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REVIEW

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A systematic review and meta-analysis on the effects of transcranial direct current stimulation in depressive episodes

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Abstract

Background: Transcranial direct current stimulation (tDCS) has shown mixed results for depression treatment.

Objective: To perform a systematic review and meta-analysis of trials using tDCS to improve depressive symptoms.

Methods: A systematic review was performed from the first date available to January 06, 2020 in PubMed, EMBASE, Cochrane Library, and additional sources. We included randomized, sham-controlled clinical trials (RCTs) enrolling participants with an acute depressive episode and compared the efficacy of active versus sham tDCS, including association with other interventions. The primary outcome was the Hedges' g for continuous depression scores; secondary outcomes included odds ratios (ORs) and number needed to treat (NNT) for response, remission, and acceptability. Random effects models were employed. Sources of heterogeneity were explored via metaregression, sensitivity analyses, subgroup analyses, and bias assessment.

Results: We included 23 RCTs (25 datasets, 1,092 participants), most (57%) presenting a low risk of bias. Active tDCS was superior to sham regarding endpoint depression scores ($k = 25$, $g = 0.46$, 95% confidence interval [CI]: 0.22–0.70), and also achieved superior response ($k = 18$, 33.3% vs. 16.56%, OR = 2.28 [1.52–3.42], NNT = 6) and remission ($k = 18$, 19.12% vs. 9.78%, OR = 2.12 [1.42–3.16], NNT = 10.7) rates. Moreover, active tDCS was as acceptable as sham. No risk of publication bias was identified. Cumulative meta-analysis showed that effect sizes are basically unchanged since total sample reached 439 participants.

Conclusions: TDCS is modestly effective in treating depressive episodes. Further well-designed, large-scale RCTs are warranted.

KEYWORDS

major depressive disorder, meta-analysis, systematic review, transcranial direct current stimulation

Abbreviations: BDNF, brain-derived neurotrophic factor; BDI, Beck's Depression Inventory; CCT, cognitive control therapy; CES, cranial electric stimulation; DLPFC, dorsolateral prefrontal cortex; HDRS, Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; NNT, number needed to treat; ORs, odds ratio; RCTs, randomized sham-controlled clinical trials; rTMS, repetitive transcranial magnetic stimulation; SO-R, supraorbital right; SD, standard deviation; tDCS, transcranial direct current stimulation.

Lais B. Razza and Priscila Palumbo contributed equally to this study.

1 | INTRODUCTION

Transcranial direct current stimulation (tDCS) is a noninvasive, nonpharmacological intervention that presents advantageous characteristics for clinical use, such as safety, tolerability, ease of use, absence of serious adverse effects, and capability to be used remotely (Brunoni, Sampaio-Junior, et al., 2018). The technique consists in the application of weak, direct currents via scalp electrodes. The injected current passes through several anatomical layers to reach the brain, where it modifies neuronal excitability and cortical activity according to stimulation parameters (Brunoni et al., 2012). In major depressive disorder (MDD) trials, the anode is positioned over the left dorsolateral prefrontal cortex (DLPFC), which is hypoactive, aiming to increase local activity and restore normal functioning (Sathappan, Luber, & Lisanby, 2019). The cathode is either positioned over the right DLPFC or the right supraorbital or frontotemporal area, leading to distinct current distributions, although the influence on clinical effects remains unclear (Csifcsák, Boayue, Puonti, Thielscher, & Mittner, 2018).

Several randomized clinical trials (RCTs) examining tDCS efficacy for MDD have been conducted hitherto. In a recent, large noninferiority trial, Brunoni et al. (2017) showed that tDCS was not noninferior to escitalopram 20 mg/day, although superior to placebo. Conversely, in another large, recent trial, Loo et al. (2018) showed no superiority of tDCS compared with placebo, though a subsequent follow-up study suggested the form of placebo stimulation used might have had some active effects (Nikolin, Martin, Loo, & Boonstra, 2018). In fact, such discrepant findings have been also observed in recent meta-analyses. For instance, in a recent network meta-analysis, Mutz et al. (2019) found that tDCS was moderately effective for depression. However, this meta-analysis did not investigate continuous outcomes (i.e., change in depression scores, which provides further information when compared with categorical outcomes). In addition, putative predictors of response (such as tDCS parameters and adjuvant therapies) were not assessed. In addition, that meta-analysis did not include trials involving participants with secondary depression (i.e., depression due to a general medical condition) trials, such as poststroke depression. Other specific meta-analyses examining tDCS for MDD also obtained mixed findings and did not include larger trials conducted in recent years (Brunoni, Moffa, Fregni, et al., 2016; Mutz, Edgcumbe, Brunoni, & Fu, 2018; Shiozawa et al., 2014).

