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Review article

Efficacy and acceptability of transcranial direct current stimulation for treating depression: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is a promising nonpharmacological intervention for treating depression. We aimed to provide an updated meta-analysis assessing the anti-depressant efficacy of tDCS.

Methods: We searched the literature from the first available date to 30 December 2020 to identify relevant randomized controlled trials (RCTs).

Results: 27 RCTs (N = 1204 patients, 653 in active tDCS and 551 in sham tDCS) were included. Active tDCS was superior to sham tDCS (g = 0.46, 95 % CI 0.15−0.76) in modulating depressive symptoms measured by depression rating scales. Active tDCS was also superior to sham tDCS in reducing response and remission rates, but these differences did not reach statistically significant levels ($OR_{response}$ = 1.75, 95 % CI 0.85–3.58; $OR_{remission}$ = 1.29, 95 % CI 0.59–2.83). The two groups had comparable dropout rates (OR = 1.28, 95 % CI 0.62–1.64).

Conclusion: For treatments of depressive episodes, tDCS may be efficacious. Specific tDCS parameters (e.g., a 2-mA stimulation current and 30-min sessions) and clinical characteristics (e.g., antidepressant-free) may augment the treatment efficacy of tDCS.

1. Introduction

Major depressive disorder (MDD) is a debilitating mental illness that affects about 6% of the adult population worldwide every year (Kessler, 2012). Among all medical conditions, MDD is one of the three leading contributors to chronic disease burden, as measured by years lived with disability (Spencer L James et al., 2018). Despite advances in our understanding of the neurobiology of MDD and progress made in its management, an estimated 30 % of patients who suffer from depression fail to experience significant clinical benefits from currently available treatments (Jha and Trivedi, 2018; Rush et al., 2006). Given that MDD is associated with self-harm and suicide, it is crucial to develop a novel and alternative intervention to complement or augment the efficacy of existing treatments based on pharmacotherapy and psychotherapy.

Neuroimaging findings from patients suffering MDD have consistently identified abnormalities in the frontoparietal cognitive control

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circuit (Brakowski et al., 2017; Dutta et al., 2014). The frontoparietal cognitive control network, including portions of the lateral prefrontal cortex and posterior parietal cortex, is implicated in various cognitive control processes, such as working memory (Murray et al., 2017), attention (Scolari et al., 2015), and inhibition (Zhang et al., 2017). A recent meta-analysis found evidence for hypoconnectivity in the dorsolateral prefrontal cortex (DLPFC) in MDD (Kaiser et al., 2015), a key region in the frontoparietal network. Furthermore, it has been suggested that MDD is characterized by an "imbalance of the left and right prefrontal activity" (Grimm et al., 2008). That is, depression is related to relative hypo- and hyperactivity in the left and right DLPFC, respectively. Such imbalance in the functional activation of the DLPFC might contribute to cognitive biases towards negative information and emotional dysregulation observed in MDD (Grimm et al., 2008).

Transcranial direct current stimulation (tDCS) is one of the emerging brain modulation techniques for modulating cortical activities related to cognitive control dysfunction in MDD. By delivering weak electric direct currents over the scalp, tDCS is a minimally invasive form of brain stimulation to modulate neural activity and excitability (Dissanayaka et al., 2017; Santos Ferreira et al., 2019). While anodal stimulation increases cortical excitability and activity, cathodal stimulation decreases them. The application of direct current leads to subthreshold polarity-specific polarization of neuronal membranes (Rae et al., 2013) and glutamatergic plasticity (Debanne et al., 2019; Mohammadi, 2016). Because the induction of lasting changes in cortical excitability is correlated with N-methyl-D-aspartate (NMDA) receptor/calcium channel activity and protein synthesis (Hunt and Castillo, 2012), the mechanism of action related to tDCS is hypothesized to owe largely to learning related to long-term potentiation and long-term depression (Ridding and Ziemann, 2010). In addition to inducing brain activity in the regions directly under the electrodes, tDCS could also alter the functional connectivity in other brain regions (Pena-Gomez et al., 2012).

Typical tDCS stimulation protocols are 1−2 mA administered over 10−30 min via an electrode placed over the DLPFC, a critical brain region of the frontoparietal network that is responsible for cognitive control and emotion regulation. Fregni et al. (2006) performed a seminal randomized controlled trial (RCT) in MDD, showing that tDCS targeting the frontoparietal network could significantly improve depressive symptoms. Since then, a growing number of studies have examined the effects of tDCS in depression (see Supplementary Fig. S1 using the search words "tDCS" AND "depression" in PubMed and Web of Science, search date 1 December 2019). Several reviews and meta-analyses (e.g., Bennabi and Haffen, 2018; Berlim et al., 2013; Brunoni et al., 2016; Kalu et al., 2012; Meron et al., 2015; Shiozawa et al., 2014) have examined the efficacy of tDCS for treating major depressive episodes. However, the findings supporting its efficacy are inconsistent, mainly due to different methodologies (e.g., the number of trials used in tDCS, continuous vs. categorical outcomes) and samples (e.g., remitted depression vs. treatment-resistant depression) (Table 1). An adequate amount of research efforts have been made to address the optimal treatment protocol of applying tDCS and the safety of its application (Bennabi et al., 2015; Brunoni et al., 2017; Loo et al., 2018; Pavlova et al., 2018; Salehinejad et al., 2017; Sampaio-Junior et al., 2018; Vanderhasselt et al., 2015). It is, therefore, necessary to perform an updated review and meta-analysis to systematically evaluate the efficacy and acceptability of tDCS for treating major depressive episodes. In this study, our aim was as follows: (1) to estimate tDCS efficacy based on continuous (symptom improvement on depression rating scales) and categorical (clinical response and remission rates) outcomes, and (2) to identify possible factors associated with tDCS efficacy and its acceptability among

Table 1
Comparison of previous published studies and the current meta-analysis of tDCS for treating depressive episodes.

