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Efficacy of non-invasive brain stimulation combined with medications for bipolar depression: a systematic review and meta-analysis of randomized controlled trials

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Abstract: Objective: Bipolar disorder is a chronic psychiatric disorder with severe disease burden, especially as induced by bipolar depression. Noninvasive brain stimulation (NIBS) has shown antidepressant potential, but its adjunctive benefit when combined with pharmacotherapy remains unclear. This meta-analysis evaluates the efficacy of NIBS combined with medication. **Methods:** A comprehensive search was conducted across PubMed, Embase, and the Web of Science, including studies up to July 31, 2024. Randomized controlled trials comparing NIBS plus medication with medication monotherapy or sham stimulation were included. The primary outcome evaluated was the change in depressive symptoms; secondary outcomes included response rate, remission rate, dropout rate, and cognitive changes. Subgroup and meta-regression analyses were conducted to explore potential sources of heterogeneity. **Results:** Seventeen randomized controlled trials (RCTs) involving 748 screened records were included, comprising 11 transcranial magnetic stimulation (TMS) trials and six transcranial direct current stimulation (tDCS) trials. Compared with pharmacotherapy alone, NIBS combined with medication was linked to greater reductions in depressive symptoms (SMD=−0.69). Both TMS and tDCS were associated with improvements in depressive symptoms and response rates, whereas a statistically significant association with remission was observed only for TMS. No significant differences were observed in dropout rates or cognitive outcomes. Meta-regression analyses did not identify consistent associations between treatment effects and demographic or stimulation-related variables, although an exploratory potential association between tDCS current intensity and symptom improvement was observed. **Conclusions:** NIBS combined with medication may offer additional benefit over pharmacotherapy alone for bipolar depression. Nevertheless, substantial heterogeneity and the limited number of available trials warrant cautious interpretation. Further well-designed randomized controlled trials are needed to confirm these findings and to clarify the role of stimulation parameters.

Key words: Bipolar disorder; Transcranial magnetic stimulation; Transcranial direct current stimulation

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1 Introduction

Bipolar disorder (BD) is a chronic psychiatric condition characterized by recurrent episodes of mania or hypomania and interspersed with depressive episodes (Nierenberg et al., 2023), affecting approximately 2% of the global population (Merikangas et al., 2011). The onset of BD typically occurs during adolescence, disrupting patients' developmental trajectories and impairing social functioning (Carvalho et al., 2020). Moreover, individuals with BD face a suicide rate that is 20-30 times higher than that of the general population (Plans et al., 2019). Depressive episodes occur more frequently than manic or hypomanic episodes over the course of BD, yet treatment options for bipolar depression remain limited (Carvalho, et al., 2020). Currently, only five medications have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute depressive episodes in adults with BD (Carvalho et al., 2020), and these conventional pharmacological therapies often require a considerable amount of time to take effect (Howes et al., 2022). Consequently, there is an urgent need to identify alternative and more effective therapeutic strategies. Noninvasive brain stimulation (NIBS) represents a rapidly advancing neuromodulatory approach that alters neuronal activity via externally applied magnetic or electrical fields. Growing evidence supports the efficacy of NIBS techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), in treating psychiatric disorders (Martinotti et al., 2019; Sabe et al., 2024). While several TMS and tDCS protocols have received FDA approval for the treatment of major depressive disorder (MDD) (Martinotti, et al., 2019; Cohen et al., 2022; Lõokene et al., 2022), the use of NIBS in patients with BD has not yet been approved by the FDA.

Research on NIBS for bipolar depression is expanding; however, findings for different intervention types remain inconsistent. For example, Mutz et al. conducted a network meta-analysis of NIBS for depressive episodes, including bipolar depression and MDD, and reported that 10 out of 18 treatment strategies were associated with higher response rates compared with sham stimulation (Mutz et al., 2019). Similarly, another meta-analysis demonstrated that repetitive transcranial magnetic stimulation (rTMS) showed superior efficacy to sham treatments in improving depressive symptoms in bipolar depression (Kishi et al., 2024). However, a meta-analysis evaluating continuous theta-burst stimulation (cTBS) in patients with MDD and bipolar depression found no significant symptom improvement (Cai et al., 2024). More recently, a network meta-analysis examined various NIBS modalities for bipolar depression and found that certain protocols improved depressive symptoms (Hsu et al., 2024). Nevertheless, most previous studies have focused on NIBS as a monotherapy. Given the clinical complexity of BD, combination strategies are often required (Dean et al., 2018). Furthermore, due to the recurrent nature of BD, patients typically require long-term psychotropic medication regimens to maintain mood stability (Nierenberg et al., 2023). While meta-analyses have assessed the combined efficacy of NIBS and antidepressants in MDD (Tao et al., 2024; Zaidi et al., 2024), there is a lack of similar analyses specific to bipolar depression.

In addition to mood symptoms, cognitive dysfunction is highly prevalent in BD (Van Rheenen et al., 2020). Evidence suggests that patients with BD exhibit deficits in several cognitive domains, including verbal memory, attention, language, and executive functioning, compared to healthy controls (Kurtz and Gerraty, 2009; Rosa et al., 2010). One study has indicated that medication may negatively impact cognitive outcomes in patients with BD (Xu et al., 2020). NIBS may not impair cognitive function, and may even improve it. Although the potential of NIBS to enhance cognitive functioning in BD has gained increasing attention, findings remain inconsistent. For instance, one randomized controlled trial (RCT) reported cognitive improvements following intermittent theta-burst stimulation (iTBS) compared with sham stimulation (Luo et al., 2024), while another RCT found no pro-cognitive effect of rTMS in BD patients (Myczkowski et al., 2018).

Given these inconsistencies, our aim in this systematic review and meta-analysis was to evaluate whether combining NIBS with medication enhances treatment efficacy for bipolar depression, with particular attention to both mood symptoms and cognitive functioning.

2 Materials and methods

2.1 Literature search

This study was conducted according to the guidelines in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and followed the Cochrane Handbook for Systematic Reviews of Interventions (Cumpston et al., 2022). The protocol for the study was prospectively registered in PROSPERO, the International Prospective Register of Systematic Reviews (registration number: CRD42024583108). Two authors independently searched the PubMed, Embase, and Web of Science databases. The search strategy combined terms related to bipolar disorder, non-invasive brain-stimulation techniques, and clinical trials. The literature search was conducted up to July 31, 2024. For details regarding inclusion and exclusion criteria, data extraction, quality control and the full search strategy, please refer to the supplementary materials and methods.