Due to the aforementioned gaps in the literature, we performed an updated systematic review and meta-analyses of placebo-controlled clinical trials evaluating the efficacy of tDCS for the improvement of depressive symptoms. If tDCS is proven to be effective for MDD, this would represent a substantial gain in the management of this disorder, considering its prevalence, burden, and limited efficacy or tolerability of pharmacotherapy for a significant subset of patients (Kupfer, Frank, & Phillips, 2012).

2 | METHODS

2.1 | Systematic review

A systematic review of MEDLINE/PubMed, EMBASE, and the Cochrane Library databases were performed from the first date available until January 06, 2020, with no language or publication restrictions. For additional references, we also searched the reference lists from the selected papers and other systematic reviews and contacted experts in the field. The study was registered on the international prospective register of systematic reviews (PROSPERO—CRD42020138615).

The first, second, and last authors independently searched the literature and screened the titles and abstracts for eligible articles. Disagreements were resolved through consensus. The search strings of the literature review performed included terms for "tDCS," "depression," and "clinical trials," and are shown in the supplementary material information.

2.2 | Eligibility criteria

Only randomized, sham-controlled trials were included. Eligibility criteria were participants with an acute depressive episode that was associated with a diagnosis of major depressive disorder, bipolar disorder, or secondary depression (e.g., poststroke depression). Regarding interventions and comparisons, we compared groups receiving active versus sham tDCS. We included studies in which tDCS was associated with other therapies (e.g., medications and behavioral interventions). In addition, studies had to report at least one main outcome or provide data under request.

2.3 | Data extraction

We extracted data regarding depression, treatment, and outcome characteristics, and metadata. Details regarding data extraction and special procedures adopted for some RCTs are described in the supplementary material information.

2.4 | Outcomes

The primary outcome was depression scores at endpoint (continuous outcome). We used endpoint scores instead of change scores as most studies did not report the standard deviations (SDs) of change scores, which would therefore require the imputation of unknown correlation coefficients. Importantly, in a review comparing 63 meta-analyses based on change versus endpoint scores, more than 90% of them showed similar results, and all discrepancies favored change scores (Fu & Holmer, 2016). Therefore, endpoint scores were a conservative choice.

TABLE 1 Characteristics of the randomized clinical trials included in the meta-analysis

