed
33 effects on response, remission, all-cause discontinuation rates and continuous depression
34 severity measures. Fifty-six studies met our criteria for inclusion ($N = 3,058$, mean age =
35 44.96 years, 61.73% female). Response rates demonstrated efficacy of high-frequency rTMS
36 over the left DLPFC (OR = 3.75, 95% CI [2.44; 5.75]), right-sided low-frequency rTMS (OR
37 = 7.44, 95%CI [2.06; 26.83]) bilateral rTMS (OR = 3.68,95%CI [1.66; 8.13]), deep TMS (OR
38 = 1.69, 95%CI [1.003; 2.85]), intermittent TBS (OR = 4.70, 95%CI [1.14; 19.38]) and tDCS
39 (OR = 4.17, 95% CI [2.25; 7.74]); but not for continuous TBS, bilateral TBS or synchronised
40 TMS. There were no differences in all-cause discontinuation rates. The strongest evidence
41 was for high-frequency rTMS over the left DLPFC. Intermittent TBS provides an advance in
42 terms of reduced treatment duration. tDCS is a potential treatment for non-treatment resistant
43 depression. To date, there is not sufficient published data available to draw firm conclusions
44 about the efficacy and acceptability of TBS and sTMS.

45

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

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48 **Highlights**

49 • Response, remission, all-cause discontinuation rates and continuous post-treatment

50 depression scores were examined

51 • Several non-invasive brain stimulation treatments seem efficacious across different

52 outcome metrics

53 • All-cause discontinuation rates indicate no differences between sham and active

54 treatment

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55 **Introduction**

56 Major depression is prevalent¹ and associated with considerable disease burden². Its course is
57 often recurrent and may become chronic with relapse rates within one year of remission
58 ranging from 35% to 80%^{3,4}. The most common treatments are pharmacological and
59 psychological therapies. Yet, even with a full course of treatment, at least one third of patients
60 fail to achieve remission⁵. Non-invasive neurostimulation therapies, such as transcranial
61 magnetic stimulation (TMS) and transcranial electrical stimulation (tES), offer a potential
62 alternative or add-on treatment strategy.

63
64 TMS was originally introduced as a tool for investigating and mapping cortical functions and
65 connectivity⁶. TMS utilises intense, rapidly-changing electromagnetic fields generated by a
66 coil of wire near the scalp and allows for a mostly undistorted induction of an electrical
67 current to alter neural activity in relatively focal, superficial areas of the brain. Standard TMS
68 involves single or paired pulses, while repetitive transcranial magnetic stimulation (rTMS)
69 involves the delivery of repeated pulses which enable the prolonged modulation of neural
70 activity. Depending on the stimulation frequency, rTMS can increase or decrease cortical
71 excitability. The prevailing hypothesis is that the aftereffects of high-frequency (usually 10Hz
72 or higher) stimulation are excitatory while those of low-frequency (≤ 1 Hz) stimulation are
73 inhibitory⁷.

74
75 The rationale for using rTMS to treat depressive illness comes from clinical symptomatology
76 and neuroanatomy as well as neuroimaging studies indicating functional impairments in
77 prefrontal cortical and limbic regions⁸. In 2008, the US Food and Drug Administration (FDA)
78 approved the first rTMS device for the treatment major depressive disorder (MDD) in which
79 there was poor response to at least one pharmacological agent in the current episode⁹, and its
80 clinical utilisation has increased since¹⁰.

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81

82 As stimulation at high frequencies can be uncomfortable during the initial stimulation period,
83 low-frequency rTMS may minimise the occurrence of undesired side effects, namely
84 headaches and scalp discomfort, and may be associated with fewer adverse events, for
85 instance by lowering the risk for developing seizures¹¹.

86

87 Bilateral applications of rTMS have also been developed: simultaneous stimulation over the
88 left and right DLPFC (rDLPFC) or stimulation over one side followed by stimulation of the
89 other side. These applications were hypothesised to be potentially additive or synergistic to
90 reinstate any imbalance in prefrontal neural activity¹². Moreover, there may be a selective
91 unilateral response and the likelihood for a clinical response may increase by providing both
92 types of stimulation¹³.

