

Review article

Comparative efficacy and acceptability of neuromodulation procedures in the treatment of treatment-resistant depression: a network meta-analysis of randomized controlled trials

Hao Li ^a, Liqian Cui ^{a,*}, Jinbiao Li ^a, Yueheng Liu ^{b,c}, Yue Chen ^d

^a Department of Neurology, The First Affiliated Hospital, Sun Yat-sen University; Guangdong Provincial Key Laboratory of Diagnosis and Treatment of Major Neurological Diseases, National Key Clinical Department and Key Discipline of Neurology, No.58 Zhongshan Road 2, Guangzhou, 510080, China

^b Department of Psychiatry, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China

^c Chinese National Clinical Research Center on Mental Disorders (Xiangya), Changsha, Hunan, China

^d The eighth Hospital Affiliated, Sun Yat-sen University, Shenzhen, 518101, Guangdong, China.

ARTICLE INFO

Keywords:

Neuromodulation procedures
depression
treatment-resistant depression
randomized clinical trials
network meta-analysis

ABSTRACT

Background: Nearly half of the patients with depression experience suboptimal benefits from antidepressants. Neuromodulation therapies, a kind of technology that can regulate neuronal firing activity by electrical or magnetic stimulation, were introduced to improve this situation. However, the results from clinical trials have been inconsistent.

Methods: We followed the extension of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to perform this network meta-analysis (NMA). The results were evaluated by relative risk (RR) for the response, remission, and discontinuation rates.

Results: In total, 49 trials with 2,941 patients were included in this study. Bilateral theta burst stimulation (TBS, RR 5.00, 95% CI 1.11–22.44), priming transcranial magnetic stimulation (pTMS, RR 2.97, 95% CI 1.20–7.39), low-frequency right repetitive transcranial magnetic stimulation (TMS) (LFR-rTMS, RR 2.62, 95% CI 1.56–4.39), high-frequency left repetitive TMS (HFL-rTMS, RR 2.18, 95% CI 1.52–3.13), and bilateral repetitive TMS (BL-rTMS, RR 3.08, 95% CI 1.78–5.31) were demonstrated to have higher response rates than sham control. BL-rTMS (RR 3.12, 95% CI 1.06–9.09) was found to have a higher response rate than deep brain stimulation in this NMA. All measures had the non-inferiority acceptability than the sham-control. BL-rTMS was more acceptable than bitemporal ECT (BT-ECT, RR 0.18, 95% CI 0.03–0.89), while pTMS was more acceptable than BT-ECT (RR 0.08, 95% CI 0.01–0.55), HFL-rTMS (RR 0.34, 95% CI 0.12–0.93), and deep TMS (RR 0.15, 95% CI 0.02–0.96).

Conclusion: Besides electroconvulsive therapy (ECT), rTMS, priming TMS, and bilateral TBS proved effective for patients with treatment-resistant depression (TRD). BL-rTMS showed high efficacy and acceptability, and bilateral TBS had the potential to be the most efficacious neuromodulation measures.

1. Introduction

The latest World Health Organization (WHO) report indicates that depression has become a common global disease, affecting more than 264 million people of all ages worldwide (W.H. Organization 2020). It is the leading cause of disability and a major contributor to the global burden of disease (W.H. Organization 2020). However, a significant proportion of patients fail to benefit enough from antidepressants. Hence, these patients have treatment-resistant depression (TRD). The

most common definition of TRD is a failure to respond to a minimum of two prior antidepressants with adequate dose and duration (Gaynes et al., 2020). Based on this definition, nearly half of patients with depression are known to have TRD (John Rush et al., 2006). Furthermore, patients with TRD are significantly less inclined to benefit from other classes of antidepressants (John Rush et al., 2006). For this reason, a number of researchers are focused on discovering novel effective treatments for TRD.

In recent years, neuromodulation techniques have made remarkable

* Corresponding author

E-mail address: cuilqian@mail.sysu.edu.cn (L. Cui).

<https://doi.org/10.1016/j.jad.2021.03.019>

Received 25 December 2020; Received in revised form 3 March 2021; Accepted 5 March 2021

Available online 11 March 2021

0165-0327/© 2021 The Authors.

Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

progress and have been recognized as having excellent potential to efficiently treat patients with TRD. This type of technology can regulate neuronal firing activity by electrical or magnetic stimulation. There are various patterns for neuromodulation, which can be classified as non-invasive and invasive. Currently, electroconvulsive therapy (ECT) is one of the most widely used treatments and is considered the most effective intervention in clinical practice (Gelenberg et al., 2010). However, the adverse effects of ECT on cognition, especially memory-related, have severely limited its clinical application (Kellner and Farber, 2016).

To remedy this situation, researchers have developed a series of novel neuromodulation therapies. For example, magnetic seizure therapy (MST) is a technology that induces seizures through high-dose magnetic stimulation with a lower risk of cognitive impairment. In addition, transcranial magnetic stimulation (TMS), including repetitive TMS (rTMS), accelerated TMS (aTMS), priming TMS (pTMS), deep TMS (dTMS), and theta-burst stimulation (TBS), can regulate the cortical neuronal activity through low-dose magnetic stimulation. The clinical efficacy of various forms of TMS in the treatment of TRD has been demonstrated, although the results have not been uniform (Avery et al., 2006, Bakim et al., 2012, Blumberger et al., 2012, Fitzgerald et al., 2006, Rossini et al., 2005, Zheng et al., 2015, Fitzgerald et al., 2013, Fitzgerald et al., 2018, Tavares et al., 2017, Li et al., 2014). Besides, transcranial direct current stimulation (tDCS), a non-invasive means to modulate cortical excitability through weak electrical signals, also contributed towards improvements in the mood of patients with TRD (Li et al., 2019, Palm et al., 2012). In terms of invasive approaches, deep brain stimulation (DBS) and Vagus nerve stimulation (VNS) are common. DBS allows researchers to implant electrodes into the target area of the brain to provide constant or intermittent delivery of electricity around the electrode, which can directly modulate the electrical activity of the specific cortex. VNS also involves the surgical implantation of electrodes around the cervical vagus nerve to deliver pulses of electrical energy, which are directed to the brain. Some studies have shown benefits from DBS and VNS in patients with TRD, while other reports have been inconsistent (Dougherty et al., 2015, Holtzheimer et al., 2017, Merkl et al., 2018, Rush et al., 2005). In general, there have been plenty of clinical trials involving neuromodulation procedures in patients with TRD; however, inconsistency seems to plague these studies as well. One important reason for the inconsistency between studies is the limited statistical power from several small sample sizes or single-center studies. In addition, there is a big challenge in directly comparing and ranking the efficacy and acceptability between various treatment modalities.

For this reason, there is a need to conduct network meta-analyses (NMA) to compare the efficacy and acceptability of different neuromodulation measures. As of now, two NMAs have assessed the effects and acceptability of neuromodulation therapies in major depressive disorder (MDD). One of them focused on the differences between various rTMS modalities, yet did not compare other neuromodulation treatments (Brunoni et al., 2017). The second study was limited to non-surgical brain stimulation and failed to include DBS and VNS (Mutz et al., 2019). In addition, both studies did not report detailed results for TRD. There is extensive heterogeneity, especially in behavioral phenotypes, neural circuits, and gene x environmental interactions between patients with TRD and those with treatment-responsive depression (Akil et al., 2018, Fagioli and Kupfer, 2003). Hence, the results from the entire population of depressive patients may not be applicable to patients with TRD. Due to limited intervening measures and missing information about TRD patients in previous NMAs, we have performed this NMA to determine the anti-depressant efficacy and acceptability of different neuromodulation measures in patients with TRD.

2. Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and its extension for network

meta-analysis to conduct this report (Shamseer et al., 2015).

2.1. Literature review

Up to June 1, 2020, we systematically searched the Pubmed, Embase, and Cochrane databases through a combination of medical subject headings (MeSH) and free words to acquire comprehensive documents. The search terms relevant to TRD, neuromodulation treatments, including deep brain stimulation, electroconvulsive therapies, magnetic seizure therapy, transcranial direct current stimulation, transcranial magnetic stimulation, vagus nerve stimulation, and various combinations were used to perform the search. Specific search strategy is shown in Table S1 (Supplemental Material). From June 1, 2020 to February 28, 2021, we performed an additional targeted search for TRD on 28 February 2021 to keep updated.