	Clinical characteristics			Depression characteristics					tDCS treatment					
Author	n	% Female	Age, mean (*SD*)	Dx	TRD	Primary scale	Previous medication use	Treatment strategy	Anode	Cathode	Current, electrode size	Session duration (min/d)	N of sessions	tDCS device
Bennabi et al. (2015)	24	64.4	60.1 (13.7)	MDD	Y	HDRS-21	Stable doses	Augmentation	F3	SO-R	2 mA; 35 cm^2	30	10	NeuroConn
Blumberger et al. (2012)	24	83.3	47.5 (10.5)	MDD	Y	HDRS-17	Stable doses	Add-on	F3	F4	2 mA; 35 cm^2	20	15	CX-6650, Rolf Schneider
Boggio et al. (2008)	31	64.5	49.4 (7.4)	MDD	N	HDRS-21	Not Allowed	Monotherapy	F3	SO-R	2 mA; 35 cm^2	20	10	Own device
Brunoni et al. (2013)	60	68.5	43.7 (13)	MDD	N	MADRS	Wash-out	Monotherapy	F3	F4	2 mA; 25 cm^2	30	12	Chattanooga Ionto
Brunoni et al. (2013)	60	68	41 (12.5)	MDD	N	MADRS	Wash-out	Augmentation	F3	F4	2 mA; 25 cm^2	30	12	Chattanooga Ionto
Brunoni et al. (2014)	37	29	43.8 (10.5)	MDD	N	HDRS-21	Stable doses	Augmentation	F3	F4	2 mA; 25 cm^2	30	10	Chattanooga Ionto
Brunoni et al. (2017)	245	57	42.7 (12.6)	MDD	N	HDRS	Wash-out	Monotherapy	F3	F4	2 mA; 25 cm^2	30	22	Soterix
Dastjerdi et al. (2015)	30	56.7	31 (8.2)	MDD	N/I	BDI	N/I	Add on	N/I	N/I	2 mA; NI	20	6	N/I
Fregni et al. (2006)	18	61	47 (9.9)	MDD	N/I	HDRS	Not Allowed	Monotherapy	F3	F8	1 mA; 35 cm^2	20	5	N/I
Loo et al. (2010)	40	55	47.3 (12.2)	MDD	N	MADRS	Stable doses	Add-on	PF3	F8	1 mA; 35 cm^2	20	5	NeuroConn
Loo et al. (2012)	64	47	47.8 (12.5)	MDD/BD	N	MADRS	Stable doses	Add-on	PF3	F8	2 mA; 35 cm^2	20	15	NeuroConn
Loo et al. (2018)	120	54	48.1 (14.9)	MDD/BD	N	MADRS	Stable doses	Add-on	F3	F8	2.5 mA; 35 cm^2	30	20	NeuroConn
Mayur et al. (2018)	16	37.5	44.9 (14.7)	MDD	Y	MADRS	Not allowed	Augmentation	F3	F4	2 mA; 25 cm^2	30	10	NeuroConn
Nord et al. (2019)	39	51.3	33.3 (10.6)	MDD	Y	HDRS	Not allowed	Augmentation	F3	Deltoid	1 mA; 35 cm^2	20	8	NeuroConn
Palm et al. (2012)	22	64	57 (12)	MDD	Y	HDRS-24	Stable doses	Add-on	F3	SO-R	1.5 mA; 35 cm^2	20	10	NeuroConn
Pavlova et al. (2018)	68	72	38.3 (10)	MDD	N	HDRS	Not Allowed	Augmentation	F3	SO-R	0.5 mA/17.5 and 35 cm^2	20 and 30	10	Reamed-polaris
Salehinejad et al. (2015)	30	56.6	28.3 (28.2)	MDD	NI	HDRS	Not Allowed	Monotherapy	F3	F4	2 mA; 35 cm^2	20	10	TCT Research Limited

(Continues)

TABLE 1 (Continued)

	Clinical characteristics			Depression characteristics					tDCS treatment					
Author	n	% Female	Age, mean (*SD*)	Dx	TRD	Primary scale	Previous medication use	Treatment strategy	Anode	Cathode	Current, electrode size	Session duration (min/d)	N of sessions	tDCS device
Salehinejad et al. (2017)	24	62.5	26.1 (5.8)	MDD	NI	BDI	Not Allowed	Monotherapy	F3	F4	2 mA; 35 cm^2	20	10	ActivaDose Ionto-phoresis
Sampaio-Junior et al. (2018)	59	68	45.9 (11)	BD	Y	HDRS-17	Stable doses	Add-on	F3	F4	2 mA; 25 cm^2	30	12	Soterix
Segrave et al. (2014)	27	37	41.6 (14.5)	MDD	NI	MADRS	Stable doses	Augmentation	F3	F8	2 mA; 35 cm^2	24	5	NeuroConn
Sharafi et al. (2019)	30	53	47.3 (11.7)	MDD	Y	HDRS-17	Stable doses	Monotherapy	F3	F4	2 mA; 20 cm^2	20	10	ENRAF
Valiengo et al. (2017)	48	50	61.6 (11.9)	Post-stroke	N	HDRS-17	Wash-out	Monotherapy	F3	F4	2 mA; 25 cm^2	30	12	NeuroConn
Vigod et al. (2019)	20	100	32.3 (4.2)	Pregnancy	Y	MADRS	Not allowed	Monotherapy	F3	F4	2 mA;35 cm^2	30	15	Magstim
Welch et al. (2019)	14	85.7	54.8 (10.3)	MDD	N/I	HDRS-21	Not allowed	Augmentation	F3	F4	2 mA; 25 cm^2	30	12	Chattanooga Ionto

Abbreviations: BD, bipolar disorder; Dx, diagnostic; F3, left dorsolateral prefrontal cortex; F4, right dorsolateral prefrontal cortex; F8, over the lateral aspect of the contralateral orbit; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; N/I, not informed; SD, standard deviation; SO-R, right supraorbital; tDCS, transcranial direct current stimulation; TRD, treatment-resistant depression.