2.2 Statistical analysis

For continuous variables, we calculated standardized mean differences (SMD), while we used odds ratios (OR) for categorical outcomes. All effect estimates were reported with 95% confidence intervals (CI). Statistical heterogeneity was quantified using the I^2 statistic and interpreted according to the Cochrane Handbook guidelines. We interpreted I^2 values as follows: 0% to 40% might not indicate significant heterogeneity, 40% to 60% could represent moderate heterogeneity, 50% to 90% could indicate substantial heterogeneity, and 75% to 100% was considered considerable heterogeneity.

Meta-analyses used random- or fixed-effects models according to anticipated clinical diversity and statistical heterogeneity, with random-effects models planned for primary outcomes and secondary outcomes modeled according to observed heterogeneity. To explore potential sources of heterogeneity, we performed prespecified subgroup analyses and meta-regression analyses using mixed-effects models with restricted maximum-likelihood (REML) estimation when sufficient data were available. Influence diagnostics were conducted for meta-regression models showing statistically significant associations. Studentized residuals, Cook's distance, DFBETAs, and hat values were examined to identify potentially influential or high-leverage studies. Sensitivity analyses were performed to evaluate the robustness of the pooled estimates. These included leave-one-out analyses, in which each study was sequentially excluded, and reanalyses using alternative plausible correlation coefficients (r=0.30, 0.50, and 0.70) for imputed change-score standard deviations.

We used the 'meta' and 'metafor' packages in R software (version R×64 4.4.1) for these analyses (Shim and Kim, 2019). We assessed publication bias using funnel plots and Egger's test, and used contour-enhanced funnel plots to evaluate whether funnel-plot asymmetry was likely attributable to publication bias rather than heterogeneity.

3 Results

3.1 Literature search

We identified 1,129 articles through database searches (PubMed: 250; Embase: 484; Web of Science: 395). After removing 381 duplicates, 748 unique articles remained. Screening of titles and abstracts excluded 627 articles, leaving 121 for full-text review. We excluded 104 articles during full-text assessment. Reasons for exclusion included irrelevant study design, unsuitable participants, duplicate datasets, lack of combination drug therapy, insufficient outcome measures, and non-English/Chinese language. Ultimately, 17 studies met the eligibility criteria and were included in the meta-analysis (Fig. 1).

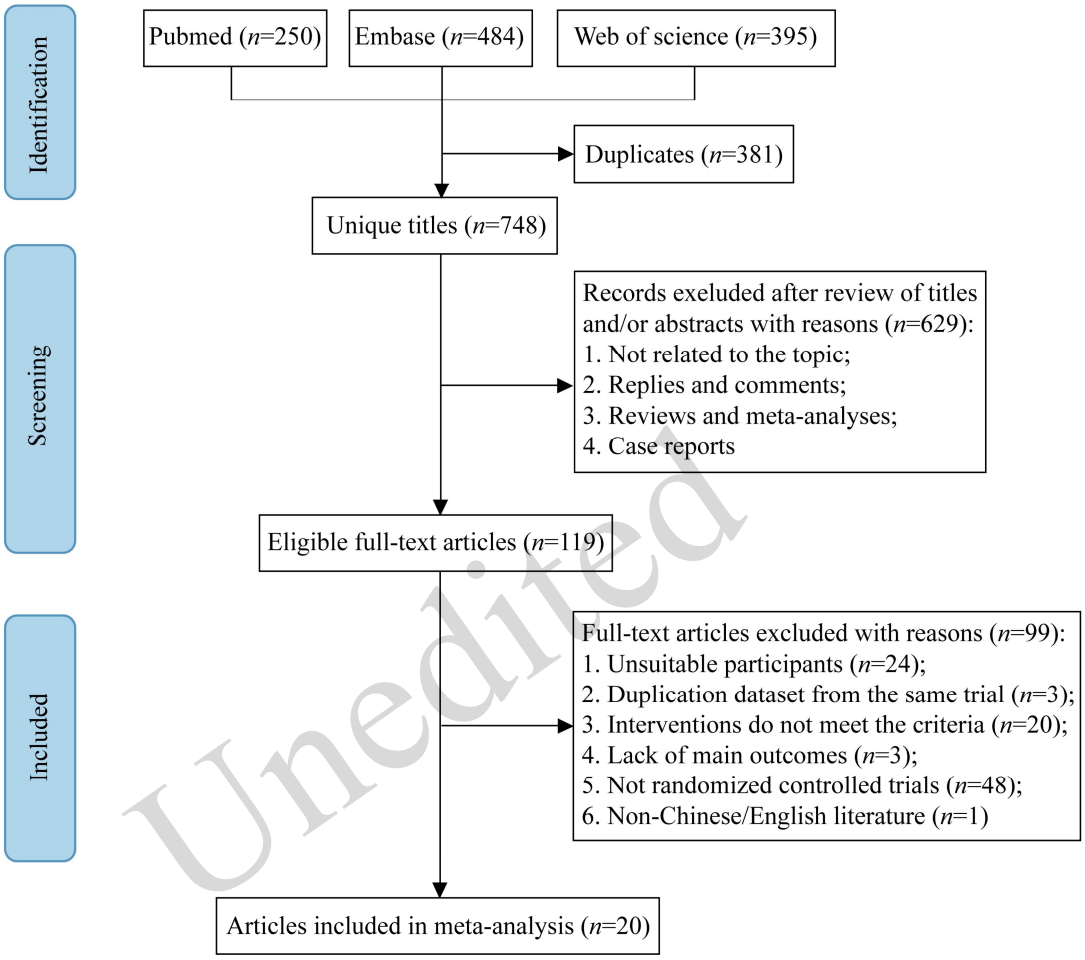

Fig. 1 Flow chart for study selection

3.2 Study characteristics

The 17 included RCTs covered a total of 743 patients with bipolar depression. The studies were published between 2013 and 2024, and participants ranged in age from sixteen to fifty-three years. The proportion of male participants ranged from 10% to 77%. The duration of NIBS interventions varied from 5 days to 6 weeks, the number of treatment sessions ranging from 10 to 42. Detailed clinical characteristics of the included studies are provided in Table 1, while the cognitive domains evaluated in studies involving cognitive functioning are presented in Table 2. The specific parameters of NIBS used in each study are summarized in Table 3. Of the included studies, 11 applied TMS combined with medication, and six applied tDCS combined with medication.