2.2. Literature screening

We conducted three rounds of screening to obtain qualified randomized clinical trials pertaining to neuromodulation procedures and TRD. The inclusion and exclusion criteria for included studies were as follows: (1) Patients: Participants were limited to adults (over 18 years) with a primary diagnosis of TRD, include unipolar or bipolar depressive episodes. TRD was defined as a failure to respond to at least two different antidepressant medications previously. Patients with depression secondary to other diseases, such as Parkinson's disease or stroke, were not accepted in this study. (2) Treatments: Studies must have included at least two of the following interventions: deep brain stimulation (DBS), electroconvulsive therapies (ECT), magnetic seizure therapy (MST), transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), and the sham control. (3) Control: The control group was restricted to the sham control or another neuromodulation approach control. (4) Outcome: Studies had to evaluate depressive symptoms using either the Hamilton depression rating scale (HDRS) or Montgomery Asberg depression rating scale (MARDS) in TRD patients. (5) Study design: The design of the included studies was limited to randomized controlled trials and randomized cross-over trials. For randomized cross-over trials, only data from the first period were included (Elbourne et al., 2002). (6) The language was limited to English, and data on primary outcomes had to be available. Two reviewers (H. L. and Y. H. L.) independently completed the study selection work. Any disagreement was submitted to the third party (L. Q. C.) to reach an agreement.

2.3. Outcome measures

We chose the response rate as the primary outcome. The remission rate and depression score were used as secondary outcomes at the endpoint. The response rate was defined as a >50% decrease in HDRS or MARDS score from baseline to endpoint. The remission rate was defined as a HAMD score no more than seven or a MADRS score no more than 10. We preferentially used the HAMD score to calculate response and remission rates, followed by the MADRS score. Acceptability, discontinuation due to any cause, was determined by the proportion of patients who dropped out of the study for any reason.

2.4. Data extraction and literature assessment

Two authors (H. L. and Y. H. L.) independently performed data extraction and literature assessment. Any discrepancy was resolved by consensus. A pre-designed standardized form was used to extract all of the necessary information for each study. This table included the following items: (1) literature sources: first author and publication year; (2) study details: period, region, sample size, demographics, intervention measures and duration, and the assessment scale of depression; (3) study results: response and remission rate, the depression scale score at

the baseline and endpoint, and the all-cause discontinuation.

According to the Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0, the bias risk of each study was assessed from the following aspects: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. Following these seven criteria, each trial was categorized as low, high, or unclear risk of bias. Risk bias was graded by two authors (Dr. Li and Dr. Liu), blinded to each other. Any disagreements were resolved through discussion until a consensus was reached.

2.5. Statistic analysis

Stata version 14.0 and R-3.6.2 software were used to complete all statistic analysis in the NMA (White, 2015). A pair-wise meta-analysis for only direct comparisons ($n \geq 2$) was conducted, followed by a network meta-analysis for both direct and indirect comparisons. Findings are expressed as relative risk (RR) for dichotomous variables and standardized mean difference (SMD) for continuous variables, with a 95% confidence interval (CI). In the pair-wise meta-analysis, results were pooled using a random-effects model in the Stata software. I^2 statistics were used to assess the heterogeneity of entries. An $I^2 < 50\%$ was considered suggestive of no significant heterogeneity (Higgins et al., 2003). For comparisons with high heterogeneity ($I^2 > 50\%$), a subgroup analysis was performed to explore the source of heterogeneity.

In the network meta-analysis, we first generated network plots for all comparisons using the R software. Secondly, the results from each trial were synthesized using a frequentist analysis approach based on multivariate meta-regression in the Network package from Stata (White, 2015, White et al., 2012). Next, the neuromodulation measures

were ranked based on a probability of being the best efficacy and acceptability using surface under a cumulative ranking curve (SUCRA). The SUCRA-values ranged from 0–1, with values closer to 1 indicating better performance (Salanti et al., 2011, Chaimani et al., 2013). The global Wald test was used to evaluate the heterogeneity of the entire network, while the inconsistency factor (IF), which compares the difference between direct and indirect comparisons, was used to evaluate loop inconsistency. $P < 0.05$ in the global Wald test and 95% CI for IF that did not include 0 were indicative of substantial global heterogeneity and loop inconsistency (White et al., 2012, Veroniki et al., 2013). In addition, we conducted subgroup analyses to detect differences between the two types of TRD (unipolar depression and bipolar depression), funnel plot analysis for included sham-controlled trials and active-active trials to detect potential publication bias, along with a sensitivity analysis excluding studies with too short treatment duration to detect the potential small study effects.

3. Results

3.1. Assessment of included studies

After a thorough search and systematic screening, 1,550 articles were retrieved from databases. Of these articles, 43 trials were considered to be eligible for this study. Combined with the six trials obtained from manual retrieval, a total of 49 randomized controlled trials (RCTs) was included in this NMA (Figure 1). These eligible RCTs incorporated 16 different neuromodulation procedures and sham controls in 108 treatment arms (Figure 2), involving a total of 2941 patients with TRD. Of these 108 treatment arms, 48 used the rTMS technology with average 3 weeks for HFL-rTMS, 3 weeks for LFR-rTMS and 3.5 weeks for BL-rTMS, 11 used ECT technologies with average 4 weeks for RUL-ECT,

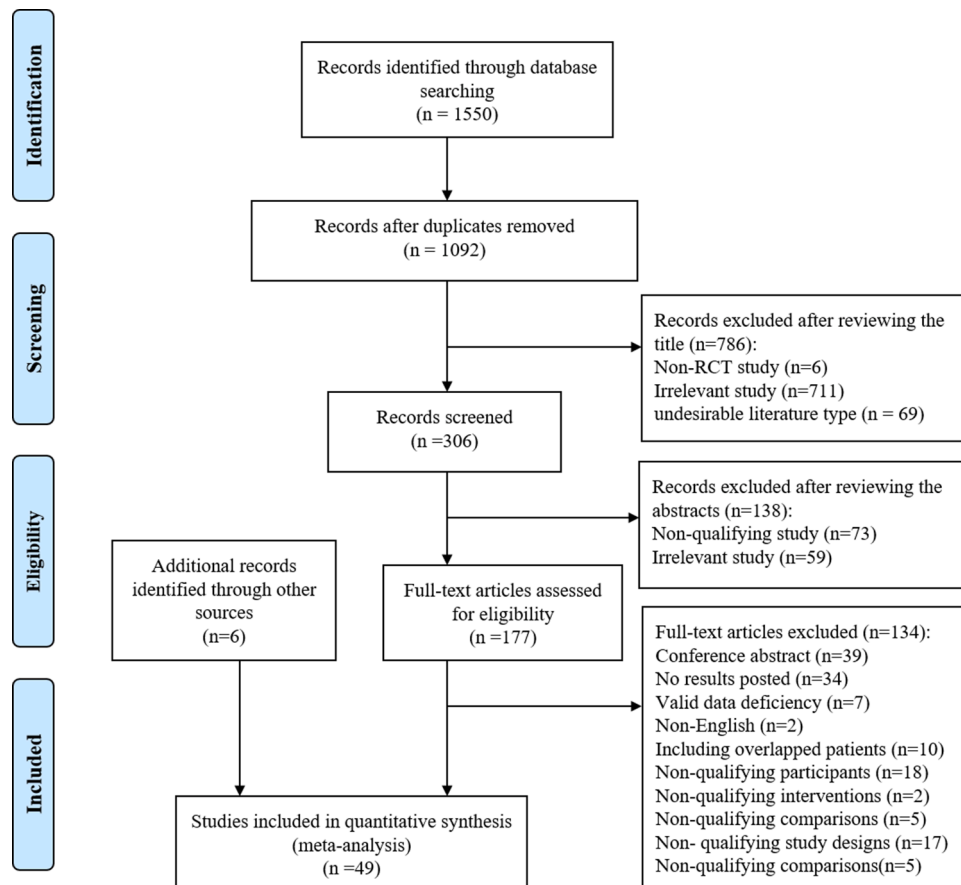


Figure 1. Flow chart of the literature search and screening.