Study	Date range	Trials	N Subjects	Outcome	Other analysis	Main results
Kalu et al (2012)	01/01/1998−02/2011	8	Active tDCS: 96 Sham tDCS: 80	Continuous—mean change in depression rating scale scores	Publication bias	tDCS was superior to sham tDCS (g = 0.743)
					Meta-regression	no significant predictors
Berlim et al (2013)	01/07/1998−20/08/2012	6	Active tDCS: 103 Sham tDCS: 97	Categorical—response and remission rates	Publication bias	non-significant in response (OR = 1.97): and remission (OR = 2.13) between tDCS and sham tDCS
					Meta-regression	
Schozawa et al (2014)	01/01/2006−31/01/2014	7	Active tDCS: 167 Sham tDCS: 152	Both categorical and continuous outcome measures	Publication bias	tDCS was superior to sham tDCS (g = 0.38)
					Meta-regression	tDCS for response (OR = 1.63) and remission (OR = 2.50) no significant predictors
Meron et al. (2015)	01/01/1995−30/04/2015	10	Active tDCS: 206 Sham tDCS: 187	Both categorical and continuous outcome measures	Publication bias	tDCS was superior to sham tDCS (g = 0.30)
					Power analyses Precision analyses	non-significant in response (LOR = 0.36): and remission (LOR = 0.25) between tDCS and sham tDCS
					Meta-regression	no significant predictors
Brunoni et al (2016)	Until 01/01/2015	6	Active tDCS: 147 Sham tDCS: 142	Categorical—response and remission rates	Publication bias	tDCS for response (OR = 2.44) and remission (OR = 2.38) superior to sham
					Meta-regression	Depression refractoriness and tDCS dose predict the efficacy
Razza et al (2020)	Until 06/01/2020	24	Active tDCS: 591 Sham tDCS: 501	Both categorical and continuous outcome measures	Publication bias	Active tDCS was superior to sham tDCS (g = 0.46), significant in response (OR = 2.28) and remission (2.12)
					Meta-regression	
Current study	Until 30/12/2020	27	Active tDCS: 653 Sham tDCS: 551	Both categorical and continuous outcome measures	Publication bias Meta-regression Inferential test for the percentages of depression improvement, and counts meeting remission and response criteria 6week endpoint analysis	tDCS was superior to sham tDCS (g = 0.46) non-significant in response (OR = 1.16) and remission (OR = 1.04) between tDCS and sham tDCS
					Sensitivity analysis Future direction proposed	no significant predictors

Note: OR: odd ratio; LOR: log odd ratios.

patients with depression.

2. Methods

2.1. Literature searching and selection

Following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (http://www.prisma-statement.org/PRISMAStatement/Checklist.aspx), we searched the PubMed and Web of Science databases using the following search strategy: ("transcranial direct current stimulation" OR "tdcs") [Title/Abstract] AND ("depress*") [Title/Abstract]. The date range extended up to 30 December 2020. We also screened the reference lists of published meta-analyses and systematic reviews of tDCS in depression (Berlim et al., 2013; Brunoni et al., 2016; Kalu et al., 2012; Meron et al., 2015; Razza et al., 2020; Shiozawa et al., 2014).

Fig. 1 illustrates the detailed literature selection procedures. The inclusion criteria were as follows: randomized, sham-controlled, and double-blind trials published in the English language that include data enabling calculation of effect size for depression rating scale change or response or remission rates, patients with major depression and/or bipolar disorder, tDCS as monotherapy or augmentation therapy for depression treatments, and a sample size of more than 10. The exclusion criteria were as follows: studies on animals, non-controlled or non-randomized trials, case reports or case series, trials of treatments for disorders other than depression, trials of interventions other than tDCS, and duplicated data sets. Three authors (RZ, XP, and DZ) performed the literature search, selection, and extraction. We only included data from intention-to-treat samples. Finally, we identified 24 studies with 27 experiments that were included in the current meta-analysis. These twenty experiments included 653 patients in the active group and 551 patients in the sham group. No significant difference was found in age or sex between the two groups ($p_s > 0.05$). Detailed information on the characteristics and available findings of each study is listed in Table 2 and Supplementary Table S1.

2.2. Outcome and data extraction

With reference to previous studies (Berlim et al., 2013; Brunoni et al., 2016; Kalu et al., 2012; Meron et al., 2015; Razza et al., 2020; Shiozawa et al., 2014), we adopted two types of outcomes: continuous and categorical. The primary interest of the current study was the continuous outcomes, which characterized the changes in ratings of depression scales between the baseline and end of treatment in each study. The categorical outcomes included response and remission rates. We estimated the acceptability of tDCS treatment using the dropout rate.

We extracted the following data: depression scale scores at the study baseline and end of treatment, remission and response rates for the active and sham groups at the end of treatment, and dropout count in each group at the end of treatment. Response rates were defined as a reduction of greater than 50 % on depression scale scores from the baseline to endpoint. Moreover, to identify the potential factors affecting the efficacy of tDCS in treating depressive episodes, we extracted population demographics such as sample size, diagnosis (unipolar/bipolar depression), tDCS characteristics (number of sessions, montage, applied current, inter-session interval, and sham stimulation characteristics), antidepressant medication (ADM), cognitive control training (CCT), publication year, the journal impact factor (for that year), scale ratings of depressive symptoms, and female proportion of the tDCS group.

2.3. Meta-analyses

We quantified the continuous treatment effect of tDCS on depression by using Hedges' *g*, a measure of effect size that describes the difference in the reduction of depression severity rating scale scores (Montgomery–Åsberg Depression Rating Scale and/or Hamilton Depression Rating Scale) between the two groups (active vs. sham tDCS). A positive *g* value indicates a decrease in depression severity rating in the active tDCS group compared to in the sham tDCS group. For each study, we computed *g* and 95 % CIs using a combination of means and standard deviations. After estimating the effect sizes, we further processed them using *R* with '*meta*' and '*metafor*' using the guideline provided by Harrer et al. (2019).