93

94 Technical and methodological efforts to improve the antidepressant efficacy of TMS have led
95 to several alternative treatment protocols. Deep TMS (dTMS) was FDA-approved in 2013,
96 which is able to stimulate larger brain volumes and deeper structures¹⁴ that could be more
97 directly relevant in the pathophysiology of depression (e.g., reward-mediating pathways and
98 areas connected to the subgenual cingulate cortex)^{8,15,16}.

99

100 Another recent modification is theta burst stimulation (TBS)¹⁷, which is a patterned form of
101 TMS pulse delivery that utilises high and low frequencies in the same stimulus train. TBS
102 delivers bursts of three at a high frequency (50Hz) with an inter-burst interval of 5Hz in the
103 theta range at 5Hz. Two different protocols are utilised: continuous theta burst stimulation
104 (cTBS), which delivers 300 or 600 pulses without interruption, and intermittent theta burst
105 stimulation (iTBS), which delivers 30 pulses every 10 seconds for a duration of 190 seconds,
106 totalling 600 pulses¹⁸. It is suggested that cTBS reduces cortical excitability while iTBS

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107 increases it, mimicking the processes of long-term potentiation and long-term depression,
108 respectively¹⁷. Notably, there is some debate as to whether prolonged stimulation periods
109 reverse the hypothesised effects of TBS¹⁹, while there is also support for a dose-response
110 relationship for iTBS²⁰.

111
112 The main advantages of TBS are its reduced administration time, which is typically less than
113 five minutes as opposed to 20–45 minutes for conventional rTMS, and the lower intensity
114 needed to produce lasting neurophysiological effects as TBS is typically administered at 80%
115 of the resting motor threshold (rMT) and might be more comfortable than stimulation at
116 higher intensities typically used with standard rTMS.

117
118 Synchronised TMS refers to magnetic low-field synchronised stimulation (sTMS), a new
119 treatment paradigm that involves rotating spherical rare-earth (neodymium) magnets
120 positioned sagittally along the midline of the scalp, which deliver stimulation synchronised to
121 an individual's alpha frequency²¹. The magnets are positioned to provide a global magnetic
122 field distributed broadly across the midline cortical surface (one magnet over the frontal polar
123 region, one magnet over the top of the head, and one magnet over the parietal region). The
124 rationale for sTMS synchronised to an individual's alpha frequency is the observation that
125 one mechanism of action of rTMS is the entrainment of oscillatory activity to the
126 programmed frequency of stimulation, thereby resetting thalamo-cortical oscillators and
127 restoring normal endogenous oscillatory activity²². This modification of TMS may be
128 associated with fewer treatment-emergent adverse and side effects because it does not cause
129 neural depolarisation. It also uses less energy than conventional rTMS as it utilises sinusoidal
130 instead of pulsed magnetic fields, which require less than 1% of the energy needed for
131 conventional rTMS and may thus be less expensive.

132

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133 Access and costs are among the major impediments to a more widespread use of rTMS,
134 although costs may be lower for TBS and sTMS. A less expensive technique is transcranial
135 electrical stimulation (tES). Its most commonly used protocol, transcranial direct current
136 stimulation (tDCS), was reappraised as a tool in research through the work of Priori et al.²³
137 and Nitsche and Paulus²⁴. tDCS involves the application of a low-amplitude electrical direct
138 current through surface scalp electrodes to superficial areas of the brain. While it does not
139 directly trigger action potentials, it modulates cortical excitability by shifting the neural
140 membrane resting potential and these effects can outlast the electrical stimulation period²⁵.
141 The direction of such excitability changes may depend on the polarity of the stimulation:
142 anodal stimulation is hypothesised to cause depolarisation and an increase in neural
143 excitability, whereas cathodal stimulation causes hyperpolarisation and a decrease in cortical
144 excitability^{26,27}.

145
146 The advantages of tDCS compared to TMS include its ease of administration, being much less
147 expensive, its more benign side effect profile, and its portability which could potentially be
148 used in the home environment²⁸.

149
150 We sought to perform a systematic review and meta-analysis of the antidepressant efficacy
151 and acceptability of non-invasive neuromodulation in treating a current depressive episode in
152 unipolar and bipolar depression from randomised sham-controlled trials. The only study to
153 date that evaluated the efficacy of a range of rTMS techniques is Brunoni et al.'s network
154 meta-analysis²⁹. However, the analysis had included trials that had co-initiated other
155 treatments (e.g. sleep deprivation and TMS); trials which had not included a sham treatment;
156 had not separated the TBS modifications; and had not included any age-related exclusion
157 criteria. Also, tDCS trials were not included in that meta-analysis. We sought to address these
158 limitations by including only trials with randomised allocation to active or sham treatments,

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159 excluding studies which had co-initiated another treatment, and limiting our sample to the
160 adult age range as geriatric depression may impact on efficacy.