Table 1 Characteristics of the included studies

Authors, Years	Country	Criteria	Diagnosis	Medication	Age (T/C)	Sample Size （T/C)	Male% (T/C)	Intervention (T/C)	Outcome Measure
Li, et al.,2013	China	DSM-5	BDI, BDII	Li, Ap	23.0±6.0/22.0±7.0	30/29	60.0/51.7	rTMS+medication/ Sham rTMS+medication	①②③④
Fitzgerald, et al.,2016	Australia	DSM-IV	BDI, BDII	MS, Ap, Ad	46.3±12.6/49.7±11.0	23/23	43.5/43.5	rTMS+medication/ Sham rTMS+medication	①②③④
Sheline, et al., 2024	Australia	DSM-5	BDI, BDII	Li, Ac, Ad, Ap	43.1±15.2/43.6±19.2	12/12	50.0/50.0	iTBS+medication/ Sham iTBS+medication	①②③④
Mak, et al., 2021	China	DSM-5	BDI, BDII	MS, Ap, Ad	40.7±11.4/39.4±11.3	26/28	30.8/35.7	rTMS+medication/ Sham rTMS+medication	①②③④
Dellink, et al., 2024	Belgium	DSM-IV	BDI, BDII	Li, Ap, Ad	48.0±7.0/51.0±14.0	18/19	27.8/31.6	cTBS+medication/ Sham cTBS+medication	①
McGirr, et al., 2021	Canada	DSM-5	BDI, BDII	MS, Ap, Ad	44.8±13.7/43.0±14.3	18/19	38.9/36.8	iTBS+medication/ Sham iTBS+medication	①②③④⑤[a]
Novak, et al., 2024	Czech Republic	DSM-IV-TR	BDI, BDII	Li, Ac, Ap, Ad	39.3±14.6/43.9±10.7 48.9±12.8/43.9±10.7	20/20 20/20	35.0/40.0 40.0/40.0	rTMS+medication/ Sham rTMS+medication	①②③④
Zengin, et al., 2022	Turkey	DSM-5	BDI, BDII	Li, Ac, Ap, Ad	42.36±9.5/38.9±10.3	14/15	42.9/53.3	rTMS+medication-Sham rTMS+medication/ Sham rTMS+medication-rTMS+medication	①②③④
Luo, et al., 2024	China	DSM-5	BDII	MS, Ap	15.6±1.8/15.8±1.6	22/20	18.2/10.0	iTBS+medication/ Sham iTBS+medication	①④⑤
Tavares, et al., 2017	Brazil	DSM-IV	BDI, BDII	Li, Ac, Ap, Ad	43.5±12.0/41.2±8.9	25/25	32.0/28.0	dTMS+medication/ Sham dTMS+medication	①②③④
Bulteau, et al., 2019	France	DSM-IV-TR	BD	MS	52.7±10.8/53.1±12.5	12/14	41.7/71.4	iTBS+medication/ Sham iTBS+medication	①②③
Zhang, et al., 2023	China	DSM-5	BD	NR	34.2±8.5/31.9±9.5	25/25	16.0/36.0	tDCS+medication/ Sham tDCS+medication	①②
Mardani, et al., 2021	Iran	NR	BDI	MS	32.1±9.4/30.3±8.6	15/15	20.0/66.7	tDCS+medication/ medication	①⑤
Riahi, et al., 2024	Iran	DSM-5	BDI, BDII	MS, Ap	15.9±1.1/15.7±1.3	20/20	55.0/55.0	tDCS+medication/ Sham tDCS+medication	①
Lee, et al., 2022	South Korea	DSM-5	BDI, BDII	Li, Ac, Ap, Ad	35.7±13.1/31.2±11.9	32/32	28.1/25.0	tDCS+medication/ Sham tDCS+medication	①④
Sampaio-Junior, et al., 2018	Brazil	NR	BDI, BDII	Li, Ac, Ap, Ad	46.2±11.8/45.7±10.3	30/29	76.7/51.7	tDCS+medication/ Sham tDCS+medication	①②③④⑤[a]

Loo, et al., 2018	Australia	DSM-IV-TR	BDI, BDII	MS, Ap, Ad	49.1±16.6/47.7±14.6	19/17	NR/ NR	tDCS+medication/ Sham tDCS+medication	①②③④⑤

Abbreviations: Ac, anticonvulsant; Ad, antidepressant; Ap, antipsychotic; BD, bipolar disorder; C, control group; cTBS, continuous theta burst stimulation; dTMS, deep transcranial magnetic stimulation; iTBS, intermittent theta burst stimulation; Li, lithium; MS, mood stabilizer; NR, not report; rTMS, repetitive transcranial magnetic stimulation; T, treatment group; tDCS, transcranial direct currentstimulation.

① depression score
② respond rate
③ remit rate
④ drop-out rate
⑤ Cognitive function ([a] Cognitive function assessment results were reported in a separate study)

Table 2 Characteristics of cognitive functioning in the included studies

Cognitive Domain	Method of Assessment	Authors, Years	Type of NIBS	Simple size	Findings by Study (SMD [95% CI])
Global Cognition	MoCA	Loo, et al., 2018	tDCS	38	-0.46 [-1.12; 0.21]
	CVLT-II, BVMT-R, TMT-A , TMT-B , CPT-IP trial 1-3, Animal Fluency, Letter-Number Sequencing, Spatial Span, Symbol Coding, Stroop Word, Stroop Colour, Stroop Colour-Word	Torres, et al., 2023	iTBS	37	0.06 [-0.65;0.76]
	DN: CAS	Luo, et al., 2024	iTBS	42	0.30 [-0.31; 0.91]
Attention/vigilance	Digit Span Forward	Myczkowski, et al., 2018[a]	rTMS	43	-0.20 [-0.80; 0.40]
	Digit Span Forward	Tortella, et al., 2020[a]	tDCS	59	-0.28 [-0.80;0.23]
	DN: CAS	Luo, et al., 2024	iTBS	42	0.28 [-0.33; 0.88]
Processing Speed	TMT-A	Myczkowski, et al., 2018[a]	rTMS	43	0.01 [-0.59; 0.60]
	TMT-A	Tortella, et al., 2020[a]	tDCS	59	-0.30 [-0.81:0.21]
Working Memory	Digit Span Backward	Myczkowski, et al., 2018[a]	rTMS	43	0.08 [-0.52; 0.68]
	Digit Span Backward	Tortella, et al., 2020[a]	tDCS	59	-0.31 [-0.82:0.21]
Executive Function	TMT-B	Myczkowski, et al., 2018[a]	rTMS	43	0.17 [-0.43; 0.77]
	TMT-B	Tortella, et al., 2020[a]	tDCS	59	-0.09 [-0.60; 0.42]
Verbal Learning/Memory	RAVLT	Myczkowski, et al., 2018[a]	rTMS	43	-0.07 [-0.66;0.53]
	RAVLT	Tortella, et al., 2020[a]	tDCS	59	0.21 [-0.30; 0.7]
	CVLT-II	Torres, et al., 2023	iTBS	37	0.20 [-0.50; 0.91]
Language	FAS Verbal Fluency Test	Myczkowski, et al., 2018[a]	rTMS	43	-0.28 [-0.88; 0.33]
	Verbal Fluency Test	Tortella, et al., 2020[a]	tDCS	59	0.09 [-0.42; 0.60]
Visual Learning	BVMT-R	Torres, et al., 2023	iTBS	37	0.02 [-0.69; 0.72]
Inhibitory Control	Stroop interference	Myczkowski, et al., 2018[a]	rTMS	43	0.22 [-0.38; 0.83]
	Stroop interference	Tortella, et al., 2020[a]	tDCS	59	-0.39 [-0.91; 0.12]
	Go/No-Go test	Mardani, et al., 2021	tDCS	30	0.61 [-0.13; 1.34]