The secondary outcomes were response, remission, and acceptability rates. All studies defined response as more than 50% depression improvement from baseline to endpoint, although different depression scales were used, such as the Hamilton Depression Rating Scale (HDRS) and the Montgomery-Asberg Depression Rating Scale (MADRS). For remission, we used the definition provided by each study according to the primary outcome (Table 1). Acceptability was measured according to the dropout rate.

As RCTs reported depression scores in more than one time point, we used data from the longest period before blinding breaking. In addition, we considered the intention-to-treat sample and calculated response and remission rates based on the number of participants entering the study.

Subgroup analyses were conducted based on the results of previous aggregate and individual patient data meta-analyses of tDCS for depression.

2.5 | Quality assessment

The methodological quality of each study was evaluated per the Cochrane risk of bias tool that assesses the risks of selection, performance, detection, attrition, reporting, and other biases according to standardized criteria (Higgins et al., 2016). The classification of each included study and additional details are shown in the supplementary material information.

2.6 | Data analysis

All analyses were performed in Stata 15 (Statacorp, College Station, TX) using the *metan* command and others. We used a random effects model (restricted maximum-likelihood method) based on previous meta-analyses (Mutz et al., 2018; Shiozawa et al., 2014), considering that study heterogeneity a priori would be high. Heterogeneity was evaluated with the I^2, with values more than 50% indicating high heterogeneity. Fixed effects analyses were also performed, obtaining similar results (data not shown).

As different depression scales have been used, a standardized mean difference and pooled SD for each comparison were initially calculated. The Hedges' *g* was used as the effect size measure, since most studies enrolled small sample sizes. The pooled effect size was weighted by the inverse variance method. Positive and negative values respectively favor active and sham tDCS.

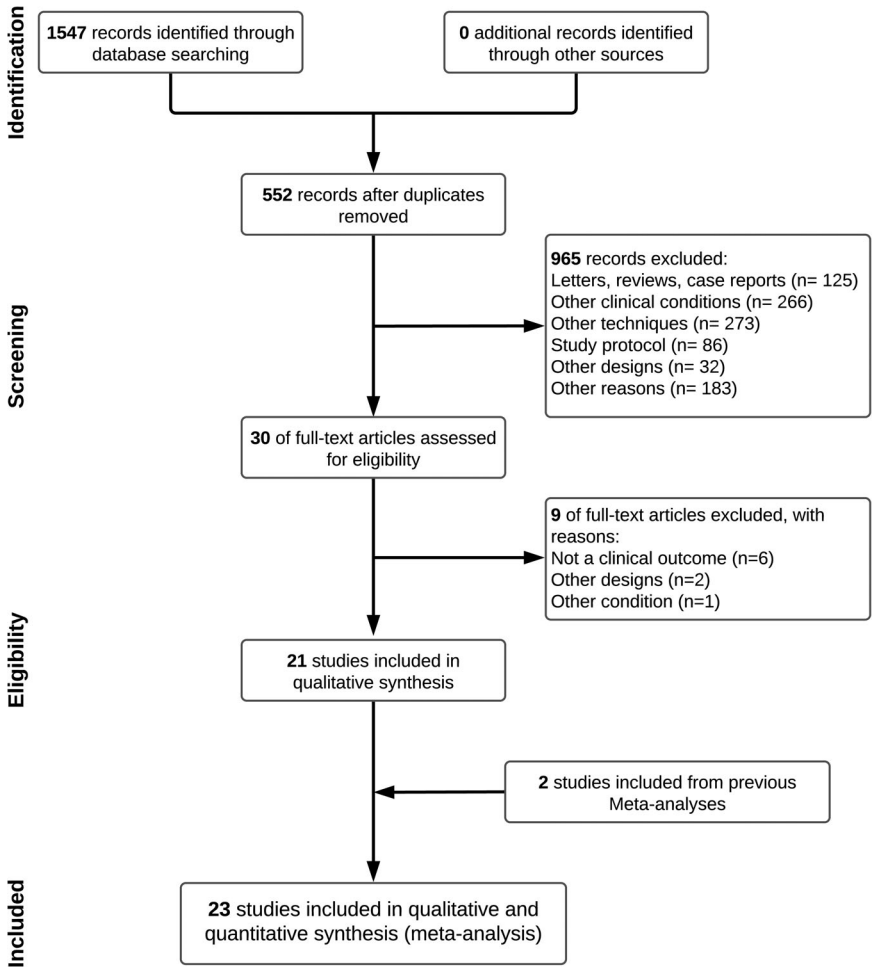

FIGURE 1 Flowchart of the study selection process

For response and remission (categorical outcomes), the effect size was measured using odds ratios (ORs) and the number needed to treat (NNT).