161

162 **Materials and Methods**

163 **Search strategy and selection criteria**

164 We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
165 (PRISMA) guidelines³⁰. A systematic search of the Embase, Medline, and PsycINFO
166 databases was performed from the first date available to 1st May 2018 (Figure 1). The
167 following search terms were used: (bipolar disorder OR bipolar depression OR major
168 depression OR unipolar depression OR unipolar disorder) AND (transcranial direct current
169 stimulation OR tDCS OR transcranial magnetic stimulation OR TMS OR theta burst
170 stimulation OR TBS OR sTMS OR dTMS), limiting searches to studies in humans and
171 English-language publications. Reference lists of included papers and of recent systematic
172 reviews and meta-analyses (Supplementary Material 1) were screened for further studies. This
173 study has not been previously registered.

174

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

180

181 Exclusion criteria were: 1) primary diagnoses other than MDD or bipolar depression; 2)
182 studies limited to a specific subtype of depression (e.g., postpartum depression or vascular
183 depression) or in which a major depressive episode was a secondary diagnosis (e.g.,

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184 fibromyalgia and major depression); 3) co-initiation of any other form of treatment, such as
185 pharmacotherapy or cognitive control training.

186

187 **Data analysis**

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

191

192 The following treatment-related parameters were extracted. For TMS: type of coil and sham
193 procedure, coil location, stimulation frequency (Hz) for each site, stimulation intensity
194 (percentage of the rMT), total number of pulses delivered, and number of treatment sessions.

195 For TBS: data on the treatment protocol (iTBS, cTBS or bilateral TBS) were also recorded.

196 For tDCS: location of the anode and cathode, electrode size (cm²), current intensity (mA) and
197 density (mA/cm²), session duration, number of sessions, and duration of active stimulation in
198 the sham condition.

199

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

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

213

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

218

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

225

226 Contour-enhanced funnel plots³³ were visually inspected to assess whether potential funnel
227 asymmetry is likely to be due to statistical significance-based publication bias.

228

229 Heterogeneity between studies was assessed with the Q_T statistic, which estimates whether the
230 variance of effect sizes is greater than what would be expected due to sampling error. A p
231 value smaller than .01 provides an indication for significant heterogeneity³⁴. The I^2 statistic
232 was computed for each analysis to provide a descriptive measure of inconsistency across the
233 results of individual trials included in our analyses. It provides an indication of what
234 percentage of the observed variance in effect sizes reflects real differences in effect sizes as

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235 opposed to sampling error. Higgins et al.³⁵ suggested that 25%, 50%, and 75% represent little,
236 moderate, and high heterogeneity, respectively.

237

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

242

243 Analyses were conducted using the ‘meta’ package³⁶ for RStudio (Version 0.98.932) and
244 STATA (Version 13.1; StataCorp, 2013) was used for data processing.

245

246 The Cochrane tool for assessing risk of bias in randomised trials³⁷ was used to evaluate
247 included studies. Each trial received a score of low, high, or unclear risk of bias for each of
248 the potential sources of bias. Two raters independently conducted the assessment of risk of
249 bias.

250

251 **Results**

252 **Overview**

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

257

258 Visual inspection of the contour-enhanced funnel plots did not suggest small study effects
259 (Figure 2; Supplementary Material 3). However, due to the small number of studies for

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260 treatment modalities other than left-sided high-frequency rTMS and tDCS, these need to be
261 interpreted with caution. The results of our risk of bias assessment are presented in
262 Supplementary Material 4.

263

264 **Response and remission rates**

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

268

269 High-frequency rTMS over the left DLPFC (IDLDFC) was associated with improved rates of
270 response as well as remission in comparison with sham treatment. The odds ratio of response
271 was OR = 3.75 compared to sham ($k = 32$, 95% CI [2.44; 5.75]). There was little evidence
272 that the heterogeneity between trials exceeded that expected by chance ($I^2 = 26.1\%$; $Q_{31} =$
273 41.96 , $p = .09$). Sensitivity analyses suggested similar effect sizes in trials that had recruited
274 patients with unipolar depression only and those that had recruited both patients with unipolar
275 and bipolar depression (Supplementary Figure 3a). Only one pilot study³⁸ had recruited
276 patients with bipolar depression only, but provided no support for antidepressant efficacy (OR
277 = 1.14, 95% CI [0.21; 6.37]). Response rates were greater in trials that (i) excluded patients
278 with psychotic features, (ii) recruited outpatients only, and (iii) recruited either treatment
279 resistant patients only or both treatment resistant patients and those that were not treatment
280 resistant (Supplementary Figures 3b-3d).