Abbreviations: BVMT-R, brief visuospatial memory test-revised version; CI, Confidence Interval; CPT-IP, continuous performance test-identical pairs; CVLT-II, california verbal learning test-2nd edition; DN:CAS, Chinese version of the das-naglieri cognitive assessment System; iTBS, intermittent theta burst stimulation; MoCA, montreal cognitive assessment; RAVLT, rey auditory verbal learning test; rTMS, repetitive transcranial magnetic stimulation; SMD, Standardized Mean Difference; tDCS transcranial direct current stimulation; TMT, trail making test.

[a] Primary outcomes were reported in a separate study.

Table 3 Characteristics of NIBS treatment

Authors, Years	Type of NIBS	Treatment duration	Machine	Cortical target	Location method	Motor threshold /Current	Sessions per day	Total sessions	Pulse per session	Total pulses
Li, et al., 2013	LF-rTMS	4 w	Magstim	RDLPFC	NR	80%	1	20	150	3000
Fitzgerald, et al., 2016	LF-rTMS+HF-rTMS	4 w	Magventure	RDLPFC+LDLPFC	Navigator	110%	1	20	1000+1000	40000
Sheline, et al., 2024	iTBS	5 d	Magventure	DLPFC	Navigator	90%	10	50	1800	90000
Mak, et al., 2021	LF-rTMS	3 w	Magstim	RDLPFC	Navigator	110%	1	15	300	4500
Dellink, et al., 2024	cTBS	4 d	Magstim	RDLPFC	Navigator	110%	5	20	900	18000
McGirr, et al., 2021	iTBS	4 w	Magventure	LDLPFC	Navigator	120%	1	20	600	12000
Novak, et al., 2024	HF-rTMS	4 w	Magventure	RVLRFC	Navigator	100%	1	20	1200	24000
	HF-rTMS	4 w	Magventure	LDLPFC	Navigator	100%	1	20	1200	24000
Zengin, et al., 2022	HF-rTMS	2 w	Neurosoft	LDLPFC	5cm	110%	2	20	1000	20000
Luo, et al., 2024	iTBS	3 w	Yiruide	LDLPFC+LITG+LPPC	10-20 system	80%	2	30	1800	54000
Tavares, et al., 2017	dTMS	4 w	Brainsway	LDLPFC	6cm	120%	1	20	1980	39600
Bulteau, et al., 2019	iTBS	3 w	MagVenture	LDLPFC	Navigator	80%	2	30	990	29700
Zhang, et al., 2023	tDCS	14 d	Neuroelectrics	LDLPFC	10-20 System	2mA	1	14	20min	-
Mardani, et al., 2021	tDCS	10 d	Mind Alive	RDLPFC	10-20 System	2mA	2	20	20min	-
Riahi, et al., 2024	tDCS	5 d	Mind Alive	DLPFC	NR	2mA	2	10	20min	-

Lee, et al., 2022	tDCS	6 w	Ybrain	Anode:LDLPFC Cathode: RDLPFC	10-20 System	2mA	1	18-42	30min	-
Sampaio-Junior, et al., 2018	tDCS	10 d	Soterix Medical	Anode:LDLPFC Cathode: RDLPFC	EASYstrap	2mA	1	12	30min	-
Loo, et al., 2018	tDCS	4 w	NR	Anode:LDLPFC Cathode: lateral right frontal	10-20 System	2.5mA	1	20	30min	-

Abbreviations: cTBS, continuous theta burst stimulation; DLPFC, dorsolateral prefrontal cortex; dTMS, deep transcranial magnetic stimulation; HF-rTMS, high frequency repetitive transcranial magnetic stimulation; iTBS, intermittent theta burst stimulation; LDLPFC, left dorsolateral prefrontal cortex; LF-rTMS, low frequency repetitive transcranial magnetic stimulation; LITG, left inferior temporal gyrus; LPPC, left posterior parietal cortex; NR, not report; RDLPFC, right dorsolateral prefrontal cortex; tDCS, transcranial direct current stimulation.

3.3 Bias risk of included studies

Only two of the included studies failed to clearly report the methods used for randomization and allocation concealment (Sampaio-Junior et al., 2018; Mardani et al., 2021). A total of 15 studies described whether any patients were lost to follow-up, with dropout rates ranging from 0% to 36% (Li et al., 2013; Fitzgerald et al., 2016; Tavares et al., 2017; Loo et al., 2018; Sampaio-Junior et al., 2018; Bulteau et al., 2019; Mak et al., 2021; Mcgirr et al., 2021; Lee et al., 2022; Zengin et al., 2022; Zhang et al., 2023; Dellink et al., 2024; Luo, et al., 2024; Novák et al., 2024; Riahi et al., 2024; Sheline et al., 2024). The reasons for patients dropout included adverse effects such as headaches, poor treatment outcomes, and disruptions caused by the coronavirus disease 2019 (COVID-19) pandemic. The quality assessment of the included studies is illustrated in Fig. 2.