The NNT assesses the effectiveness of a clinical intervention, representing the number of patients with clinical depression that is necessary to treat with active tDCS for one additional patient to experience response or remission. NNT was obtained using the *metannt* function and estimated as the reciprocal of the absolute value of the risk difference (NNT = 1/|risk difference|).

For studies that reported zero responders/remitters in any group, we added 0.5 in the cells of both groups to allow estimation of effect size, which cannot be calculated when there are no events (Higgins & Green, 2009). Such an approach tends to be conservative as it incorporates in the pooled results trials where no events were observed, but it is considered valid since the exclusion of these "zero event" trials may overestimate the overall effects of the intervention (Friedrich, Adhikari, & Beyene, 2007).

Additional analyses were performed based on our primary outcome and included:

(1) publication bias, evaluated using Egger's regression intercept test, and the funnel plot. The "trim-and-fill" method was not used as no publication bias was detected;
(2) univariate metaregression (for variables reported in more than five RCTs) and subgroup analyses, to evaluate the influence of continuous and categorical moderators, respectively, as described below;
(3) sensitivity analyses for studies with low risk of bias; and
(4) cumulative meta-analysis, in which the results of RCTs are added chronologically to identify patterns of stability of evidence over time.

3 | RESULTS

3.1 | Overview

Our review yielded 1,547 articles of which 1,526 were excluded for several reasons. Twenty-one articles were included from our