281

282 The odds of achieving remission were over twice that of sham ($k = 26$, OR = 2.51, 95% CI
283 [1.62; 3.89]). There was no evidence for significant heterogeneity ($I^2 = 1.4\%$; $Q_{25} = 22.35$, $p =$
284 $.44$). Sensitivity analyses for remission rates were in line with those for response rates,
285 although we did not find left-sided high-frequency rTMS to be effective in samples that had

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286 recruited both treatment resistant and non-treatment resistant patients (Supplementary Figures
287 6a-6d).

288

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

294

295 The odds of remission were greater than those of sham ($k = 2$, OR = 14.10 (95% CI [2.79;
296 71.42]). Heterogeneity between trials was not greater than expected due to sampling error (I^2
297 = 0.0%; $Q_1 = 0.50$, $p = .48$). No sensitivity analyses were conducted due to the small number
298 of treatment comparisons.

299

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

309

310 Bilateral rTMS was associated with significant improvement in response but not remission
311 rates compared to sham. There was a significant improvement in response rates compared to

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

322

323 There were significant improvements in both response and remission rates for dTMS
324 compared to sham. The response rates were marginally higher while statistically significant
325 for dTMS relative to sham ($k = 2$, OR = 1.69, 95% CI [1.003; 2.85]). The variance in effect
326 sizes between trials did not exceed that expected due to sampling error ($I^2 = 0.0\%$; $Q_1 = 0.97$,
327 $p = .33$). No sensitivity analyses were conducted due to the small number of treatment
328 comparisons. The remission rates were greater for dTMS compared to sham ($k = 2$, OR =
329 2.24, 95% CI [1.24; 4.06]). There was no evidence for significant heterogeneity between trials
330 ($I^2 = 0.0\%$; $Q_1 = 0.02$, $p = 0.88$), and no sensitivity analyses were conducted due to the small
331 number of treatment comparisons.

332

333 Neither response nor remission rates for sTMS were significantly higher than for sham. There
334 was no evidence for increased response rates compared to sham ($k = 2$, OR = 2.71, 95% CI
335 [0.44; 16.86]). There was significant heterogeneity between these two studies ($I^2 = 75.9\%$;
336 $Q_1 = 4.15$, $p = .04$). No sensitivity analyses were conducted due to the small number of
337 treatment comparisons. There were also no significant improvements in remission rates for

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338 sTMS compared to sham ($k = 2$, OR = 2.51 (95% CI [0.23; 26.76])). There was evidence for
339 significant heterogeneity between the two studies though ($I^2 = 75.7\%$; $Q_1 = 4.12$, $p = .04$). No
340 sensitivity analyses were conducted due to the small number of treatment comparisons.

341
342 iTBS over the IDLPFC was associated with a fivefold improvement in response rates
343 compared to sham ($k = 2$, OR = 4.70 (95% CI [1.14; 19.38])). The heterogeneity between trials
344 did not exceed that expected by chance ($I^2 = 0.0\%$; $Q_1 = 0.02$, $p = .89$). No sensitivity
345 analyses were conducted due to the small number of treatment comparisons. For only one
346 trial³⁹ was data on remission rates for iTBS available, with no evidence for antidepressant
347 efficacy compared to sham.

348
349 Neither cTBS over the rDLPFC nor bilateral TBS were statistically different from sham in
350 terms of response rates ($k = 1$, OR = 1.63, 95% CI [0.23; 11.46] and $k = 2$, OR = 4.28, 95% CI
351 [0.54; 34.27])). For bilateral TBS there was evidence that the variance in effect sizes between
352 studies was greater than what would be expected due to sampling error ($I^2 = 65.7\%$; $Q_1 =$
353 2.91 , $p = .09$). No sensitivity analyses were conducted due to the small number of treatment
354 comparisons. The only trial of bilateral TBS for which remission rates were available⁴⁰ found
355 no evidence for its antidepressant efficacy compared to sham. No remission rates were
356 available for cTBS.