We characterized the clinical outcomes, remission and response rates, and dropout rates (acceptability) for both the active and sham groups at the randomized, blinded treatment endpoint as categorical outcomes by using odds ratios (ORs), which we also selected as the effect size indexes. An OR value > 1 represents a likelihood of response or remission in the active tDCS group relative to that in the sham tDCS

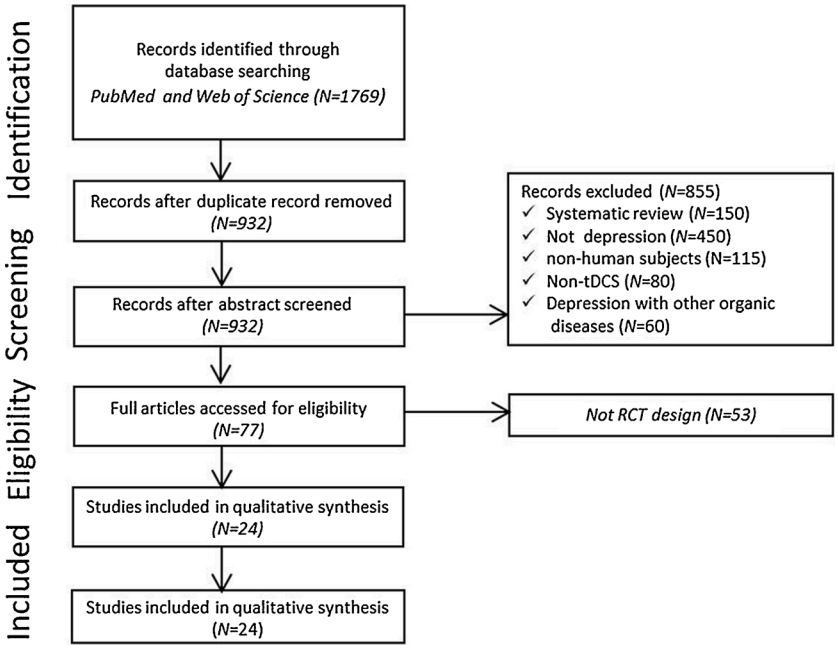

Fig. 1. Study selection flowchart. RCT, randomized controlled trials.

Table 2
Sample characteristics and tDCS setting of the included studies.

Study	Diagnosis	N (Act/ Sam)	%Female (Act/ Sham)	Age (SD)	Illness Duration (years)	Illness onset of age	Episodes of Illness	Outcome		tDCS setting	Treatment resistance level	Concurrent ADM	Concurrent CCT
								Rating scale	Remission/ Response/ Acceptability (Y = yes, N = No)	tDCS current/tDCS sessions /duration/tDCS/Montage/ Number of TDCS sessions			
Fregni et al (2006)	MDD	9/9	56 %/67 %	47.6 (10.4)	9.78	NA	2.33	HDRS	N/N/Y	1mA/20 min./F3/5	NA	No	No
Boggio et al (2008)	MDD	21/10	67 %/70 %	51.6 (7.7)	7.1	NA	NA	HDRS	Y /Y/N	2 mA/20 min./F3/10	Act:1.7; Sham: 1.5	No	No
Loo et al (2010)	MDD	20/20	55 %/55 %	48.9 (10.0)	4.05	31.20	NA	MADRS	Y /Y/Y	1mA/20 min./pF3/5	Act:1.0; Sham: 1.7	Yes	No
Blumberger et al (2012)	MDD	13/11	77%/91 %	45.3 (11.6)	4.3	NA	2.9	HDRS	Y /Y/Y	2 mA/20 min./F3,F4/15	Act:4.3; Sham: 4.1	Yes	No
Loo et al. (2012)	BD	31/29	45%/48 %	47.8 (12.5)	4.6	28.3	NA	MADRS	Y /Y/Y	2 mA/20 min./pF3/15	Act: 3.13; Sham: 2.79	Yes	No
Palm et al (2012)	MDD	11/11	55 %/73 %	56 (12)	0.58	44	NA	HDRS	N/N/Y	1−2 mA/20 min./F3/10	Act:2.9 ShaMm:2.9	Yes	No
*Brunoni et al (2013)a	MDD	30/30	70 %/67 %	41 (12)	0.3	NA	2	MADRS	Y/Y/Y	2 mA/30 min/F3/10 + 2	NA	No	No
*Brunoni et al (2013)b	MDD	30/30	80%/56 %	41 (13)	0.19	NA	3	MADRS	Y/Y/Y	2 mA/30 min/F3/10 + 2	NA	Yes	No
Segrave et al. (2013)	MDD	9/9	22%/63 %	42.6 (18.3)	11.8	17.4	2.14	MADRS	Y/Y/Y	2 mA/24 min. /F3/5	NA	Yes	Yes
Brunoni et al. (2014)	MDD	20/14	35 %/31 %	46.1 (10.4)	1.5	29..6	4.4	HDRS	Y/Y/Y	2 mA/30 min/F3,F4/10	Act: 35 %;	Yes	Yes
Brunoni et al. (2014)	MDD	15/19	67 %/63 %	41 (12)	NA	NA	NA	MDRAS	N/Y/N	2 mA/30 min /F3,F4/10	Act:40 % Sham: 37 %	Yes	No
Bennabi et al (2015)	MDD	12/11	83%/31 %	60.4 (12)	NA	NA	NA	HDRS	Y/Y/Y	2 mA/30 min /F3.FP2/10	NA	Yes	No
Vanderhasselt et al (2015)	MDD	19/14	68 %/79 %	46.3 (10.7)	2.6	30.0	0.58	HDRS	N/N/Y	2 mA/30 min /F3,F4/10	NA	Yes	Yes
Dastjerdi et al. (2015)	MDD	10/10	60 %/60 %	34.1 (7.17)	NA	NA	NA	BDI	Y/N/Y	NA/20 min./NA/12	NA	Yes	No
*Brunoni et al (2017)	MDD	94/60	68 %/68 %	44.6 (11.8)	NA	20.4	NA	HDRS	Y/Y/Y	2 mA/30 min. /F3,F4/15 + 7	Act: 33 %; Sham: 32 %	Yes	No
Salehinejad et al (2017)	MDD	12/12	58%/67 %	26.8 (7.1)	NA	NA	NA	HDRS	N/N/Y	2 mA/20 min. /F3,F4/10	NA	Yes	No
Loo et al (2018)a	MDD	37/39	NA	48.9 (12.3)	12.8	NA	12.64	MADRS	Y/Y/Y	1mA/20 min. /F3,F8/20	Act:4.3 Sham: 4.3	Yes	No
Loo et al (2018)b	BD	18/17	NA	49.1 (16.1)	11.9	NA	23	MADRS	Y/Y/Y	1mA/20 min. /F3,F8/20	Act: 5.53; Sham: 4.35	Yes	No
Pavlova et al (2018)a	MDD	21/20	81 %/75 %	36.0 (10.8)	0.7	NA	NA	HSRS	Y/Y/Y	2 mA/20 min. /F3/10	Act: 0.05; Sham:0.1	Yes	No
Pavlova et al (2018)b	MDD	27/20	63 %/75 %	37.0 (8.8)	0.5	NA	NA	HDRS	Y/Y/Y	2 mA/30 min /F3/10	Act: 0.11; Sham: 0.1	Yes	No
*Sampaio et al (2018)	BD	30/29	47%/17 %	46.2 (11.8)	NA	23.5	15.2	HDRS	Y/Y/Y	2 mA/30 min /F3,F4/10 + 2	Act: 5.1 Sham: 5.2	Yes	No
Mayur et al. (2018)	MDD	9/9	NA	47.0 (12.5)	NA	NA	NA	MADRS	N/Y/Y	2 mA/30 min/F3/10	NA	Yes	No
McClintock et al. (2020)	Mxied	61/59	54%51 %	49.0 (13.7)	0.225	NA	NA	MADRS	N/N/Y	2.5 mA/20 min./F3/20	NA	Yes	No
Vigod et al. (2019)	MDD	8/9	NA	31.2 (4.0)	NA	NA	NA	EPDS	N/N/Y	2 mA/30 min/NA/15	NA	Yes	No
Nord et al (2019)	MDD	20/19	45%/57 %	35.6 (12.9)	NA	22.8	2.5	HAMD	N/N/Y	1mA/20 min./F3/8	NA	Yes	No
Sharafi et al (2019)	MDD	15/15	60 %/40 %	50.7 (10.7)	12.3	NA	NA	HAMD	Y/Y/Y	2 mA/20 min./F3/10	Act: 100 % Sham:100 %	Yes	No
Zhou et al. (2020)	MDD	47/43	67 %/67 %	43.91 (11.2)	7.09	NA	NA	SDS	N/N/Y	2msA/30 min/NA/20	NA	Yes	No