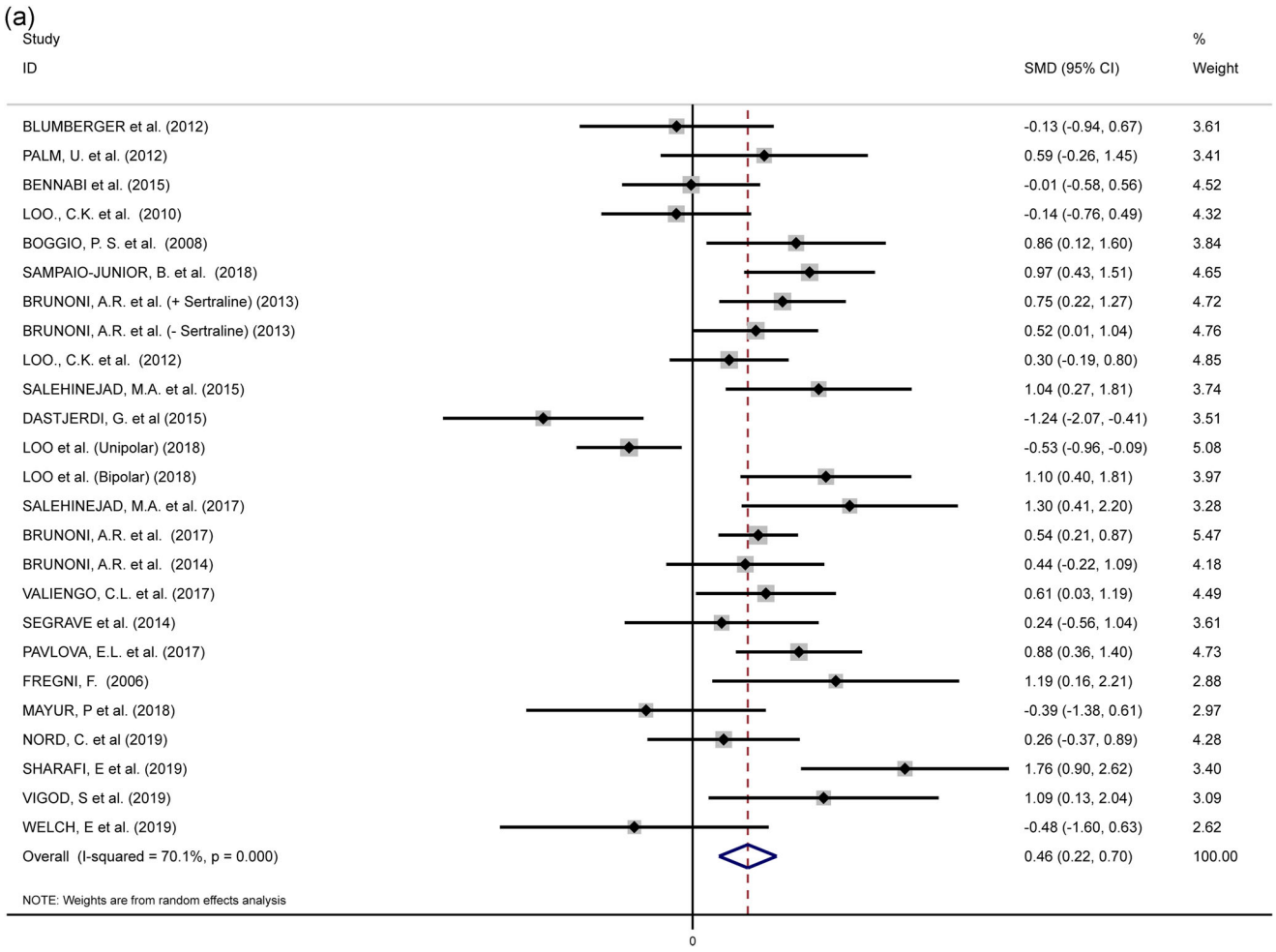

FIGURE 2 Forest plot of (a) effect sizes (Hedges' *g*), (b) response rates (OR), (c) remission rates (OR). The forest plot illustrates the relative strength of treatment effects for each selected study. In all outcomes, active tDCS was superior to sham. OR, odds ratio; tDCS, transcranial direct current stimulation