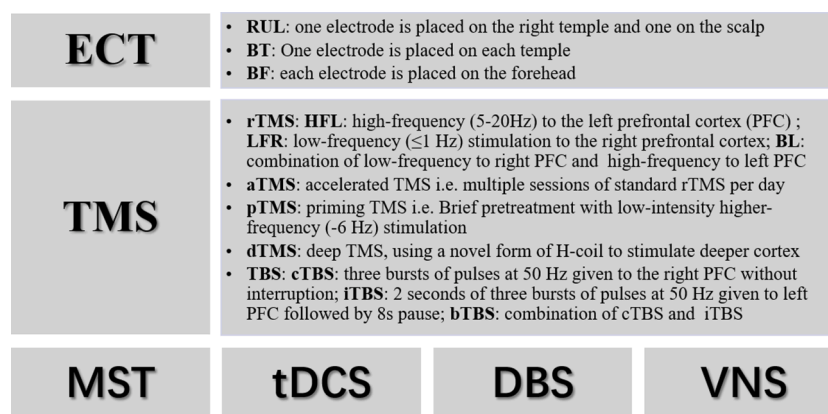


Figure 2. Neuromodulation procedures and their classification in the NMAs of this study.

2.5 weeks for BT-ECT and 4.5 weeks for BF-ECT, 3 used TBS technology with average 3 weeks, 3 used MST technology with average 5 weeks, 3 used DBS technology with average 2 weeks and 1 used VNS or tDCS or pTMS or aTMS or dTMS with a treatment duration of 10 weeks, 3 weeks, 4 weeks, 4 weeks, respectively. There is a weak female preponderance with a female-to-male ratio of 1.53:1, and the mean age range is 26.9 and 75.2. In terms of bias risks, 2 studies were graded as high risk of bias, 16 as unclear risk of bias, and 31 as low risks of bias. These data from trials with a high risk of bias were excluded from subsequent pair-wise and network meta-analyses. Main characteristics of included studies can be found in Table 1. Detailed information on the literature characteristics and bias risk for each included study can be found in Table S2-S3 and Figure S1.

3.2. Pair-wise meta-analysis

Measured by response rates, seven different neuromodulation therapies with nine groups of inter-comparisons were explored in the present pair-wise meta-analysis. Among these, DBS (3 RCTs), BL-rTMS (8 RCTs), HFL-rTMS (22 RCTs), and LFR-rTMS (3 RCTs) were individually compared with the sham control. BF-ECT (3 RCTs) and MST (2 RCTs) were compared with RUL-ECT, respectively. BL-rTMS (2 RCTs) and HFL-rTMS (3 RCTs) were compared with LFR-rTMS, respectively. BL-rTMS (2 RCTs) was compared with HFL-rTMS. The BL-rTMS (RR 3.89, 95% CI 2.02-7.51, 8 RCTs), HFL-rTMS (RR 2.41, 95% CI 1.40-4.16, 22 RCTs), and LFR-rTMS (RR 2.01, 95% CI 0.80-5.02, 3 RCTs) were identified to be more efficacious than the sham control. There were no significant differences in the comparisons between the two active groups.

In terms of the heterogeneity test, all comparisons were indicated to be low heterogeneity ($I^2 < 50\%$) except HFL-rTMS, relative to the sham controls ($I^2 = 58.40\%$). Hence, we divided HFL-rTMS into three subgroups according to the stimulation intensity during rTMS: HFL group (the intensity is greater than or equal to resting motor threshold, 15 RCTs), sub-HFL group (the intensity is weaker than resting motor threshold, 5 RCTs), mixed group (including the supra-threshold and subthreshold stimuli, 2 RCTs), and performed subgroup analysis by the three groups. No significant heterogeneity was found in the comparisons between the three subgroups and sham controls. All three subgroups (RR 2.54, 95% CI 1.29-4.99, 15 RCTs; RR 2.50, 95% CI 1.43-4.3, 5 RCTs; RR 5.38, 95% CI 1.85-15.69, 2 RCTs, respectively) were proved to be more effective than the sham groups. Detailed information and other results of the remission rate, endpoint depression scores, and all-cause discontinuation can be found in Figure S2 and Table S4 (Supplemental Materials).

3.3. Network meta-analysis

3.3.1. Efficacy

Forty-seven trials reported response rates and were included in our NMA (two trials with high risk of bias were excluded). The network plot was shown in Figure 3A. There was no significant heterogeneity in the global Wald test ($p = 0.912$) or large incongruent in the test of loop inconsistency (Figure S3.A in Supplemental Materials) between the studies. The analysis of pooled data shows that bilateral TBS (RR 5.00, 95% CI 1.11-22.44), priming TMS (RR 2.97, 95% CI 1.20-7.39), LFR-rTMS (RR 2.62, 95% CI 1.56-4.39), HFL-rTMS (RR 2.18, 95% CI 1.52-3.13), and BL-rTMS (RR 3.08, 95% CI 1.78-5.31) were more effective than the sham control (Figure 4). In the comparison of two active treatments, BL-rTMS (RR 3.12, 95% CI 1.06-9.09) was demonstrated to be more effective than DBS. No significant differences were found in other comparisons of active treatments (Figure 5). Furthermore, according to the ranked orders in SUCRA (Figure 6), bilateral TBS (SUCRA = 81.7%) may have the highest probability of being the most effective treatment, followed by BL-rTMS (SUCRA = 76.6%) and priming TMS (73.4%). Detailed SUCRA results can be found in Figure S4A and Table S5 (Supplemental Materials). The results of secondary outcomes, including remission rates and endpoint scores, are provided in the Supplemental Materials (Figure S5-S8, Table S6).

3.3.2. Acceptability

Forty-six trials are available in all-cause discontinuation rates and were included in the NMA for comparing acceptability. The network plot is shown in Figure 3B. The test for global heterogeneity and loop inconsistency were not significant ($P = 0.963$) in the global Wald test, and IF with 95% CI included zero (Figure S3: Supplemental Materials). Results from the NMA show that there is no significant difference between any treatment measures and sham controls (Figure 4B). However, BL-rTMS was found to be more acceptable than BT-ECT (RR 0.18, 95% CI 0.03-0.89), while priming TMS was more acceptable than BT-ECT (RR 0.08, 95% CI 0.01-0.55), HFL-rTMS (RR 0.34, 95% CI 0.12-0.93), and deep TMS (RR 0.15, 95% CI 0.02-0.96). The specific results are shown in Figure 5. Based on the SUCRA values, we ranked the acceptability for all active treatment measures and sham controls (Figure 6). Priming TMS (SUCRA=90.7%) had the highest probability to be the most acceptable measures, followed by BL-rTMS (SUCRA=76.8%) and LFR-rTMS (SUCRA=59.4%). Detailed SUCRA results are presented in Figure S4.B and Table S5 (Supplemental Materials).