357
358 tDCS was associated with significant improvement in both response and remission rates in
359 comparison to sham stimulation. There was a significant improvement in response rates
360 relative to sham ($k = 9$, OR = 4.17, 95% CI [2.25; 7.74])). There was little evidence for
361 significant heterogeneity between studies ($I^2 = 26.2\%$; $Q_8 = 10.83$, $p = .21$) and sensitivity
362 analyses suggested tDCS to be effective only in patients with non-treatment resistant

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363 depression and in trials that had recruited patients with both treatment resistant and non-
364 treatment resistant depression (Supplementary Figure 5).

365

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

371

372 **Effects on continuous measures**

373 Forty-six treatment comparisons reported post-intervention continuous depression scores.

374 There was evidence for the antidepressant efficacy of high-frequency rTMS over the IDLPFC
375 compared to sham ($k = 29$, Hedge's $g = -0.72$, 95% CI [-0.99; -0.46]), dTMS compared to
376 sham ($k = 2$, Hedge's $g = -0.29$, 95% CI [-0.55; -0.03]), and tDCS compared to sham ($k = 7$,
377 Hedge's $g = -0.76$, 95% CI [-1.31; -0.21]). There was evidence for significant heterogeneity
378 between trials for several treatment modalities (Table 7; Figure 5).

379

380 **Acceptability**

381 Sixty-four treatment comparisons were available for all-cause discontinuation rates. There
382 were no significant differences in drop-out rates for any treatment modalities (Table 8; Figure
383 6).

384

385 **Discussion**

386 The present systematic review and meta-analysis examined the efficacy and acceptability of
387 non-invasive brain stimulation techniques for a current depressive episode in unipolar and

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388 bipolar depression. We sought to investigate the efficacy of the brain stimulation techniques
389 without the potential confound of co-initiation of another treatment and in trials which had
390 included randomised allocation to a sham stimulation treatment arm in order to account for
391 potential placebo effects.

392

393 The largest evidence base to date is for high-frequency rTMS over the IDLPFC which is
394 associated with 3.75 times greater odds of response than sham stimulation as well as odds of
395 remission that are 2.52 times greater than sham. These findings are consistent with previous
396 systematic reviews and meta-analyses⁴¹ and have led to the consensus review and treatment
397 guideline by the *Clinical TMS Society* for daily high-frequency rTMS over the IDLPFC for
398 the treatment of medication-resistant or medication-intolerant depressive episodes⁴².

399

400 Additional support for treatment efficacy was revealed for low-frequency rTMS over the
401 rDLPFC, which was associated with improved rates of response as well as remission.
402 Bilateral rTMS was associated with higher rates of response but not remission. It is unclear
403 whether any advantages of bilateral rTMS compared to left-sided high-frequency or right-
404 sided low-frequency rTMS would be due to the treatment protocol. As bilateral stimulation
405 delivers a greater number of pulses than unilateral stimulation, unless the number of treatment
406 sessions or the treatment duration are adjusted for accordingly, it is difficult to reliably assess
407 whether the difference in stimulation protocol (bilateral vs. unilateral stimulation) or the
408 difference in the number of stimuli delivered leads to differences in clinical effects⁴³.

409

410 To date, no studies have directly compared dTMS and standard rTMS protocols. In an
411 exploratory meta-analysis of nine open-label trials, including a total of 150 patients, Kedzior
412 et al.⁴⁴ provided evidence for the antidepressant efficacy of dTMS. The present meta-analysis
413 found that dTMS was associated with 1.69 times greater odds of response and 2.24 greater

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414 odds of remission than sham which were statistically significant. While the open-label trials
415 included in Kedzior et al.'s analysis may have overestimated the true efficacy of dTMS, we
416 provide initial support for the clinical efficacy of dTMS that was greater than for sham
417 treatment but less than for high-frequency rTMS over the IDLPFC, low-frequency rTMS over
418 the rDLPFC or bilateral rTMS.