Note: "*", outliner analyses suggested that the study was an outliner; MDD, major depressive disorder; BD, bipolar disorder; NA, not data available; Act/Sham: Active/Sham group; ADM, anti-depressant medication; CCT, cognitive control training. Outcome could be classified as continuous treatment effects measured by HDRS, Hamilton depression rating scale with 17 items or 21 items ; MADRS: Montgomery-Asberg Depression Rating Scale; BDI, Beck Depression Inventory; SDS, Zung Self-Rating Depression Scale;EPDS, Edinburgh Postnatal Depression Scale. The degree of treatment resistance was characterized by the number of anti-depressant medication (ADM) trials failed prior to tDCS treatment.

group.

Notably, we applied a random effect model to analyze the overall effect size. The random effect model assumes that each study estimated different values from the distribution of population parameters, which would be flexible to heterogeneous effect sizes and the conservative nature of estimation (Tufanaru et al., 2015). We assessed heterogeneity across effect sizes with the Cochran's *Q* test, which we calculated as the weighted sum of squared differences between effects of individual studies and the pooled effect across studies, with the weights being those used in the pooling method. In addition, we estimated the I^2 index to quantify heterogeneity between included studies, with values of 25 %, 50 %, and 75 % reflecting small, medium, and large degrees of heterogeneity, respectively (Higgins and Thompson, 2002).

To further characterize heterogeneity across treatment effects, we estimated the impact of potential categorical and continuous moderators of treatment effects, including diagnosis, treatment-resistant depression, proportion of females, illness duration, CCT, the rating scale for depressive symptoms, number of episodes, age at illness onset, density of current stimulation, dose of the electric current, number of days, current electric charge, year of publication, and journal impact factor during the publication year (detailed information in Table 2 and Supplementary Table S2).

In addition to pooling each study as an overall effect size (Hedges' *g* or OR), we calculated for each study the percentage reduction of the depression rating scale scores; the counts of patients reaching a clinical response, defined as $\geq$ 50 % reduction on depression scale scores from baseline; and remission criteria, defined as the cutoff on depression scale scores at the end of tDCS treatment, in active and sham tDCS groups. We then performed two-sample *t*-tests or Chi-square tests to identify significant differences between the two groups at $\alpha = 0.05$.

2.4. Publication and sensitivity bias analysis

We evaluated publication bias using Egger's regression intercept test and funnel plots, which displayed CI boundaries for visualizing whether the studies were distributed symmetrically within the funnel, and assessed sensitivity using the leave-one-out cross-validation procedure to indicate the impact of each study in the net results.

3. Results

3.1. Treatment effects of tDCS on depressive symptoms

The mean for percentage reduction of symptom severity in the active tDCS group was 36 % (ranging from 15 % to 65 %), while that in the sham tDCS group was 26 % (ranging from 12 % to 43 %) (Supplementary Fig. S2). A *t*-test indicated that the percentage reduction of symptom severity was significantly greater for the active tDCS group ($t = 2.78$, $p = 0.007$).

Fig. 2 shows the estimated pooled effect size (Hedges' *g*) for the reduction of depressive symptoms or the percentage reduction of symptom severity between the active and sham tDCS groups. The pooled estimate of effect size was 0.46 ($t = 3.09$, $p = 0.005$, 95 % CI 0.15−0.76), indicating a significant low to medium effect size. However, the test for study heterogeneity was significant ($Q = 105.53$, $df = 26$, $p < 0.001$; $I^2 = 73.0$ %), indicating that variation in outcomes between the studies exceeded that expected by chance.

Fig. 3 depicts the funnel plots to portray the measures of publication bias, which showed symmetry and, further, insignificant results for Egger's regression intercept test ($t = 2.28$, $p = 0.06$). We performed two separate analyses to further confirm whether the pooled effect estimate was dependent heavily on one single study. First, we detected and removed extreme effect sizes (outliers) (Fregni et al., 2006; Salehinejad et al., 2017) and found what the equivalent figures were as follows: Hedges' $g = 0.34$ [95 % CI 0.08−0.60, $t = 2.77$, $p = 0.01$]. Second, we performed a sensitivity analysis by leaving one experiment out each time and re-estimating the pooled effect sizes. No matter which studies were excluded, the Hedges' *g* ranged from 0.39 to 0.50 (Supplementary Table S3). In sum, the pooled effect size remained significant in both cases.