3.4. Subgroup Analysis

3.4.1. Unipolar depression TRD

Twenty-six trials that included only unipolar TRD patients were included in the sub-group analysis. These studies involved a total of ten

Table 1
Main characteristics of included studies

Source	Sample size (M/F)	Failed trails(min/mean)	Interventions	Duration	With antidepressant	Evaluationscale
Darin D. Dougherty 2014	30(17/13)	$\geq 4/10.8 \pm 3.2$	DBS, SHM	16 weeks	Yes	MADRS
Angela Merkel 2018	8(6/2)	$\geq 2/N.A.$	DBS, SHM	4 weeks	Yes	HAMD-24
Paul E Holtzheimer 2017	90(43/47)	$\geq 4/N.A.$	DBS, SHM	6 months	Yes	MADRS
Gerhard 2007	92(39/53)	$\geq 2/N.A.$	BF-ECT, RUL-ECT	3 weeks	Yes	HAMD-21
Alberto Stoppe 2006	39(17/22)	$\geq 2/N.A.$	RUL-ECT, BT-ECT	1-5 weeks	No	MADRS
P. Sienaert 2009	81(39/82)	N.A..	RUL-ECT, BF-ECT	6 weeks	No	HRS-17
Philp G. Janicak 2002	26(17/9)	N.A..	HFL-rTMS, BT-ECT	1-4 weeks	No	HDRS-24
Sarah Kayser 2017	25(13/12)	$\geq 2/N.A.$	MST, RUL-ECT	3 weeks	Yes	HAMD-28
Sarah Kayser 2011	20(7/13)	$\geq 2/N.A.$	MST, RUL-ECT	6 weeks	Yes	MADRS
Paul B. Fitzgerald 2018a	40(16/21)	$\geq 2/N.A.$	MST, RUL-ECT	up to 5 weeks	Yes	HAMD-17
David H. Avery 2005	68(31/37)	$\geq 2/N.A.$	HFL-rTMS, SHM	4 weeks	Yes	HDRS-17
Paul B. Fitzgerald 2012	66(29/37)	$\geq 2/5.20 \pm 3.3$	BL-rTMS, HFL-rTMS, SHM	3 weeks	Yes	HAMD-17
Paul B. Fitzgerald 2016	46(20/26)	$\geq 2/N.A.$	BL-rTMS, SHM	4 weeks	Yes	HAMD-17
Daniel M. Blumberger 2012a	68(28/40)	$\geq 2/N.A.$	BL-rTMS, HFL-rTMS, SHM	3 weeks	Yes	HAMD-17
Paul B. Fitzgerald 2009	27(15/12)	$\geq 2/6.1 \pm 2.6$	HFL-rTMS, LFR-rTMS	3 weeks	Yes	MADRS
Paul B. Fitzgerald 2011	218(71/147)	$\geq 2/5.4 \pm 2.8$	BL-rTMS, LFR rTMS	4 weeks	Yes	HAMD-17
Paul B. Fitzgerald 2006	50(19/31)	$\geq 2/5.9 \pm 3.0$	BL-rTMS, SHM	up to 6 weeks	Yes	MADRS
Paul B. Fitzgerald 2018b	115(49/66)	$\geq 2/N.A.$	aTMS, HFL-rTMS	4 weeks	Yes	HAMD-17
Huirong Zheng 2015	32(20/12)	$\geq 2/N.A.$	HFL-rTMS, SHM	4 weeks	Yes	HAMD-17
Tung-Ping Su 2005	33(8/22)	$\geq 2/N.A.$	HFL-rTMS, SHM	2 weeks	Yes	HAMD-21
Xuan Hong Zhang 2011	30(20/8)	$\geq 2/N.A.$	HFL-rTMS, SHM	4 weeks	Yes	HAMD-17
Andrew M. Speer 2014	24(11/13)	$\geq 2/N.A.$	HFL-rTMS, SHM	3 weeks	No	HAMD-28
William M Mconald 2006	62(30/32)	$\geq 3/8.5$	BL-rTMS, SHM	2 weeks	No	HAMD-21
Moacyr Alexandro Rosa 2006	42(22/20)	$\geq 2/N.A.$	HFL-rTMS, RUL-ECT	4 weeks	No	HAMD-17
Paul B. Fitzgerald 2013	179(54/125)	$\geq 2/5.10 \pm 3.1$	BL-rTMS, pTMS	4 weeks	Yes	HMAD-17
Huirong Zheng 2010	34(22/12)	$\geq 2/N.A.$	HFL-rTMS, SHM	4 weeks	Yes	HMAD-17
Marie-Laure Paillere Martinot 2009	33(11/21)	$\geq 2/N.A.$	HFL-rTMS, SHM	2 weeks	Yes	MADRS
Chris Baeken 2013	21(8/13)	$\geq 3/N.A.$	HFL-rTMS, SHM	1 week	No	HAMD17
Nashaat N. Boutros 2002	22(16/5)	$\geq 2/N.A.$	HFL-rTMS, SHM	2 weeks	Yes	HAMD-25
Keith Isenberg 2005	30(12/16)	$\geq 2/N.A.$	HFL-rTMS, LFR rTMS	2 or 4 weeks	No	HAMD-21
Mauro Garcia-Toro 2001	35(20/15)	$\geq 2/N.A.$	HFL-rTMS, SHM	2 weeks	Yes	HAMD-21
Frank Padberg 1999	18(7/11)	$\geq 2/3.4 \pm 1.5$	HFL-rTMS, LFR-rTMS, SHM	1 week	Yes	HAMD-21
Urs P. Mosimann 2004	24(14/10)	$\geq 2/N.A.$	HFL-rTMS, SHM	2 weeks	Yes	HAMD-21
William J. Triggs 2010	48(19/29)	$\geq 2/N.A.$	HFL-rTMS, SHM	2 weeks	Yes	HAMD-24
Paul E Holtzheimer 2004	15(8/7)	$\geq 2/N.A.$	HFL-rTMS, SHM	2 weeks	No	HAMD-17
Curtis D. Kauffmann 2004	12(1/11)	$\geq 2/N.A.$	LFR-rTMS, SHM	2 weeks	Yes	HAMD-21
Shaw-Ji Chen Bahadir Bakim 2012	20(9/12) 35(4/31)	$\geq 2/N.A.$ $\geq 2/N.A.$	HFL-rTMS, SHM HFL-rTMS, SHM	4 weeks 6 weeks	Yes Yes	HAMD-17 HAMD-17

(continued on next page)

Table 1 (continued)

Source	Sample size (M/F)	Failed trails)min/mean)	Interventions	Duration	With antidepressant	Evaluationscale
David Rossini 2005	54(16/38)	≥ 2 /N.A.	HFL-rTMS, SHM	2 weeks	Yes	HAMD-21
Diego F Tavares 2017	50(15/35)	≥ 2 /N.A.	dTMS, SHM	4 weeks	No	HAMD-17
Christos Theleritis 2017	98(50/48)	≥ 2 /N.A.	HFL-rTMS, SHM	3 weeks	Yes	HAMD-17
Daniel M. Blumberger 2016	121(44/77)	$\geq 2/7.4 \pm 5.9$	BL-rTMS, HFL-rTMS, SHM	3 or 6 weeks	Yes	HAMD-17
S. Pallanti 2010	60(25/35)	$\geq 2/5.91 \pm 1.74$	BL-rTMS, LFR-rTMS, SHM	3 weeks	Yes	HAMD-17
Cheng-Ta Li 2014	60(20/40)	≥ 2 /N.A.	cTBS, iTBS, bTBS, SHM	2 weeks	Yes	HAMD-17
Daniel M. Blumberger 2012	24(4/24)	$\geq 2/4.2 \pm 2.3$	tDCS, SHM	3 weeks	Yes	HAMD-17
Johh Rush 2005	235(82/134)	≥ 2 /N.A.	VNS, SHM	10 weeks	Yes	HAMD-24
Mauro Garcia-Toro 2005	20(9/11)	≥ 2 / N.A.	BL-rTMS, SHM	2 weeks	Yes	HAMD-21
van Eijndhoven 2020	31(9/21)	≥ 2 / N.A.	HFL, SHM	4 weeks	Yes	HAMD-17
Paul B. Fitzgerald 2020	300(87/213)	≥ 2 / N.A.	HFL, LFR	4 weeks	Yes	HAMD-17