419

420 The meta-analytic estimates did not indicate significant treatment effects associated with low-
421 frequency rTMS over the IDLPFC or with sTMS. However, these have been trialled in
422 only three⁴⁵⁻⁴⁷ and two studies^{21,48}, respectively. Specific treatment effects of TMS that depend
423 on side and frequency of stimulation have been proposed but it may be possible that low-
424 frequency rTMS over the IDLPFC has a marginal effect in at least a small number of
425 patients⁴⁷. Leuchter et al.⁴⁸ found sTMS to only be effective when administered at the
426 individual's alpha frequency and with a minimum of 80% treatment adherence, suggesting a
427 dose-response relationship.

428

429 With theta burst stimulation, the duration of each treatment session is reduced to a few
430 minutes. Our meta-analysis did demonstrate almost five times greater odds of response
431 compared to sham for iTBS over the IDLPFC. However, this estimate is based on two trials
432 only. One trial had examined remission rates as well³⁹, reporting remission rates of 0% for
433 sham and 9.1% for active stimulation. The meta-analytic estimates for cTBS and the bilateral
434 modification of TBS did not show any advantage over sham in terms of response rates. The
435 only trial that reported remission rates for bilateral TBS did not provide evidence for its
436 antidepressant efficacy either and no data were available to evaluate remission rates following
437 cTBS.

438

439 Transcranial direct current stimulation is a form of neurostimulation that offers greater

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440 portability and lower costs relative to TMS. The meta-analysis revealed significant
441 improvements in response and remission rates following tDCS treatment in comparison to
442 sham, which was 4.17 times greater for response rates and 2.88 times greater for remission
443 rates. We have been able to identify the effects of tDCS without potential confounds of co-
444 initiation of another treatment, revealing significantly greater odds of response as well as
445 remission⁴⁹. The clinical efficacy of tDCS is evident also in the non-treatment resistant form
446 of depression, in contrast to most rTMS trials, suggesting that tDCS is a potential initial
447 therapeutic option for depression.

448

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

454

455 We chose response and remission rates as our main outcome measures, which are commonly
456 used in the medical sciences and arguably constitute clinically-useful estimates of the
457 antidepressant efficacy of treatment. However, the dichotomisation of outcome data has
458 received criticism because it is known to produce a loss of signal and might inflate Type I
459 error rates, for example an individual who has a 49% reduction in their depressive severity
460 scores would not be included in the clinical response rate while a 51% reduction would be
461 included in the response rate⁵⁰. To address these limitations, we had also analysed continuous
462 depression severity scores. However, outcome data were not reported for each trial, and some
463 missing data could not be obtained. Studies have also suggested that the antidepressant
464 efficacy of active stimulation may separate from sham only after multiple weeks of treatment,
465 for both rTMS⁹ and cTBS⁵¹. We had examined the acute antidepressant effects at primary

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466 study endpoint, and we cannot estimate the long-term effects.

467

468 A significant number of TMS studies used active magnetic stimulation with the coil being
469 angulated at 45 or 90 degrees to the scalp surface as sham condition. Because differences in
470 coil orientation may produce considerably different sensations on the scalp and coil
471 angulation might still produce a limited degree of intracortical activity⁵², ensuring a valid
472 control condition constitutes a methodological challenge. One study placed an inactive coil on
473 the patient's head while discharging an active coil at least one meter away in order to mimic
474 the auditory effects of rTMS⁵³.

475

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

487

488 For tDCS, the sham condition typically involves delivering active stimulation for up to 30
489 seconds, which mimics the initial somatic sensations without inducing a therapeutic effect.
490 However, the adequacy of blinding of tDCS sham has also been called into question⁵⁵.

491

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

501
502 Finally, compared to the network meta-analysis (NMA) on TMS²⁹, we were not able to
503 compare the active treatments. In the NMA priming rTMS seemed most effective. However,
504 the two RCTs that used this treatment modality compared it with another active stimulation
505 and could not be included in the present meta-analysis.

506

507 **Conclusion**

508 The present systematic review and meta-analysis supports the efficacy and acceptability of
509 non-invasive brain stimulation techniques in adult unipolar and bipolar depression. The
510 strongest evidence was for high-frequency rTMS over the IDLPFC, followed by low-
511 frequency rTMS over the rDLPFC and bilateral rTMS. Intermittent TBS provides a potential
512 advance in terms of reduced treatment duration and the meta-analysis did find support for
513 improved rates of response. tDCS is a potential treatment for non-resistant depression which
514 has demonstrated efficacy in terms of response as well as remission. All the trials included in
515 the present meta-analysis had included randomised allocation to a sham treatment arm and we
516 had excluded trials in which there was co-initiation of another treatment. Some of the more

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517 recent treatment modalities though require additional trials and more direct comparisons
518 between different treatment modalities are warranted.