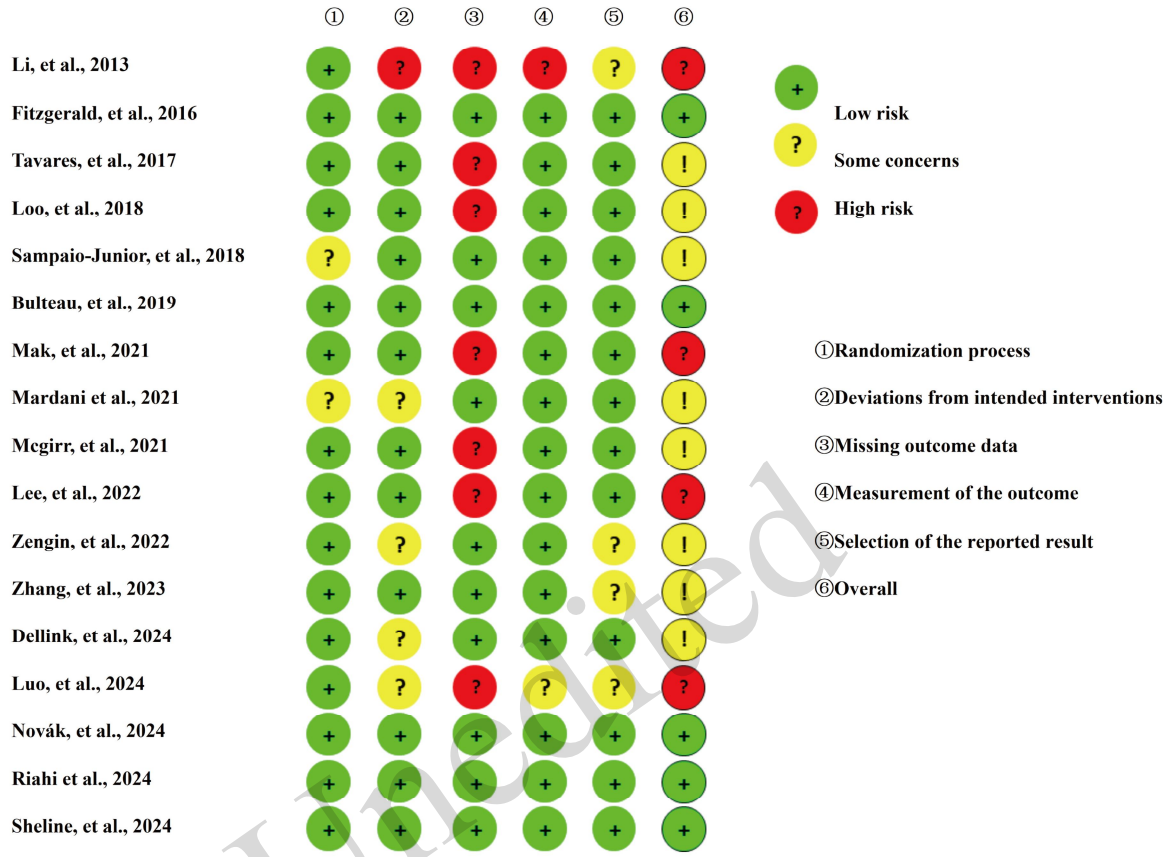

Fig. 2 Results of bias risk evaluation of included studies

3.4 Overall effects of NIBS treatments for depression

3.4.1 Depression scores

As shown in Fig. 3, all included studies reported depression scores both before and after the intervention. The pooled effect size was estimated using a random-effects model. Substantial heterogeneity was observed (I^2=76.6%, P<0.01). Compared to either sham stimulation combined with medication or medication alone, NIBS combined with medication was associated with greater reductions in depressive symptoms (SMD=−0.69, 95% CI [−1.04, −0.33], I^2=76.6%, P<0.01). To further investigate the sources of heterogeneity, subgroup analyses were conducted based on the NIBS model and target location. The results of subgroup analysis based on intervention type showed that both TMS in combination with medication (SMD=−0.44, 95%CI [−0.67, −0.20], I^2 = 54.7%, P<0.01) and tDCS in combination with medication (SMD=−1.03, 95%CI [−1.79, −0.27], I^2 = 86.0%, P<0.01) were associated with improvements in depressive symptoms compared to medication alone. Additionally, we performed subgroup analysis based on the stimulation target location, categorized as dorsolateral prefrontal cortex (DLPFC), non-DLPFC, or combined (DLPFC along with other sites). As shown in Fig. S5, stimulation targeting the DLPFC subgroup yielded the largest effect size, with a significant summary estimate (SMD=−0.80, 95% CI [−1.16, −0.44], P<0.01). However, considerable heterogeneity was observed in this subgroup (I^2 =75%). In contrast, the single study that applied non-DLPFC stimulation showed no statistically significant effect (SMD=−0.63, 95% CI [−1.26, 0.01], P=0.054). Similarly, the pooled estimate from two studies using combined target stimulation showed a negligible and non-significant effect (SMD=0.13, 95% CI [− 0.57, 0.83], I^2=56.3%, P=0.65).

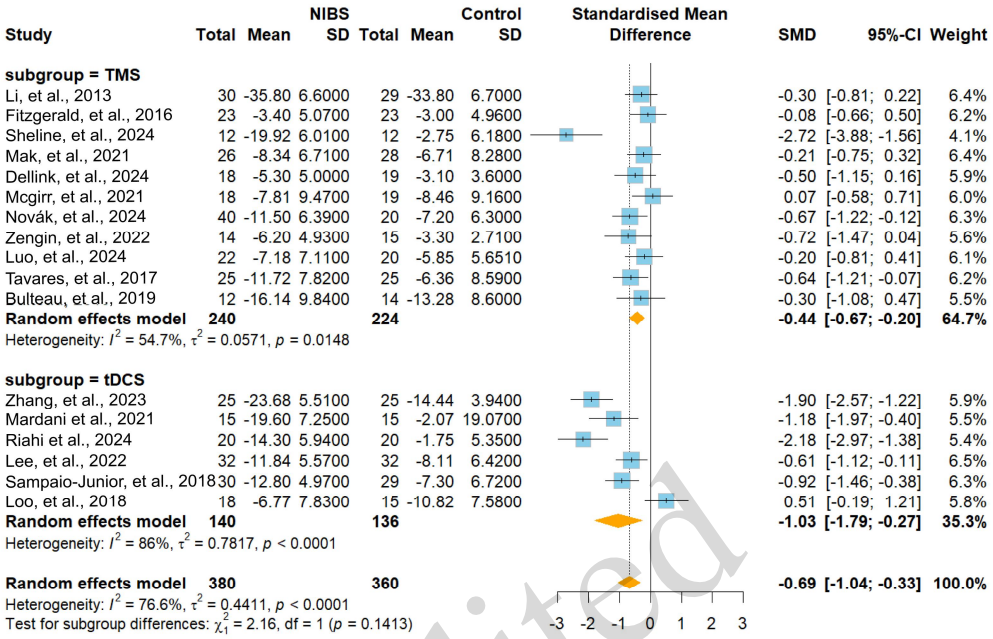

Fig. 3 Forest plot of depression scores.

When the effect size was less than zero, as presented by the standardized mean difference, the treatment under investigation resulted in a greater reduction in depression scores compared to the control.