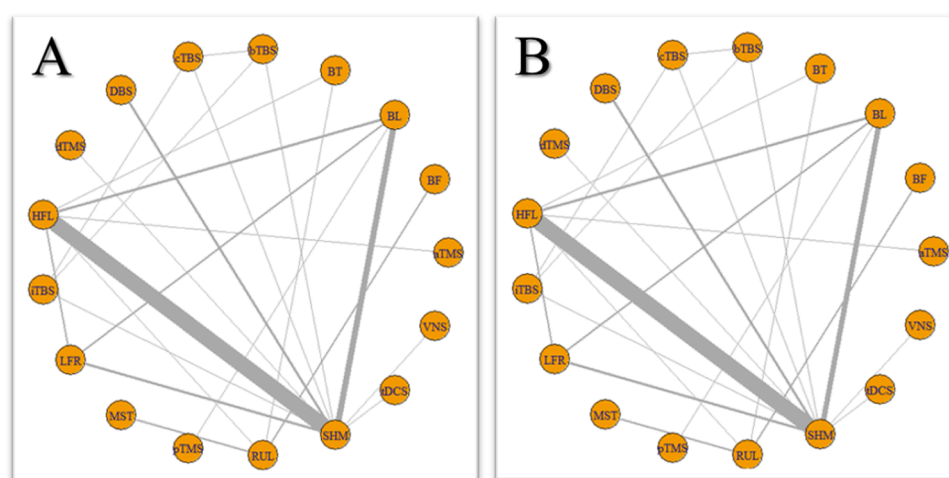


Figure 3. Network plot for included treatment comparisons. (A) Network plot for response rate, (B) network plot for all-cause discontinuation rate; each node represents different included neuromodulation methods; each edge represents a direct comparison between two methods; and the thickness of edge represents the number of trials included in this NMA.

active treatments, including 1,093 patients diagnosed with unipolar TRD. The subgroup analysis results have shown that BL-rTMS (RR 3.48, 95% CI 1.50–8.03) and HFL-rTMS (RR 2.06, 95% CI 1.23–3.46) were more effective than the sham control. There are no significant differences in the comparisons of the two active treatments. While in the comparisons of acceptability, no active treatments were proved to be less acceptable than the sham control. Results of the subgroup analysis were provided in the Supplemental Materials (Figure S9–11).

3.4.2. Bipolar TRD

We identified two trials that included only patients with bipolar TRD. Thus, due to the insufficiency of existing RCTs, we failed to conduct this subgroup analysis for bipolar depression. These two trials used deep TMS and bilateral rTMS to treat refractory bipolar depression, respectively. Among these two treatments, deep TMS showed weak efficacy, while rTMS was negative.

3.4.3. Funnel plot analysis

Trials of active treatments compared to the sham control and active treatments compared to another active treatments were included to produce two funnel plots, respectively. Overall, visual inspection of the

funnel plots does not reveal substantial asymmetry.(Figure 7)

4. Discussion

The treatment of TRD has always been a difficult challenge in clinical practice. A significant proportion of patients with depression seem resistant to conventional antidepressants, which may contribute to a lower quality of life, more financial burden, and a higher risk of suicide (Fostick et al., 2010, Hantouche et al., 2010). Therefore, many researchers are committed to addressing this issue, and some novel therapies have been developed as alternative options for TRD patients. Among them, various neuromodulation therapies have shown a promising effect. However, a considerable number of studies have proven the efficacy of ECT, rTMS, and other neuromodulation measures in TRD patients (Avery et al., 2006, Blumberger et al., 2012, Fitzgerald et al., 2006, Rossini et al., 2005, Li et al., 2014, Eschweiler et al., 2007, Sie-naert et al., 2009). Several studies still remain inconsistent (Fitzgerald et al., 2018, Tavares et al., 2017, Li et al., 2014, Palm et al., 2012, Dougherty et al., 2015, Holtzheimer et al., 2017, Merkl et al., 2018, Fitzgerald et al., 2012, Holtzheimer et al., 2004). Additionally, there is a lack of comprehensive comparisons of these neuromodulation therapies

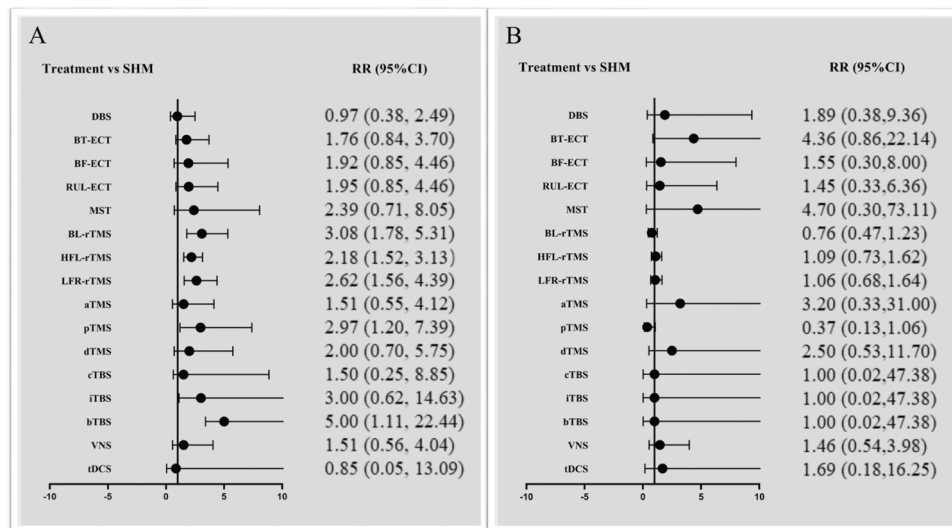


Figure 4. Forest plot of active treatments compared to the sham control. (A) Forest plot for response rate, the higher RR, the better, (B) forest plot for all-cause discontinuation rate, the lower RR, the better.

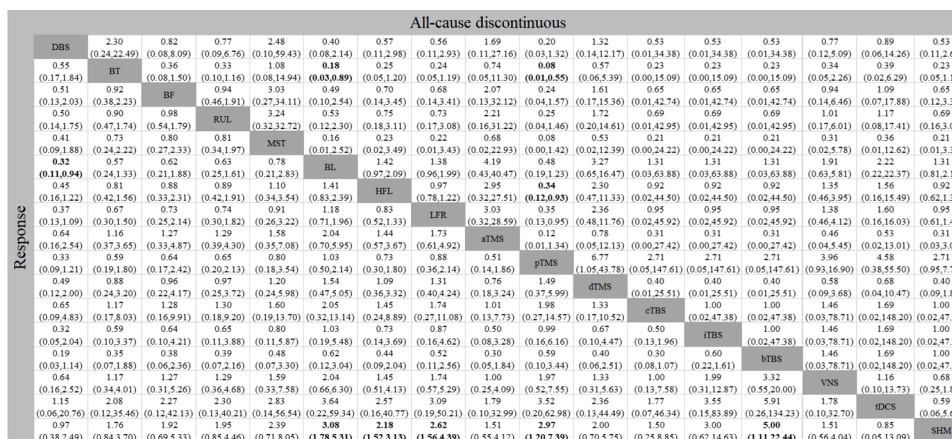


Figure 5. Treatment comparisons of response and all-cause discontinuation rates. RR of response rates are indicated in the left lower area, while the RR of all-cause discontinuation rates are shown in the right upper area. RR is considered significant if the 95% CI does not include one (shown in bold).

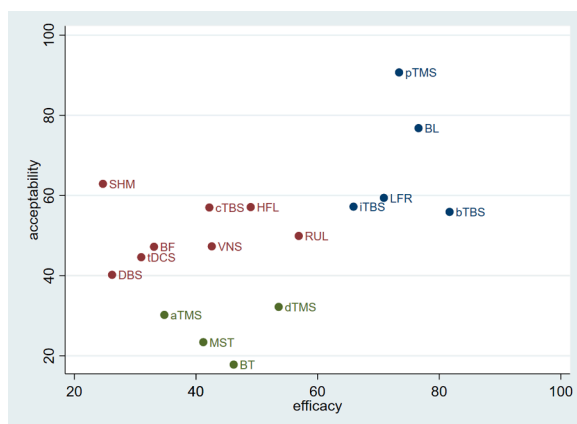


Figure 6. Ranking orders of all treatment measures and sham control based on the SUCRA. Horizontal axis shows SUCRA values for efficacy, while vertical axis shows SUCRA values for acceptability. Larger SUCRA values are indicative of a greater probability of higher ranking.

in TRD patients. Thus, we performed a systematic review of studies using neuromodulation methods to treat TRD and synthesize results from these studies. We compared and ranked the efficacy and acceptability of sixteen different neuromodulation procedures and sham controls in TRD patients. Response rates and all-cause discontinuation rates were used as the primary evaluation criteria of efficacy and acceptability.