519

520 **Authorship contributions**

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

526

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528 The authors declare no conflict of interest.

529

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540 and not necessarily those of the individuals who have provided data for the analyses.

541

542 **Supplementary material**

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543 Supplementary information is available online.

544

545 **Figure 1**

546 Caption: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

547 flow diagram of literature search.

548

549 **Figure 2**

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

551 rates.

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

553

554 **Figure 3**

555 Caption: Forest plot of response rates.

556

557 **Figure 4**

558 Caption: Forest plot of remission rates.

559

560 **Figure 5**

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

562

563 **Figure 6**

564 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
		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°

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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°

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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°
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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									

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Li et al., 2014 (3)	DLPFC	50	50	80 ⁱ	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. ¹⁻⁵Two active treatment groups were combined. ^aTwo patients received active stimulation at 100% rMT. ^bStimulation delivered at estimated prefrontal threshold. ^cDuring the 5th session, stimulation was delivered for 2min at 10Hz. ^dDuring the 5th session, stimulation was delivered for 2min at 60% rMT. ^eTwo patients received sham treatment with the coil angulated at 90°. ^fReceived treatment twice daily. ^gDuring the first week, 110% rMT could be used for tolerability. ^hDuring the first three treatment session, rMT could be titrated from 100% to 120%. ⁱReceived treatment five times daily. ^jStimulation delivered at active motor threshold.

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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

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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

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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) ^c	32.8 (7.6) ^c	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) ^c	24.0 (4.6) ^c	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

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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) ^c	24 (4.6) ^c	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

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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

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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. ¹MADRS based on the intention-to-treat sample who received ≥ 1 session of active stimulation. ²Numbers are based on the intention-to-treat sample. ^{3,4,5,8,9}Two active treatment groups were combined. ⁶Numbers based on the intention-to-treat sample who received ≥ 1 session of active stimulation. ⁷HDRS based on the intention-to-treat sample. ¹⁰Age based on the intention-to-treat sample who received ≥ 1 session of active stimulation. ¹¹Age based on 11 patients. ¹²Two patients had mixed features. ¹³Indicates Median and IQR. ^aHDRS-17. ^bHDRS-21. ^cHDRS-25. ^dHDRS-24. ^eHDRS-28.

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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/cm². 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. ¹Two sham treatment groups were combined. ²Patients in sham group also

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received an oral placebo tablet.³Omnilateral electrode system.

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Table 4

Sample characteristics: tDCS studies

Authors	Number of participants		Age		Diagnosis	HDRS		Excluded psychosis	Status	Treatment resistance
	(female)									
	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

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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
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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. ¹Two sham treatment groups were combined. ^{2,3,4,7,8}Numbers are based on the intention-to-treat sample. ⁵Numbers based on participants of age ≤ 70 years. ⁶Patients in sham group also received an oral placebo tablet. ⁸Excluded “other psychiatric disorders.” ^bHDRS-21. ^cHDRS-17. ^dHDRS-24.

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Table 5

Random-Effects Meta-Analysis of Response Rates

Treatment Modality	<i>k</i>	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%
bITBS	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; bITBS = bilateral theta burst stimulation; sTMS = synchronised transcranial magnetic stimulation; tDCS = transcranial magnetic stimulation. *inverse variance method used.

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Table 6

Random-Effects Meta-Analysis of Remission Rates

Treatment Modality	<i>k</i>	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	-	-	
bITBS*	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; bITBS = bilateral theta burst stimulation; sTMS = synchronised transcranial magnetic stimulation; tDCS = transcranial magnetic stimulation. *inverse variance method used.

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Table 7

Random-Effects Meta-Analysis of Continuous Treatment Effects

Treatment Modality	<i>k</i>	<i>g</i>	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	-
bITBS	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; bITBS = bilateral theta burst stimulation; sTMS = synchronised transcranial magnetic stimulation; tDCS = transcranial direct current stimulation. *inverse variance method used.

BRAIN STIMULATION DEPRESSION META-ANALYSIS

Table 8

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

Treatment Modality	<i>k</i>	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; bITBS = bilateral theta burst stimulation; sTMS = synchronised transcranial magnetic stimulation; tDCS = transcranial direct current stimulation. *inverse variance method used.