3.4.2 Depression response rates

Eleven RCTs reported depression response rates (Li, et al., 2013; Fitzgerald, et al., 2016; Tavares, et al., 2017; Loo, et al., 2018; Sampaio-Junior, et al., 2018; Bulteau, et al., 2019; Mak, et al., 2021; Mcgirr, et al., 2021; Zengin, et al., 2022; Novák, et al., 2024; Sheline, et al., 2024), among which nine applied TMS and two applied tDCS. The results are detailed in Fig. 4. A fixed-effects model was adopted due to I^2 <50%. Subgroup analysis showed that both TMS combined with medication (OR=2.90, 95%CI [1.65, 5.08], I^2 =0%, P<0.01) and tDCS combined with medication (OR=2.75, 95%CI [1.11, 6.82], I^2 =62.0%, P=0.03) led to higher clinical response rates in patients with bipolar depression compared to the control group.

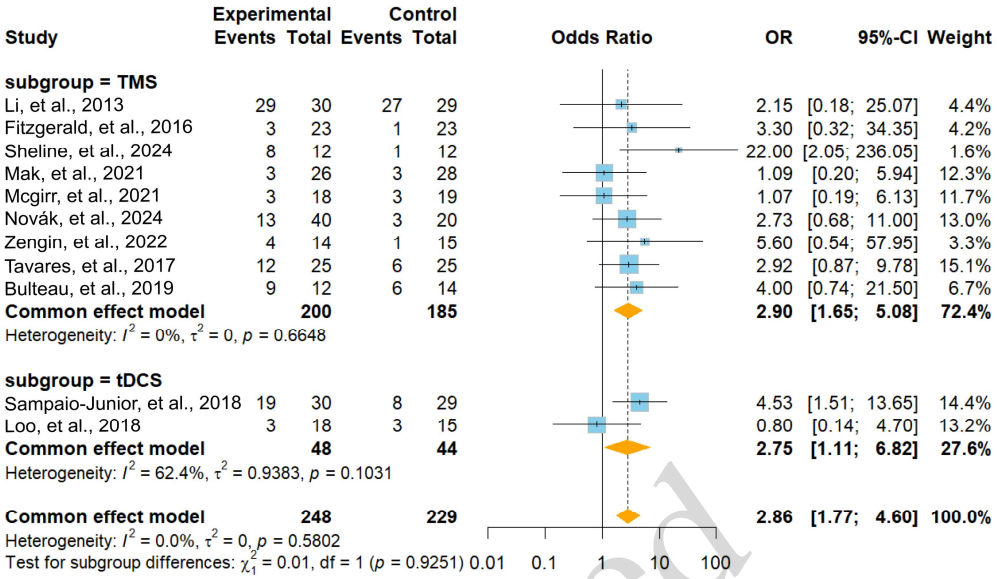

Fig. 4 Forest plot of response rate.

When the effect size was more than one, as presented by the odds ratio, the treatment under investigation demonstrated higher response rate compared to the control.

3.4.3 Remission rate of depression

Ten studies reported remission rates (Li, et al., 2013; Fitzgerald, et al., 2016; Tavares, et al., 2017; Loo, et al., 2018; Sampaio-Junior, et al., 2018; Bulteau, et al., 2019; Mak, et al., 2021; Mcgirr, et al., 2021; Novák, et al., 2024; Sheline, et al., 2024), including eight studies that used TMS and two that used tDCS, as shown in Fig. 5. We adopted a fixed-effects model due to I^2 <50%. TMS combined with medication improved the clinical remission rate in patients with bipolar depression compared to the control group (OR=2.76, 95%CI [1.57, 4.86], I^2 =0%, P<0.01), while the remission rate in the group for tDCS combined with medication was not significantly different from the control group (OR=1.64, 95% CI [0.57, 4.70], I^2 =39.9%, P=0.36).

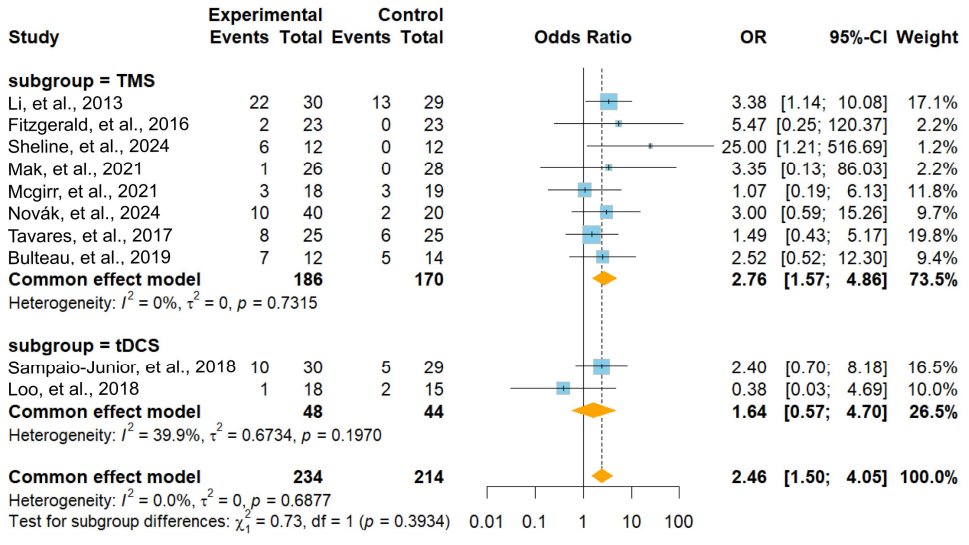

Fig. 5 Forest plot of remission rate.

When the effect size was more than one, as presented by the odds ratio, the treatment under investigation demonstrated higher remission rate compared to the control.

3.4.4 Drop-out rate

As shown in Fig. 6, 15 RCTs reported the number of participants who dropped out (Li, et al., 2013; Fitzgerald, et al., 2016; Tavares, et al., 2017; Loo, et al., 2018; Sampaio-Junior, et al., 2018; Bulteau, et al., 2019; Mak, et al., 2021; Mcgirr, et al., 2021; Lee, et al., 2022; Zengin, et al., 2022; Zhang, et al., 2023; Dellink, et al., 2024; Luo, et al., 2024; Novák, et al., 2024; Sheline, et al., 2024). Since the heterogeneity between studies was not significant (I^2 =0%, P=0.92), we used a fixed-effects model. The combined effect size (OR=1.05, 95%CI [0.68,1.63], I^2 =0%, P=0.81) indicated no significant difference in drop-out rates between groups.