3.2. Treatment effects of tDCS on clinical outcomes

Data for response rates were available from 18 of the 27 experiments. Across these 18 experiments, 180/467 individuals showed a clinical response in the active tDCS group, compared to 108/375 individuals in the sham tDCS group. Tellingly, active tDCS was superior to sham tDCS

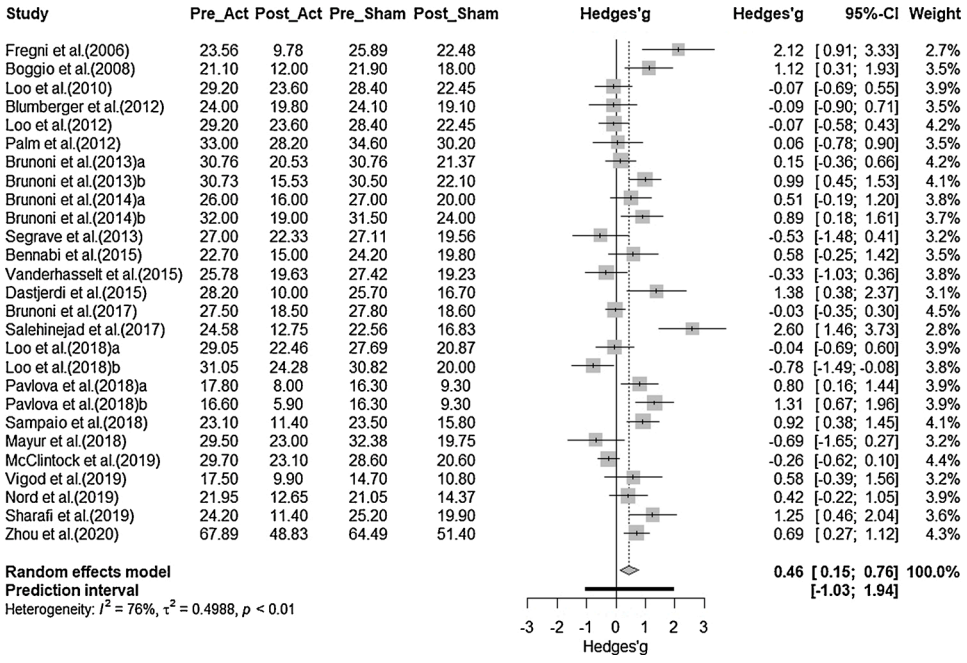

Fig. 2. Forest plot of effect sizes (Hedges' g) on the continuous outcome. Error bars are 95 % confidence intervals (CI). *Note*. Active tDCS_pre/post: depression ratings at baseline and post-tDCS training for the active tDCS group; ShamDCS_pre/post: depressive ratings at baseline and post-tDCS training for the sham tDCS group.

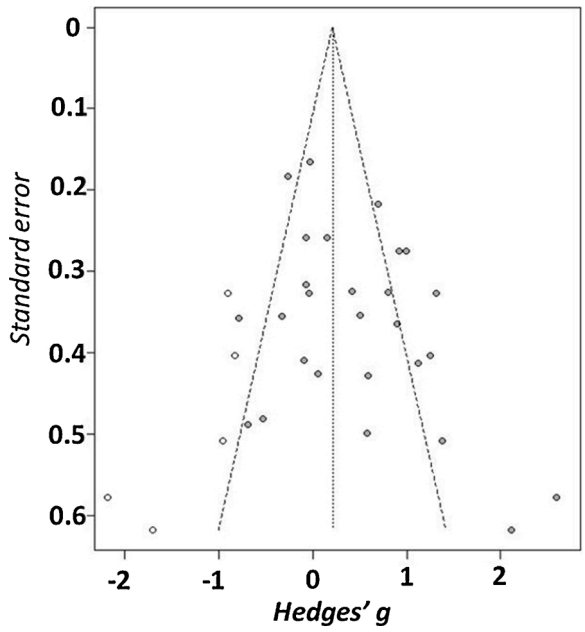

Fig. 3. Funnel plot of standard errors plotted against effect sizes for identification of publication bias in the depressive symptoms measured by depression rating scales.

in reaching a clinical response, but there was no significant difference between the two groups (active tDCS: 40.3 %, sham tDCS: 28.3 %; $t = 1.67$, $p = 0.10$) (Supplementary Fig. S8). Further analysis on individual studies showed that the pooled OR for a clinical response was larger than 1 but did not reach significance ($k = 18$, OR = 1.75, 95 % CI 0.85–3.58, $p = 0.12$; Fig. 4).

Regarding remission rates, data were available from 17 of 27 experiments. Across the seventeen experiments, 92/445 individuals met the remission criteria in the active tDCS group, compared to 59/350 individuals in the sham tDCS group. Active tDCS was superior to sham tDCS for remission rates, but there was no significant difference in the proportion of remission rates between groups (active tDCS: 23 %, sham tDCS: 17 %; $t = 0.88$, $p = 0.38$; Supplementary Fig. S9). Further pooling of the individual study data revealed that the pooled OR for remission was > 1 (Fig. 5) but did not reach significance ($k = 17$, OR = 1.29, 95 % CI 0.59–2.83, $p = 0.49$). Meta-regression results of the categorical outcomes revealed no significant modulators ($p_s > 0.05$, data not shown).

Heterogeneity analysis revealed significant differences in both response and remission rates ($Q > 25$, $p < 0.05$), which might indicate publication bias on the categorical outcomes.

3.3. Moderator analyses for depressive symptom changes

Supplementary Table S2 displays the meta-regression analyses for the treatment effect of tDCS). Concurrent ADM showed a significant trend in moderating the efficacy of tDCS ($F_{(1,25)} = 3.95$, $p = 0.05$). In the subgroup analysis comparing the effect sizes of concurrent ADM studies with non-concurrent ADM studies, the concurrent ADM studies showed a smaller effect size than the non-concurrent ADM studies (Hedges' $g = 0.38$ vs. 1.01; Fig. S3), suggesting that medication treatment status may contribute to variations in tDCS efficacy.

In addition, we performed subgroup analysis for tDCS current and found that patients who received 2 mA showed larger treatment effects (Hedges' $g = 0.55$, 95 % CIs 0.23−0.88) than those who received 1 mA (Hedges' $g = 0.25$, 95 % CIs −1.01–1.52) ($t = 3.09$, $p = 0.004$). The subgroup analyses on the duration of tDCS stimulation, concurrent CCT (concurrent CCT vs. non-concurrent CCT), and diagnosis (unipolar vs. bipolar depression) are illustrated in Supplementary Fig. S4 to S7.