According to the response rates reported by the present NMA, which included 47 randomized controlled trials involving 2833 patients, the efficacy of rTMS (BL-rTMS, HFL-rTMS, LFR-rTMS), bilateral TBS, and priming TMS were confirmed in TRD patients. This is consistent with previous studies based on patients with non-TRD[23]. These findings together support the therapeutic effect of TMS for non-TRD and TRD patients. Also, we ranked all included therapeutic interventions and found that bilateral TBS was most likely to be the most efficient measures. TBS is a novel special protocol of rTMS, which consists of three burst pulses delivered at 50 Hz and an interval of 200 ms (Suppa et al., 2016, Chung et al., 2015). This stimulation pattern mimics hippocampal firing frequency and induces long-term potentiation (LTP) or long-term depression (LTD) between synapses, while further modulating cortical excitability (Suppa et al., 2016, Chung et al., 2015). More precisely, the continuous TBS (cTBS, burst stimulation without interruption) could

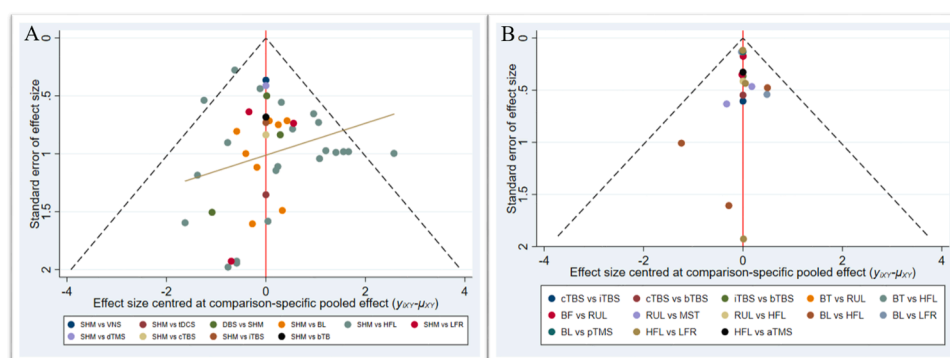


Figure 7. Funnel plot of included treatment comparisons on response rates. (A) Funnel plot of active treatments compared to the sham control; (B) Funnel plot of active treatments compared to another active treatments;

reduce cortical excitability, and intermittent TBS (iTBS, 2 s of burst stimulation followed by 8 s pause) could enhance cortical excitability (Suppa et al., 2016, Chung et al., 2015). This finding, together with a pervasive belief that depression is associated with an imbalance between bilateral DLPFC activity, makes it possible to effectively treat depression with bilateral TBS (Grimm et al., 2008). A recent large RCT also reported that iTBS is non-inferior to the standard rTMS for treating depression in substandard TRD patients (Blumberger et al., 2018). However, we must be cautious about the finding that bilateral TBS is better for TRD patients. On the one hand, this finding was not supported by the reports of remission rates, endpoint-scores in this NMA and results from another NMA which is based on non-TRD patients (Mutz et al., 2019). Secondly, only one RCT directly compared bilateral TBS with sham controls in our NMA. More clinical data are needed to support this finding.

It should be noted that ECT proved to be ineffective in treatment of TRD patients in present NMA, which is contrary to clinical intuition and previous studies on MDD patients. This paradox may be due a publication bias for ECT studies (Cattaneo et al., 2020). In fact, there is no sham-controlled RCTs on ECT since 1985, which resulted in few studies comparing ECT to the sham controls included in the present NMA. Besides, many studies involving ECT were outdated and excluded due to the poor quality, as described in a recent review of quality of ECT trials (Read et al., 2020). While, ECT is proposed as a “second” or “third-line” option to be applied to treatment-resistant patients in most guidelines and clinical practice (American, 2008). For this reason, we adjusted the requirement of TRD patients in inclusion criteria for ECT studies. Studies using ECT are just required not to contain any illumination or evidence that show included subjects were conflicted with our inclusion criteria for patients. This added several studies to conduct an extended analysis. With these additional studies, the efficacy of BT-ECT (RR 3.17, 95% CI 1.67–6.01), BL-ECT (RR 3.50, 95% CI 1.75–6.99), and RUL-ECT (RR 3.02, 95% CI 1.62–5.65) were established in our NMA (Figure S12, Supplemental Materials). Besides, although BT-ECT demonstrated a slight trend towards better efficacy comparing to RUL-ECT, no significant difference was found. This is inconsistent with previous network meta-analysis for patients with MDD (Mutz et al., 2019). One reason could be that the patients included in our network meta-analysis had higher levels of depression and higher resistance to treatments. The same reason could also explain the negative results for tDCS and MST in our network meta-analysis, which is opposite to a previous study based on non-TRD patients (Mutz et al., 2019). The two invasive stimulations, DBS and VNS, showed negative results in our study. In the present study, we focused on short-term efficacy. Three previous RCTs have proved long-term benefits from DBS in TRD patients (Mutz et al., 2019). This should be the focus of further deep brain stimulation studies in TRD. The results from VNS were based on data from only one randomized, sham-controlled trial (Rush et al., 2005), and additional data are needed.

Besides, the recognition of depression subtypes is an important

element in the evaluation and management of TRD, since potential bipolar disorder is an important reason for treatment resistance (Fornaro and Giosuè, 2010). Among 67 patients clinically diagnosed with TRD, 17% were re-diagnosed as bipolar after the Structured Clinical Interview, and 69% developed bipolar after one-year follow-up (Ventura et al., 1998). Considering such a situation, we performed a sub-group analysis to detect the differences between unipolar depression and bipolar depression. Potential Results from the sub-group analysis on unipolar TRD showed that BL-rTMS and HFL-rTMS have good therapeutic efficacies. There were subtle differences among the results of the overall and this sub-group analysis. Due to the lack of eligible studies on these two treatments, bilateral TBS and priming TMS were excluded. Besides, LFR-TMS showed an insufficient efficacy in the treatment of unipolar TRD. Compared to the sham control, LFR-TMS still showed a trend of effectiveness with an RR value on the critical edge (RR 2.73, 95% CI 1.00–7.34). This subtle difference may be due to the smaller sample size in the subgroup analysis, which would lead to weak sensitivity of detecting real but small effects. On the other hand, we failed to conduct a subgroup analysis for bipolar TRD. The existing RCTs are insufficient to perform it. Strict definition of TRD in this NMA help improve the consistency, but also resulted in the limited studies included, especially for bipolar TRD. While, some trials were not necessarily primarily intended to treat TRD cases, but also included a TRD subset in these studies. Set a proportion of TRD patients as threshold for inclusion may help address the issue (Fornaro et al., 2020). Qualitative analysis results from these two trials conducted in patients with bipolar depression showed limited, even negative efficacy. There is a trend for insufficient efficacy of currently neuromodulation producers in bipolar depression. Another study reported that patients with bipolar TRD require longer rTMS treatment to achieve remission (Cohen et al., 2010). Another critical issue is treatment-emergent effective switches. Traditional antidepressants have the risk of causing patients with bipolar depression to turn to mania/hypomania. A systematic review of bipolar depression treatment with rTMS supported that the risk of treatment-emergent mania in patients with bipolar depression is minimal (McGirr et al., 2016). This treatment-emergent mania also was not reported in the previous two RCTs on bipolar TRD included in our NMA. It seems safe to apply rTMS on patients with bipolar depression, while the precise effect requires further studies to accumulate evidence.

Beyond the efficacy, we also explored the acceptability of these neuromodulation measures. In addition, we found that the acceptability of all included active measures was non-inferior to the sham-controls. Among these measures, priming TMS and BL-rTMS tend to have better acceptability. Considering the size of available data in our NMA, the results of BL-rTMS were more robust than those of priming TMS.