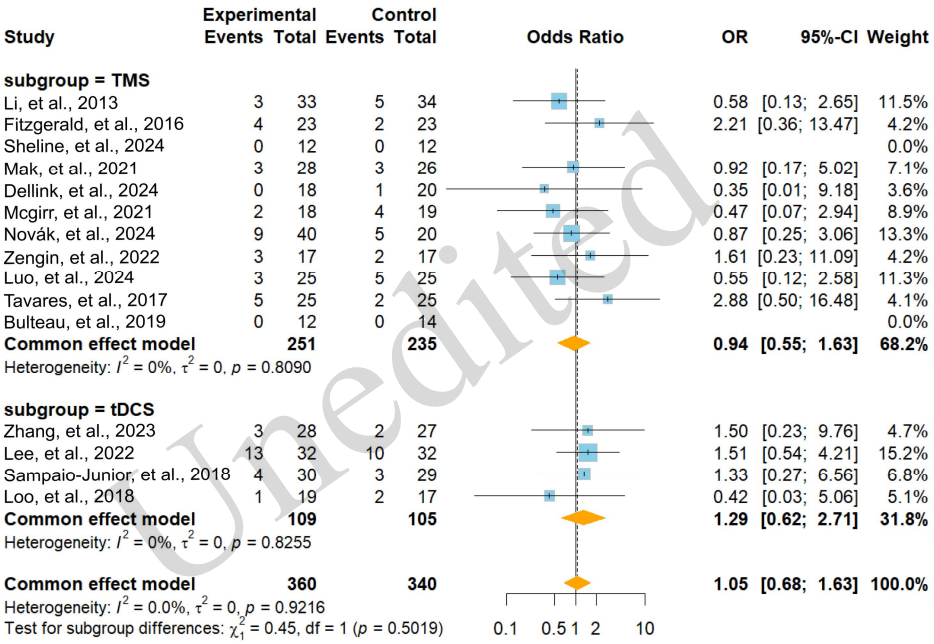

Fig. 6 Forest plot of drop-out rate.

When the effect size was less than one, as presented by the odds ratio, the treatment under investigation demonstrated lower drop-out rate compared to the control.

3.4.5 Changes in cognitive function

The results of the cognitive studies included did not reveal a consistent pattern of improvement or decline. Given the small sample size, the results are summarized in Table 2. We categorized cognitive function into nine cognitive domains: global cognition, attention/vigilance, processing speed, working memory, executive function, verbal learning/memory, language, visual learning and inhibitory control. A total of six studies explored cognitive functioning (Loo, et al., 2018; Myczkowski, et al., 2018; Mardani et al., 2021; Tortella et al., 2021; Torres et al., 2023; Luo, et al., 2024). Three studies assessed global cognition, yielding inconsistent results ranging from small negative effects to small positive effects (Loo, et al., 2018; Torres, et al., 2023; Luo, et al., 2024). Regarding attention/alertness and processing speed, the results were also inconsistent, with two studies showing non-significant negative trends using digit span forward and trail making test (TMT)-A, while another reported a small positive effect(Myczkowski, et al., 2018; Tortella, et al., 2021; Luo, et al., 2024). The effects on working-memory and executive-function domains were predominantly neutral or slightly negative in rTMS and tDCS studies using traditional tests (digit span, TMT-B) (Myczkowski, et al., 2018; Tortella, et al., 2021). Verbal and visual memory outcomes (rey auditory verbal learning test (RAVLT), california verbal

learning test (CVLT), brief visuospatial memory test-revised version (BVMT-R)) in the included studies were almost uniformly neutral (Myczkowski, et al., 2018; Tortella, et al., 2021; Torres, et al., 2023). The results for the inhibitory-control domain showed the greatest inconsistency, with effects ranging from negative (stroop interference) to strongly positive (Go/No-Go test) (Myczkowski, et al., 2018; Mardani, et al., 2021; Tortella, et al., 2021). These discrepancies underscore the importance of assessment-tool selection in shaping observed outcomes.

3.5 Sensitivity analysis

Given the considerable heterogeneity across studies, we performed sensitivity analyses for all outcomes. Sequential exclusion of individual studies did not materially alter the overall results (Figs. S1-S4). Notably, only one study employed a medication-only control condition without sham stimulation n. Exclusion of this study (Mardani, et al., 2021) resulted in a pooled effect size (SMD=−0.66, 95% CI [−1.03, −0.29]) and heterogeneity (I^2=77.3%).

In addition, sensitivity analyses using alternative plausible correlation coefficients (r=0.30 and r=0.70) for imputation of change-score standard deviations yielded consistent direction and statistical significance of the pooled effects, with effect sizes remaining within a comparable range to the primary analysis (Table S1). Although higher assumed correlations were associated with larger estimated effect sizes and increased heterogeneity, the overall conclusions regarding the antidepressant efficacy of NIBS remained unchanged.

3.6 Publication bias

We assessed publication bias using funnel plots and Egger's test. The results of Egger's test for depression scores, response rates, remission rates, and dropout rates were not statistically significant (P=0.05, P=0.42, P=0.75 and P=0.19), as shown in Table S2. However, the funnel plot for remission rates indicated the presence of publication bias. A "trim-and-fill" analysis suggested that two additional studies would be required to account for the bias (Material S2: Fig. S6). After adjusting for this, the effect size remained significant (OR=2.12, 95% CI [1.28, 3.50], P<0.01).

3.7 Meta-regression results

Meta-regression analyses did not identify significant associations between treatment effects (including changes in depression scores, response rates, remission rates, and drop-out rates) and demographic variables or overall NIBS characteristics such as stimulation type or number of sessions (Tables S3-S6).

To further explore potential sources of heterogeneity in TMS studies (k=11), we performed additional meta-regression analyses focused on stimulation intensity and total pulse count. When stimulation intensity was modeled as a continuous variable (motor threshold, expressed as a percentage of resting motor threshold), no significant association was observed between stimulation intensity and changes in depression scores (Coef(B)=0.004, 95% CI [−0.01, 0.02], P=0.677). This model did not explain between-study heterogeneity (R^2 =0%), and substantial residual heterogeneity remained (I^2 =54.1%) (Table S7). Similarly, total pulse count was negatively associated with effect size (P=0.019), but the regression coefficient was minimal (Coef(B)=−0.00), and the model accounted for none of the observed heterogeneity (R^2 =0%). Influence diagnostics flagged one study as highly influential. Excluding this study resulted in only minimal changes to the estimated coefficients, suggesting that the observed associations were generally consistent (Table S8; Fig. S7). For tDCS studies (k=6), meta-regression indicated a positive association between current intensity and treatment effect on depression scores (Coef(B)=3.66, 95% CI [0.81, 6.51], P=0.012). This model explained 59.1% of the observed between-study heterogeneity. Influence diagnostics showed that no single study substantially altered the regression results (Table S9; Fig. S8).