3.4. Acceptability of tDCS treatment

Eighteen experiments reporting the dropout count were available for us to assess tDCS acceptability in the depressive population. By analyzing the available data with a random effect model using the OR as an effect size measure (effect sizes > 1 indicating a greater likelihood of dropout in the active than in the sham tDCS group), we found that there was no significant difference between the two groups in dropout rates ($k = 25$, OR = 1.28, 95 % CI 0.62–1.64, $t = 0.81$, $p = 0.43$, $I^2 = 0\%$, and $Q = 15.58$; Fig. 6).

4. Discussion

4.1. Efficacy of tDCS for treating depression

This meta-analysis included 27 RCTs comprising 1204 individuals with major depressive episodes. Our findings show that active tDCS relative to sham tDCS significantly modulated depressive symptoms

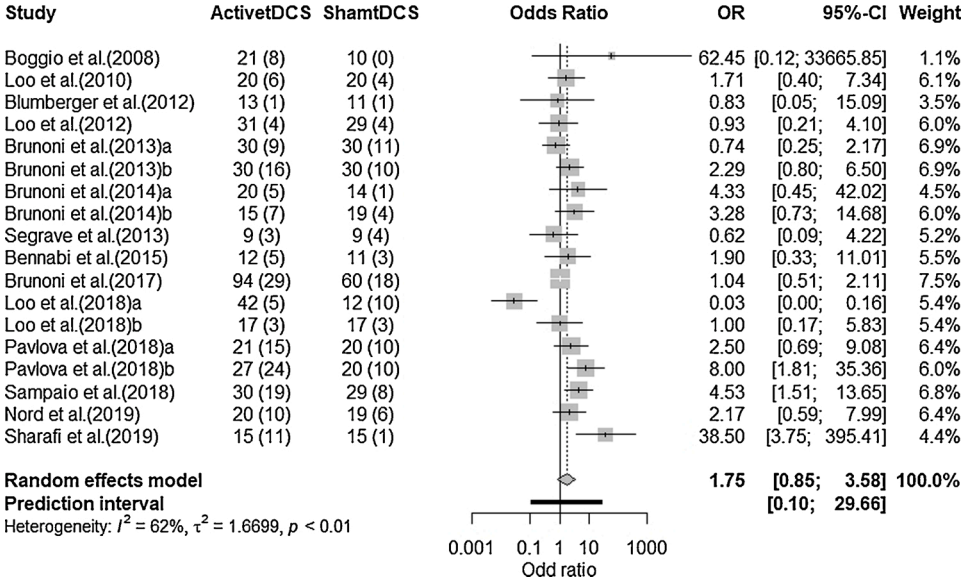

Fig. 4. Forest plot of effect sizes for response rates in active versus sham treatment. Error bars are 95 % confidence intervals (CI).

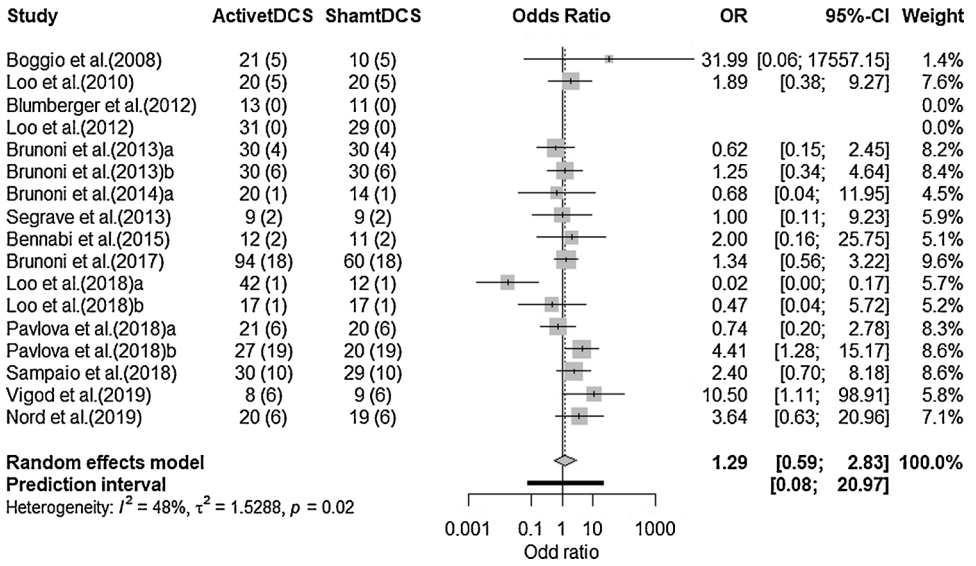

Fig. 5. Forest plot of effect sizes for remission rates in active versus sham treatment. Error bars are 95 % confidence intervals (CI).

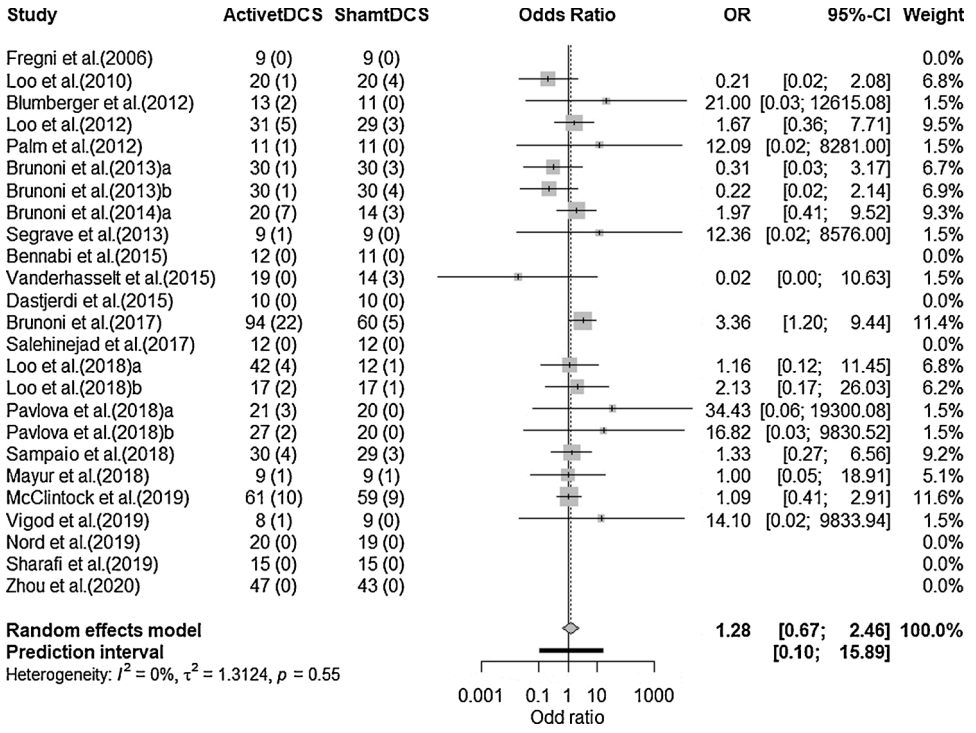

Fig. 6. Forest plot of effect sizes for acceptability in active versus sham treatment. Error bars are 95 % confidence intervals (CI).