There are also several limitations to this network meta-analysis. One limitation is the bias risk of included studies. Although we have excluded studies with high bias risk, there is still a third of the remaining studies with unclear risk of bias. The main defects of these trials are the

lack of description for randomization and assignment schemes, which can directly lead to the decline of reliability of these trials and corresponding meta-analysis results. Another key limitation is the interference from medications. Nearly 80% of RCTs included in our NMA allowed antidepressants during the study. This makes it challenging to rule out antidepressant factors. However, it is not allowed to increase the type or dose of antidepressants for TRD patients included in these studies. In this way, medication-related bias can be minimized without violating ethics. Besides, we noticed that the treatment durations of three protocols were too short, limited to only one week, which may impact the evaluation of treatment efficacy. Thus, we conducted a sensitivity analysis to shake off the influence from the short treatment courses, by excluding the three trials. Results from the sensitivity analysis remain unchanged, which supports the robustness of the present NMA. Details of the sensitivity analysis can be found in Figure S13 (Supplemental Materials). Besides, there are too little data available for some newly-developed treatment measures. Our network meta-analysis on bilateral TBS, priming TMS, and tDCS became more unstable and less precise for this reason. On the other hand, predictors of treatment-outcomes in neuromodulation intervention is a matter of concern. Previous studies have shown that mixed features in both unipolar and bipolar can predict treatment resistant (Fornaro et al., 2020). More well-designed randomized control trials and further analysis are needed to clarify this matter.

5. Conclusion

In summary, we explored the efficacy and acceptability of sixteen different neuromodulation procedures and sham controls for TRD patients in this network meta-analysis. In addition to ECT, repetitive TMS, priming TMS, and bilateral TBS proved effective in patients with TRD. BL-rTMS has both the advance of promising efficacy and high acceptability. Bilateral TBS may be the most efficacious neuromodulation measures in the treatment of TRD.

Author statement

Hao Li and Liqian Cui contributed equally to this article. Conception and design of the study: Hao Li, Liqian Cui; Acquisition of data: Hao Li, Yue Chen; Analysis and/or interpretation of data: Hao Li, Yueheng Liu; Drafting the manuscript: Hao Li; Revising the manuscript: Liqian Cui; All authors reviewed and approved the final version of this manuscript.

Data Availability Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical approval

This article does not contain any data from any of the authors' studies of human participants or animals.

Authorship statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the Journal of Affective Disorders.

Declaration of Competing Interest

The authors declare no potential conflicts of interest.

Funding

The study was supported by the grants from the Guangdong Provincial Key Laboratory for Diagnosis and Treatment of Major Neurological Diseases (2017B030314103); The Southern China International Cooperation Base for Early Intervention and Functional Rehabilitation of Neurological Diseases (2015B050501003); Guangdong Provincial Engineering Center for Major Neurological Disease Treatment; and the Guangdong Provincial Translational Medicine Innovation Platform for Diagnosis and Treatment of Major Neurological Disease.

Acknowledgements

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.jad.2021.03.019](https://doi.org/10.1016/j.jad.2021.03.019).

References

- W.H. Organization, Home/Newsroom/Fact sheets/Detail/Depression, 2020.
- Gaynes, B.N., Lux, L., Gartlehner, G., Asher, G., Forman-Hoffman, V., Green, J., Boland, E., Weber, R.P., Randolph, C., Bann, C., Coker-Schwimmer, E., Viswanathan, M., Lohr, K.N., 2020. Defining treatment-resistant depression. *DEPRESS ANXIETY* 37, 134–145.
- John Rush, A., Trivedi, Madhukar H., Wisniewski, Stephen R., Nierenberg, Andrew A., Stewart, Jonathan W., Diane Warden, P.D.M.B., Niederehe, George, Thase, Michael E., Lavori, Philip W., Lebowitz, Barry D., McGrath, Patrick J., Rosenbaum, Jerrold F., Sackeim, Harold A., Kupfer, David J., James Luther, M.A., Maurizio Fava, M.D., 2006. Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. *AM J PSYCHIAT* 163, 1905–1917.
- Gelenberg, A.J., Freeman, M.P., Markowitz, J.C., Rosenbaum, J.F., Thase, M.E., Trivedi, M.H., Van Rhoads, R., 2010. American Psychiatric Association practice guidelines for the treatment of patients with major depressive disorder. *Am J Psychiatry* 167, 9–118.
- C.H. Kellner, K.G. Farber, Electroconvulsive therapy and cognition: a salutary reappraisal., 2016, pp. 459–460.
- Avery, D.H., Holtzheimer, P.R., Fawaz, W., Russo, J., Neumaier, J., Dunner, D.L., Haynor, D.R., Claypoole, K.H., Wajdik, C., Roy-Byrne, P., 2006. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. *Biol Psychiatry* 59, 187–194.
- B. Bakim, U.E. Uzun, O. Karamustafalioglu, B. Ozcelik, G. Alpak, O. Tankaya, The combination of antidepressant drug therapy and high-frequency repetitive transcranial magnetic stimulation in medication-resistant depression, 22 (2012) 244–253.
- Blumberger, D.M., Mulsant, B.H., Fitzgerald, P.B., Rajji, T.K., Ravindran, A.V., Young, L. T., Levinson, A.J., Daskalakis, Z.J., 2012. A randomized double-blind sham-controlled comparison of unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant major depression. *World J Biol Psychiatry* 13, 423–435.
- Fitzgerald, P.B., Benitez, J., de Castella, A., Daskalakis, Z.J., Brown, T.L., Kulkarni, J., 2006. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry* 163, 88–94.
- Rossini, D., Lucca, A., Zanardi, R., Magri, L., Smeraldi, E., 2005. Transcranial magnetic stimulation in treatment-resistant depressed patients: a double-blind, placebo-controlled trial. *Psychiatry Res* 137, 1–10.
- Zheng, H., Jia, F., Guo, G., Quan, D., Li, G., Wu, H., Zhang, B., Fan, C., He, X., Huang, H., 2015. Abnormal Anterior Cingulate N-Acetylaspartate and Executive Functioning in Treatment-Resistant Depression After rTMS Therapy. *Int J Neuropsychopharmacol* 18, pyv059.
- Fitzgerald, P.B., Hoy, K.E., Singh, A., Gunewardene, R., Slack, C., Ibrahim, S., Hall, P.J., Daskalakis, Z.J., 2013. Equivalent beneficial effects of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in a large randomized trial in treatment-resistant major depression. *Int J Neuropsychopharmacol* 16, 1975–1984.
- P.B. Fitzgerald, K.E. Hoy, D. Elliot, R.N. Susan McQueen, L.E. Wambeck, Z.J. Daskalakis, Accelerated repetitive transcranial magnetic stimulation in the treatment of depression., 2018, pp. 1565–1572.
- Tavares, D.F., Myczkowski, M.L., Alberto, R.L., Valiengo, L., Rios, R.M., Gordon, P., de Sampaio-Junior, B., Klein, I., Mansur, C.G., Marcolin, M.A., Lafer, B., Moreno, R.A., Gattaz, W., Daskalakis, Z.J., Brunoni, A.R., 2017. Treatment of Bipolar Depression with Deep TMS: Results from a Double-Blind, Randomized, Parallel Group, Sham-Controlled Clinical Trial. *NEUROPSYCHOPHARMACOL* 42, 2593–2601.
- Li, C.T., Chen, M.H., Juan, C.H., Huang, H.H., Chen, L.F., Hsieh, J.C., Tu, P.C., Bai, Y.M., Tsai, S.J., Lee, Y.C., Su, T.P., 2014. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. *BRAIN* 137, 2088–2098.