4 Discussion

This meta-analysis included 17 RCTs comprising 743 patients with bipolar depression, and the pooled results suggest that adjunctive use of TMS or tDCS in combination with medication is associated with greater reductions in depressive symptoms and higher response rates compared with pharmacotherapy alone. Furthermore, TMS, but not tDCS, was associated with improved remission rates. No consistent benefits were observed across cognitive domains, and dropout rates did not significantly differ between the intervention and control groups, indicating comparable tolerability.

Subgroup analyses demonstrated that both TMS- and tDCS-based combination therapies were associated with significant improvements in depressive-symptom severity and higher response rates compared with medication alone, indicating that both stimulation modalities may have potential adjunctive benefits. Notably, while reductions in symptom severity and increases in response rates were observed for both modalities, a statistically significant improvement in remission rates was evident only in the TMS subgroup. In contrast, the corresponding effect for tDCS did not reach statistical significance. Although this variability may reflect differences in stimulation parameters or patient characteristics, the limited number of included studies precludes firm conclusions and underscores the need for further well-powered trials. Additionally, this may be related to the combination of medications used. Previous research has suggested that benzodiazepines, mood stabilizers, or antipsychotics attenuate the effects of tDCS (Berlim et al., 2013; Brunoni et al., 2013), with similar interference also reported for TMS (Kochanowski et al., 2024). Although all included studies indicated that patients maintained stable medication regimens during treatment, the lack of separate clarification regarding medication use in the sham and real stimulation groups, coupled with the fact that many patients were on multiple medications, may have further influenced treatment efficacy. Future studies should investigate the efficacy of monotherapy versus combination therapy with NIBS to provide more robust evidence supporting clinical diagnosis and treatment.

The choice of target may also influence therapeutic efficacy. Stimulation targeting the DLPFC was associated with larger antidepressant-effect sizes compared with non-DLPFC or composite targets. This finding aligns with the established role of the DLPFC in emotional regulation and cognitive-emotional control networks, and is consistent with recent network meta-analysis results on non-invasive brain-stimulation interventions for bipolar depression. That study confirmed that multiple TMS and tDCS protocols targeting the DLPFC effectively alleviate depressive symptoms (Hsu, et al., 2024). However, despite considerable research heterogeneity, studies targeting other brain regions remain limited in number.

Meta-regression analyses provided additional, albeit exploratory, insights into potential sources of heterogeneity. Within the TMS subgroup, neither stimulation intensity (expressed as motor threshold) nor total pulse count explained between-study heterogeneity, and residual heterogeneity remained substantial. Although total pulse count showed a statistically significant association with effect size, the magnitude of the regression coefficient was negligible and did not translate into meaningful explanatory power, suggesting limited clinical relevance. For tDCS studies, higher current intensity was positively associated with greater reductions in depressive symptoms, and explained a moderate proportion of between-study heterogeneity. However, given the small number of available tDCS trials and the potential interdependence among stimulation parameters, this finding should be interpreted cautiously and regarded as hypothesis-generating rather than confirmatory. Overall, these results highlight the complexity of stimulation parameter-outcome relationships and underscore the need for adequately powered trials specifically designed to examine dose-response effects in bipolar depression.

No consistent pro-cognitive effects were observed across six studies assessing nine cognitive domains. Heterogeneous results are likely attributable to the use of inconsistent assessment tools, small sample sizes, and variation in NIBS parameters. Previous meta-analyses also report conflicting findings (Begemann et al., 2020; Hyde et al., 2022), underscoring the importance of standardized cognitive assessment in future trials.

This meta-analysis examines the efficacy of randomized controlled trials investigating the use of NIBS in

combination with stabilizing medications to improve bipolar depression. However, several limitations should be acknowledged. First, there is significant clinical and methodological heterogeneity, which may stem from differences in stimulation parameters, treatment duration, outcome measures, and concomitant medications. Second, although most studies used sham stimulation combined with stable medication as the control condition, one trial employed medication alone without sham stimulation. Sensitivity analyses excluding this study yielded highly comparable pooled estimates and heterogeneity measures, suggesting that the primary findings were not driven by this design difference. Third, although publication bias was suggested as the cause of discrepancies in remission outcomes, trim-and-fill analyses did not materially change the conclusions. Cognitive outcomes were further limited by inconsistent definitions and measurement approaches. Finally, although all included studies were randomized controlled trials, variations in methodological quality and the lack of stratification by bipolar disorder subtype limit the generalizability of the findings.

Future research should prioritize large-scale, rigorously designed trials that standardize stimulation parameters, account for concomitant medications, and incorporate comprehensive, harmonized cognitive assessment batteries. Such efforts will contribute to the development of more precise and individualized treatment strategies in clinical practice.

5 Conclusions

This meta-analysis suggests that NIBS combined with pharmacotherapy is associated with improvements in depressive symptoms and higher response rates in patients with bipolar depression. Furthermore, combining medication with TMS rather than tDCS is associated with higher remission rates. While these findings are encouraging, they should be interpreted with caution due to significant clinical and methodological heterogeneity, as well as the limited number of existing trials. Further large-scale, rigorously designed randomized controlled trials are needed to confirm these effects and to clarify the optimal stimulation parameters and clinical implementation strategies.

Data availability statement

All data supporting the findings of this study are available within the paper and its Supplementary Information.

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Author contributions

Shaohua HU and Hetong ZHOU conceptualized the study and developed the protocol. Shuangyu QI and Xiaonan GUO deisigned the search strategy and conducted the literature search. Shuangyu QI and Yuanyuan ZENG performed data screen and extraction. Shuangyu QI, Qianfeng CHEN and Hetong ZHOU assessed data quality. Shuangyu QI and Qianfeng CHEN conducted data analysis. Xiaonan GUO and Saboor SAEED provided supervision during data extraction and analysis. Shuangyu QI drafted the initial manuscript. Shaohua HU and Hetong ZHOU critically revised the manuscript for important intellectual content and supervised data interpretation. All authors had full access to the data and shared final responsibility for the decision to submit for publication.

Compliance with ethics guidelines

Shuangyu QI, Qianfeng CHEN, Yuanyuan ZENG, Saboor SAEED, Xiaonan GUO, Hetong ZHOU and Shaohua HU declare that they have no conflicts of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

Declaration on the use of generative AI tools

During the preparation of this work, the authors used ChatGPT in order to improve language and readability. After using this

tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Supplementary information:

Materials and methods; Figs. S1-S8; Tables S1-S9