measured by depression rating scales (k = 27, g = 0.46, t = 3.09, p = 0.005, 95 % CI 0.15−0.76). However, we did not observe a statically significant reduction in clinical response and remission rates associated with active tDCS. These results are consistent with earlier meta-analyses (Berlim et al., 2013; Kalu et al., 2012; Meron et al., 2015) supporting the use of tDCS as a potential treatment for major depressive episodes. For example, Meron et al. (2015) found that active tDCS was more effective at reducing depressive symptoms than sham tDCS, but there were no significant differences in clinical response and remission rates between groups.

Several meta-analyses reported that active tDCS was statistically superior to sham tDCS with respect to the categorical measures of depression. For example, Brunoni et al. (2016) found that active tDCS was significantly superior to sham tDCS for reducing clinical remission rates (Table 1). The discrepancy in the findings between dimensional and categorical measures might owe to several factors such as the number of included studies—for example, 11 studies in Meron et al. (2015) and 6 studies in Brunoni et al. (2016) vs. 20 in our study)—different methodologies (e.g., continuous vs. categorical outcomes), and the included data for effect size estimation.

In the current meta-analysis, we analyzed the outcomes immediately following the end of the tDCS treatment phase as opposed to those following the top-up sessions (Brunoni et al., 2017, 2013; Sampaio-Junior et al., 2018). We chose these post-treatment outcomes because most RCTs included in the current meta-analysis defined an endpoint as the termination of the intensive tDCS treatment phase. Moreover, choosing these outcomes would also allow us to make a direct comparison of our findings with earlier meta-analytic studies adopting a similar approach

(Meron et al., 2015). To estimate the long-term impact of tDCS, we ran a supplementary analysis using the outcome data following week 6 or week 10 as an endpoint. Crucially, we observed an increase in the magnitude of the effect size (Hedges' $g = 0.55$, 95 % CI 0.24−0.86, $t = 3.09$, $p = 0.003$; Fig. S10a), an increase remission rate (OR = 2.01, 95 % CI 1.06–3.82, $t = 2.35$, $p = 0.03$, Fig. S10b) and clinical response (OR = 2.37, 95 % CI 1.45–3.86, $t = 3.72$, $p = 0.001$, Fig. S10c), suggesting that tDCS could be an alternative treatment tool to ameliorate depressive symptoms with long-lasting impacts. These findings were encouraging and in line with other RCTs reporting the long-term effect of tDCS (Bennabi et al., 2015; Boggio et al., 2008; Loo et al., 2018, 2010; Segrave et al., 2014). Some follow-up studies reported that the beneficial effect of tDCS on depressive mood was evident after 6 months (Martin et al., 2013; Aparicio et al., 2019).

4.2. Factors affecting the efficacy

We observed a significant trend of concurrent ADM on tDCS efficacy. Specifically, patients who were ADM-free ($g = 1.01$) showed a greater treatment effect with active tDCS than those who were taking it ($g = 0.38$), which might suggest that the antidepressant treatment effect of tDCS was better in patients who were medication free. This finding was consistent with some studies reporting beneficial effects of tDCS in antidepressant-free patients (Boggio et al., 2008; Brunoni et al., 2013; Fregni et al., 2006)Depressed patients who were on stable ADM were considered treatment-resistant (usually defined as a failure to achieve remission or inability to tolerate antidepressants from separate classes) and did not appear to benefit from tDCS of the prefrontal cortex (Blumberger et al., 2012; Palm et al., 2012). However, the impact of antidepressants on the efficacy of tDCS has not been fully explored in the literature. To our knowledge, only one research group employed a 2 (antidepressant/placebo) x 2 (active/sham tDCS) factorial design to examine the combined effect of antidepressants and tDCS. In this study (Brunoni et al., 2013), the authors concluded that tDCS and medication by themselves had comparable treatment effects; but combining tDCS with ADM yielded the largest treatment effect. Hence, there is a need for more factorial trials and RCTs to evaluate the effect of ADM on the efficacy of tDCS.

Second, active tDCS with a 2-mA stimulation current might induce a greater antidepressant efficacy relative to active tDCS with a 1-mA stimulation current. Most clinically depressed participants appeared to tolerate this increase in stimulation intensity: No chronic adverse side-effects were reported in the RCTs included in this meta-analysis. Nonetheless, the safety and efficacy of tDCS in bipolar depression warrant further investigations. Loo et al. (2012) reported a case of treatment-induced hypomania in a patient with bipolar disorder after receiving active 2-mA tDCS. In the current meta-analysis, we also observed a sizable reduction in the efficacy of tDCS in patients with bipolar depression ($g = 0.04$) compared to in patients with unipolar depression ($g = 0.54$).

Third, several groups evaluating the efficacy of tDCS stimulation suggest a longer aftereffect of tDCS could be achieved with longer stimulation (Nitsche et al., 2003; Nitsche and Paulus, 2001). Specifically, Pavlova et al. (2018) showed that patients receiving a 30-min active tDCS had a greater improvement in depressive mood and a greater proportion of remitters than patients receiving a 20-min active tDCS. Our subgroup analyses revealed that 20- and 30-minute tDCS showed comparable effect sizes ($g = 0.49$ and $g = 0.54$, respectively) for the treatment of depression. It is notable, though, that heterogeneity was higher for the 20-minute tDCS studies (81 %) than for the 30-minute tDCS ones (73 %). We speculate that tDCS with a longer duration (i.e., 30 min) might be more optimal for improving depressive symptoms. Taken together, a 2-mA current and 30-minute duration might optimize the antidepressant effect of tDCS in patients with unipolar depression.