- M. Li, X. Du, H. Chu, Y. Liao, W. Pan, Z. Li, G.C. Hung, Delayed effect of bifrontal transcranial direct current stimulation in patients with treatment-resistant depression: a pilot study., 2019, pp. 180.
- Palm, U., Schiller, C., Fintescu, Z., Obermeier, M., Keeser, D., Reisinger, E., Pogarell, O., Nitsche, M.A., Möller, H., Padberg, F., 2012. Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind. placebo-controlled study 242–251.
- Dougherty, D.D., Rezai, A.R., Carpenter, L.L., Howland, R.H., Bhati, M.T., O'Reardon, J. P., Eskandar, E.N., Baltuch, G.H., Machado, A.D., Kondziolka, D., Cusin, C., Evans, K. C., Price, L.H., Jacobs, K., Pandya, M., Denko, T., Tyrka, A.R., Brelje, T., Deckersbach, T., Kubu, C., Malone, D.J., 2015. A Randomized Sham-Controlled Trial of Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Chronic Treatment-Resistant Depression. *Biol Psychiatry* 78, 240–248.
- Holtzheimer, P.E., Husain, M.M., Lisanby, S.H., Taylor, S.F., Whitworth, L.A., McClintock, S., Slavin, K.V., Berman, J., McKhann, G.M., Patil, P.G., Et, A., 2017. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised. sham-controlled trial 4, 839–849.
- A. Merkl, S. Aust, G.H. Schneider, V. Visser-Vandewalle, A. Horn, A.A. Kühn, J. Kuhn, M. Bajbouj, Deep brain stimulation of the subcallosal cingulate gyrus in patients with treatment-resistant depression: a double-blinded randomized controlled study and long-term follow-up in eight patients, 227 (2018) 521–529.
- Rush, A.J., Marangell, L.B., Sackeim, H.A., George, M.S., Brannan, S.K., Davis, S.M., Howland, R., Kling, M.A., Rittberg, B.R., Burke, W.J., Et, A., 2005. Vagus nerve stimulation for treatment-resistant depression: a randomized. controlled acute phase trial 58, 347–354.
- Brunoni, A.R., Chaimani, A., Moffa, A.H., Razza, L.B., Gattaz, W.F., Daskalakis, Z.J., Carvalho, A.F., 2017. Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes: A Systematic Review With Network Meta-analysis. *JAMA PSYCHIATRY* 74, 143–152.
- J. Mutz, V. Vipulanathan, B. Carter, R. Hurlmann, C.H.Y. Fu, A.H. Young, 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., 2019, pp. 11079.
- Akil, H., Gordon, J., Hen, R., Javitch, J., Mayberg, H., McEwen, B., Meaney, M.J., Nestler, E.J., 2018. Treatment resistant depression: A multi-scale, systems biology approach. *NEUROSCI BIOBEHAV R* 84, 272–288.
- Fagioli, A., Kupfer, D.J., 2003. Is treatment-resistant depression a unique subtype of depression? *BIOL PSYCHIATRY* 53, 640–648.
- L. Shamseer, D. Moher, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, P. Shekelle, L.A. Stewart, Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation., 2015, pp. g7647.
- Elbourne, D.R., Altman, D.G., Higgins, J.P., Curtin, F., Worthington, H.V., Vail, A., 2002. Meta-analyses involving cross-over trials: methodological issues. *INT J EPIDEMIOL* 31, 140–149.
- White, I.R., 2015. Network meta-analysis. *The Stata Journal* 15, 951–985.
- Higgins, J.P.T., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed.)* 327, 557–560.
- White, I.R., Barrett, J.K., Jackson, D., Higgins, J.P.T., 2012. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *RES SYNTH METHODS* 3, 111–125.
- Salanti, G., ADES, A.E., Ioannidis, J.P., 2011. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J CLIN EPIDEMIOL* 64, 163–171.
- Chaimani, A., Higgins, J.P.T., Mavridis, D., Spyridonos, P., Salanti, G., 2013. Graphical tools for network meta-analysis in STATA. *PLOS ONE* 8, e76654.
- Veroniki, A.A., Vasilidis, H.S., Higgins, J.P.T., Salanti, G., 2013. Evaluation of inconsistency in networks of interventions. *INT J EPIDEMIOL* 42, 332–345.
- L. Fostick, A. Silberman, M. Beckman, B. Spivak, D. Amital, The economic impact of depression: resistance or severity?, 2010, pp. 671–675.
- E. Hantouche, J. Angst, J. Azorin, Explained factors of suicide attempts in major depression., 2010, pp. 305–308.
- G.W. Eschweiler, R. Vonthein, R. Bode, M. Huell, A. Conca, O. Peters, S. Mende-Lechler, J. Peters, D. Klecha, M. Prapotnik, A. Et, Clinical efficacy and cognitive side effects of bifrontal versus right unilateral electroconvulsive therapy (ECT): a short-term randomised controlled trial in pharmaco-resistant major depression, 101 (2007) 149–157.
- Sienaert, P., Vansteelandt, K., Demyttenaere, K., Peuskens, J., 2009. Randomized comparison of ultra-brief bifrontal and unilateral electroconvulsive therapy for major depression: clinical efficacy. *J Affect Disord* 116, 106–112.
- Fitzgerald, P.B., Hoy, K.E., Herring, S.E., McQueen, S., Peachey, A.V., Segrave, R.A., Maller, J., Hall, P., Daskalakis, Z.J., 2012. A double blind randomized trial of unilateral left and bilateral prefrontal cortex transcranial magnetic stimulation in treatment resistant major depression. *J Affect Disord* 139, 193–198.
- P.E. Holtzheimer, J. Russo, K.H. Claypoole, P. Roy-Byrne, D.H. Avery, Shorter duration of depressive episode may predict response to repetitive transcranial magnetic stimulation., 2004, pp. 24–30.
- Suppa, A., Huang, Y., Funke, K., Ridding, M.C., Cheeran, B., Di Lazzaro, V., Ziemann, U., Rothwell, J.C., 2016. Ten Years of Theta Burst Stimulation in Humans: Established Knowledge. *Unknowns and Prospects* 323–335.
- S.W. Chung, K.E. Hoy, P.B. Fitzgerald, Theta-burst stimulation: a new form of TMS treatment for depression?, 2015, pp. 182–192.
- S. Grimm, J. Beck, D. Schuepbach, D. Hell, P. Boesiger, F. Bermpohl, L. Niehaus, H. Boeker, G. Northoff, Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder., 2008, pp. 369–376.
- D.M. Blumberger, F. Vila-Rodriguez, K.E. Thorpe, K. Feffer, Y. Noda, P. Giacobbe, Y. Knyahnytska, S.H. Kennedy, R.W. Lam, Z.J. Daskalakis, J. Downar, Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial., 2018, pp. 1683–1692.
- Cattaneo, C.I., Ressico, F., Fornaro, M., Fazzari, G., Perugi, G., 2020. The shocking attitude towards ECT in Italy. *CNS Spectr* 1–12.
- Read, J., Kirsch, I., McGrath, L., 2020. Electroconvulsive therapy for depression: A review of the quality of ECT versus sham ECT trials and meta-analyses. *Ethical Human Psychology and Psychiatry*.
- American, P.A., 2008. The practice of electroconvulsive therapy: recommendations for treatment, training, and privileging (A task force report of the American Psychiatric Association). *American Psychiatric Pub*.
- Fornaro, M., Giosuè, P., 2010. Current nosology of treatment resistant depression: a controversy resistant to revision. *Clin Pract Epidemiol Ment Health* 6, 20–24.
- Ventura, J., Liberman, R.P., Green, M.F., Shaner, A., Mintz, J., 1998. Training and quality assurance with the Structured Clinical Interview for DSM-IV (SCID-I/P). *Psychiatry Res* 79, 163–173.
- Fornaro, M., Carvalho, A.F., Fusco, A., Anastasia, A., Solmi, M., Berk, M., Sim, K., Vieta, E., de Bartolomeis, A., 2020. The concept and management of acute episodes of treatment-resistant bipolar disorder: a systematic review and exploratory meta-analysis of randomized controlled trials. *J AFFECT DISORDERS* 276, 970–983.
- R.B. Cohen, A.R. Brunoni, P.S. Boggio, F. Fregni, Clinical predictors associated with duration of repetitive transcranial magnetic stimulation treatment for remission in bipolar depression: a naturalistic study., 2010, pp. 679–681.
- McGirr, A., Karmani, S., Arsappa, R., Berlim, M.T., Thirhalli, J., Muralidharan, K., Yatham, L.N., 2016. Clinical efficacy and safety of repetitive transcranial magnetic stimulation in acute bipolar depression. *World psychiatry : official journal of the World Psychiatric Association (WPA)* 15, 85–86.
- Fornaro, M., Fusco, A., Novello, S., Mosca, P., Anastasia, A., De Blasio, A., Iasevoli, F., de Bartolomeis, A., 2020. Predictors of Treatment Resistance Across Different Clinical Subtypes of Depression: Comparison of Unipolar vs. Bipolar Cases. *FRONT PSYCHIATRY* 11, 438.