4.3. Acceptability of tDCS in treating depression

We found no statistically significant differences in dropout rates between the active and sham tDCS groups in the RCTs. Previous studies consistently showed that tDCS has good safety and acceptability profiles, with only mild adverse effects in most trials, including itching, skin redness, and tingling (e.g., Sampaio-Junior et al., 2018; Segrave et al., 2014; Vanderhasselt et al., 2015). Only one published study with an RCT design reported a severe adverse event (a case of suicide), and the authors considered that that suicidal behavior was not likely directly related to tDCS (Loo et al., 2010). Early reports of tDCS trials included descriptions of burns to the skin underlying scalp electrodes, but such effects have not been reported since researchers started using physiological saline rather than water to soak electrodes prior to use. Moreover, Sampaio-Junior et al. (2018) systematically recorded the frequency of adverse events possibly associated with tDCS administration and detected no significant differences between the active and sham tDCS groups, which indicates that tDCS has an acceptable tolerability profile.

Can tDCS be used as an adjunct treatment to augment other standard interventions such as Cognitive Behavioral Therapy (CBT) for depression? An early single case reported that a patient with treatment-resistant depression showed a good response to tDCS plus CBT after suffering from a relapse (D'Urso et al., 2013). A recent clinical trial reported an overall change on depression scale (HAMD-21) of 28 % for depressive patients who received tDCS plus computerized CBT (Welch et al., 2019). Encouragingly, a few larger randomized clinical trials are under way to address this important clinical question (e.g. Bajbouj et al., 2018; Nord et al., 2020). There is initial evidence to suggest a modest but non-significant effect on clinical outcome over-and-above CBT (Nord et al., 2020) for treating depression. Further evidence for the clinical efficacy and acceptability of tDCS combined with CBT awaits.

4.4. Neural correlates and predictors of tDCS efficacy

Depressive disorders are common and refractory mental disorders. A substantial portion of patients suffering from depression do not benefit from conventional treatments such as antidepressant medication and cognitive behavioral therapy (DeRubeis et al., 2005). In line with previous systematic reviews and expert recommendations on the clinical efficacy of tDCS in depression (Fregni et al., 2020; Razza et al., 2020), our findings support that prefrontal tDCS is effective in treating depressive episodes. In previous clinical trials, the anode is primarily positioned over the left dorsolateral prefrontal cortex (DLPFC) while the cathode is applied above the right DLPFC or the right frontotemporal area (Csifcsák et al., 2018). Nonetheless, the neural mechanism underlying tDCS treatment and how it is associated with behavioral changes in depressed patients remain to be addressed. We conducted a search in the PubMed using searching words ((("tDCS"[Title/Abstract]) AND "depress*"[Title/Abstract])) AND ("fMRI"[Title/Abstract]), 3rd Jan 2021) and found only a few studies testing the possible mechanisms of tDCS and the associated neural pathways. While the immediate effect of tDCS occurs within the stimulated regions, the mechanisms driving symptomatic improvement resulting from the intervention may be more distally located, such as the parietal cortex (Nord et al., 2019). In studying the network connectivity of the brains, the salience network and the ventromedial networks are often implicated in depression (Kaiser et al., 2015; van Tol et al., 2013). The salience network is crucial for cognitive control and response inhibition, while the ventromedial network is important for reward and punishment (Menon, 2019). Future studies could conduct network analyses to specify the neural networks in which tDCS targets. Moreover, there is initial evidence that the baseline DLPFC activation in a working memory task prior to treatment could predict subsequent symptomatic improvement in a combined tDCS and CBT trial (Nord et al., 2019). Mechanistic trial of this type could provide insightful information about which patients are likely to respond to tDCS

and what neural correlates tDCS are implicated.

4.5. Strengths and limitations of the current meta-analysis

Compared with existing meta-analyses, the present study has the following strengths (Table 1): (1) the number of the included RCTs and subjects (increased by 100 % compared to existing meta-analyses), (2) assessment of both continuous and categorical outcomes to reflect the antidepressant efficacy of tDCS, (3) descriptive analysis of continuous and dichotomous outcomes with inferential statistics, and (4) a moderator analysis to clarify the effect of potential moderators (e.g., clinical variables, tDCS setting, and data quality).

The main limitations of the current study include the following: First, the number of participants was small in most of the included trials. Although this is one of the largest studies to date summarizing the treatment efficacy of tDCS, caution is required when interpreting the results, as underpowered RCTs reduce the chance of detecting a true effect and the likelihood of a statistically significant result (Button et al., 2013; Guolo & Varin, 2017). Second, potential publication bias or inclusion of poor-quality trials might have affected the reliability of our findings. We have attempted to address this by systematically reviewing the literature, using stringent inclusion criteria, objectively examining publication bias and study heterogeneity, and quantitatively characterizing the contribution of each study. We excluded 40 studies as a result of these selection criteria and analyzed publication bias with Egger's regression intercept tests. The pooled effect size remained significant after the leave-one-out procedure. Overall, we believe that the results of the current study are reliable. Thirdly, we included a relatively clean sample of patients suffering from unipolar depression or bipolar disorders in the present analysis because the sample would be more homogenous for concluding the treatment effect of tDCS. However, psychiatric disorders are often highly comorbid: patients with post-traumatic stress disorder (PTSD) may suffer from depression. A recent study investigating the efficacy of tDCS treatment in PTSD found that tDCS could reduce PTSD symptoms and affective symptoms simultaneously (Ahmadizadeh et al., 2019). Whether tDCS could reduce the affective symptoms only, or whether it could also ameliorate other symptoms beyond the affective dimensions (e.g. PTSD symptoms, cognitive functioning) would be important factors to address in future tDCS studies.

5. Conclusion

This meta-analytic study of twenty RCTs suggests that tDCS may be considered an effective treatment option for patients suffering from major depressive episodes. It has an acceptable tolerability profile, which could be an effective alternative for patients who do not benefit from existing pharmacological and/or psychological treatments. Specific tDCS parameters (e.g., 2-mA stimulation over 30 min/session) and clinical characteristics (e.g., antidepressant-free) may augment the efficacy of tDCS. Further studies of tDCS in treating depression are warranted, especially ones assessing larger samples and addressing factors that impact the procedure's efficacy on clinical outcomes such as rates of remission and relapse.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.03.026.

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