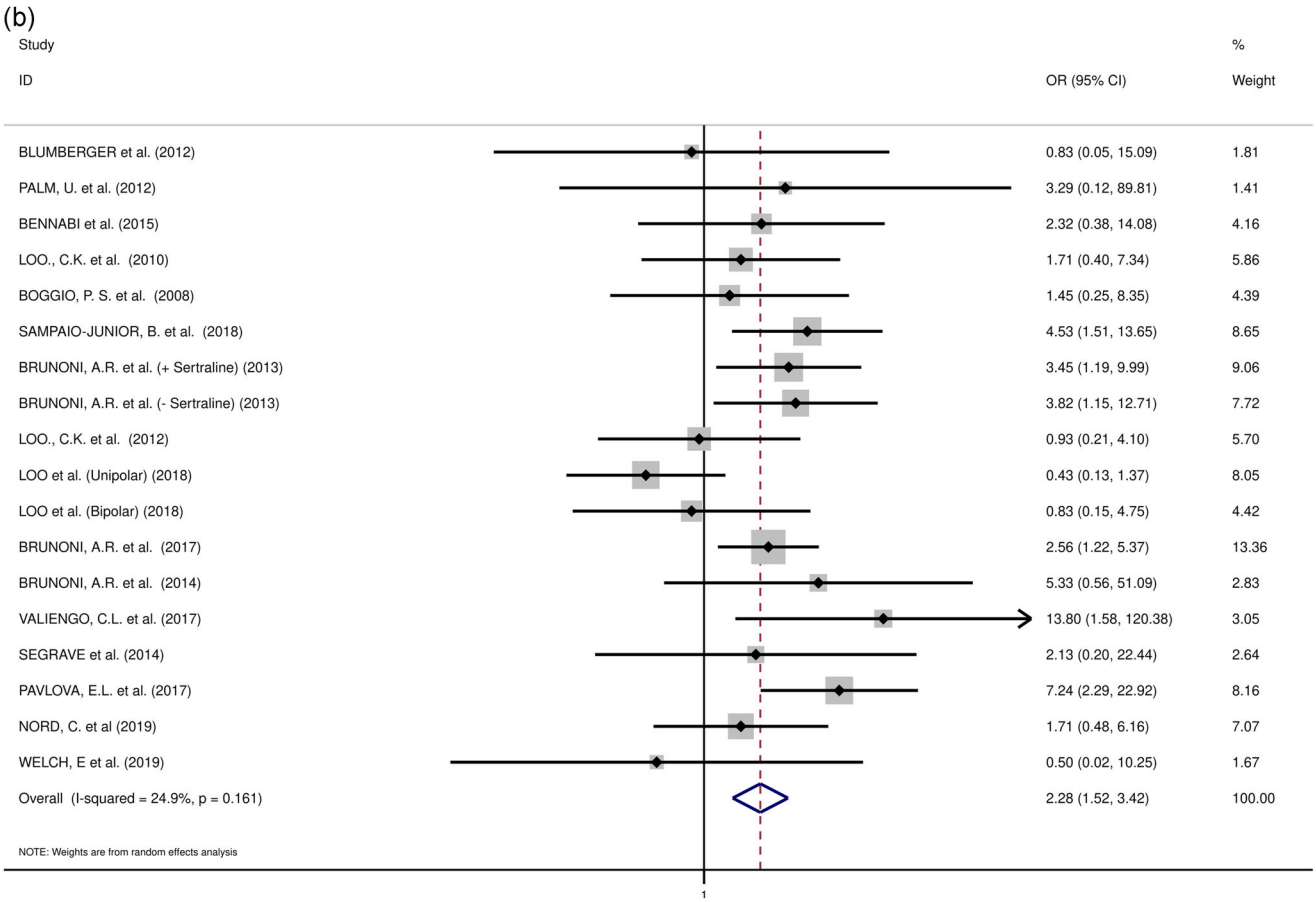

FIGURE 2 Continued

systematic review and two additional studies were obtained from previous meta-analyses (Mutz et al., 2019, 2018). Thus, 23 studies (25 datasets; Bennabi et al., 2015; Blumberger, Tran, Fitzgerald, Hoy, & Daskalakis, 2012; Boggio et al., 2008; Brunoni et al., 2013; Brunoni et al., 2014; Brunoni et al., 2017; Dastjerdi, Mirhoseini, & Mohammadi, 2015; Fregni, Boggio, Nitsche, Rigonatti, & Pascual-Leone, 2006; Loo et al., 2010, 2012, 2018; Mayur, Howari, Byth, & Vannitamby, 2018; Nord et al., 2019; Palm et al., 2012; Pavlova et al., 2018; Salehinejad, Ghanavai, Rostami, & Nejati, 2017; Salehinejad, Rostami, & Ghanavati, 2015; Sampaio-Junior et al., 2018; Segrave, Arnold, Hoy, & Fitzgerald, 2014; Sharafi, Taghva, Arbabi, Dadarkhah, & Ghaderi, 2019; Valiengo et al., 2017; Vigod et al., 2019; Welch et al., 2019) met inclusion criteria (Figure 1).

Overall, there were 1,092 participants (591 receiving active tDCS and 501 receiving sham tDCS), with a mean age of 44.4 years (*SD* = 9.4) and 60.4% being women. General characteristics of the included studies are described in Table 1. Quality assessment revealed that 57%, 13%, and 30% of the included studies presented low risk, some concerns, and high risk of biases, respectively (see the supplementary material information).

3.2 | Primary outcome

We calculated the effect sizes of endpoint depression scores for each study. Meta-analysis results showed that active tDCS was superior to sham (k = 25, Hedges's g = 0.46, 95% confidence interval [CI]: 0.22–0.70; Figure 2a). High heterogeneity was observed (I^2= 70.1%, 95% CI: 57–81.1).

3.3 | Secondary outcomes

The response rates in the active and sham groups were, respectively 33.3% (*SD* = 21.1) and 16.56% (*SD* = 10.53), favoring active tDCS (k = 18, OR = 2.28, 95% CI: 1.52–3.42, NNT = 6.00). Low heterogeneity was observed (I^2= 24.9%, 95% CI: 0–55; Figure 2b).

Likewise, remission rates in the active and sham groups were, respectively 19.12% (*SD* = 16.34) and 9.78% (*SD* = 16.34), favoring active tDCS (k = 18, OR = 2.12, 95% CI: 1.42–3.16, NNT = 10.7). Low heterogeneity was observed (I^2= 0%, 95% CI: 0–50; Figure 2c).

For acceptability, we found dropout rates of 14.04.5% (*SD* = 11.1) and 13.77% (*SD* = 13.78) in the active and sham groups, respectively. The

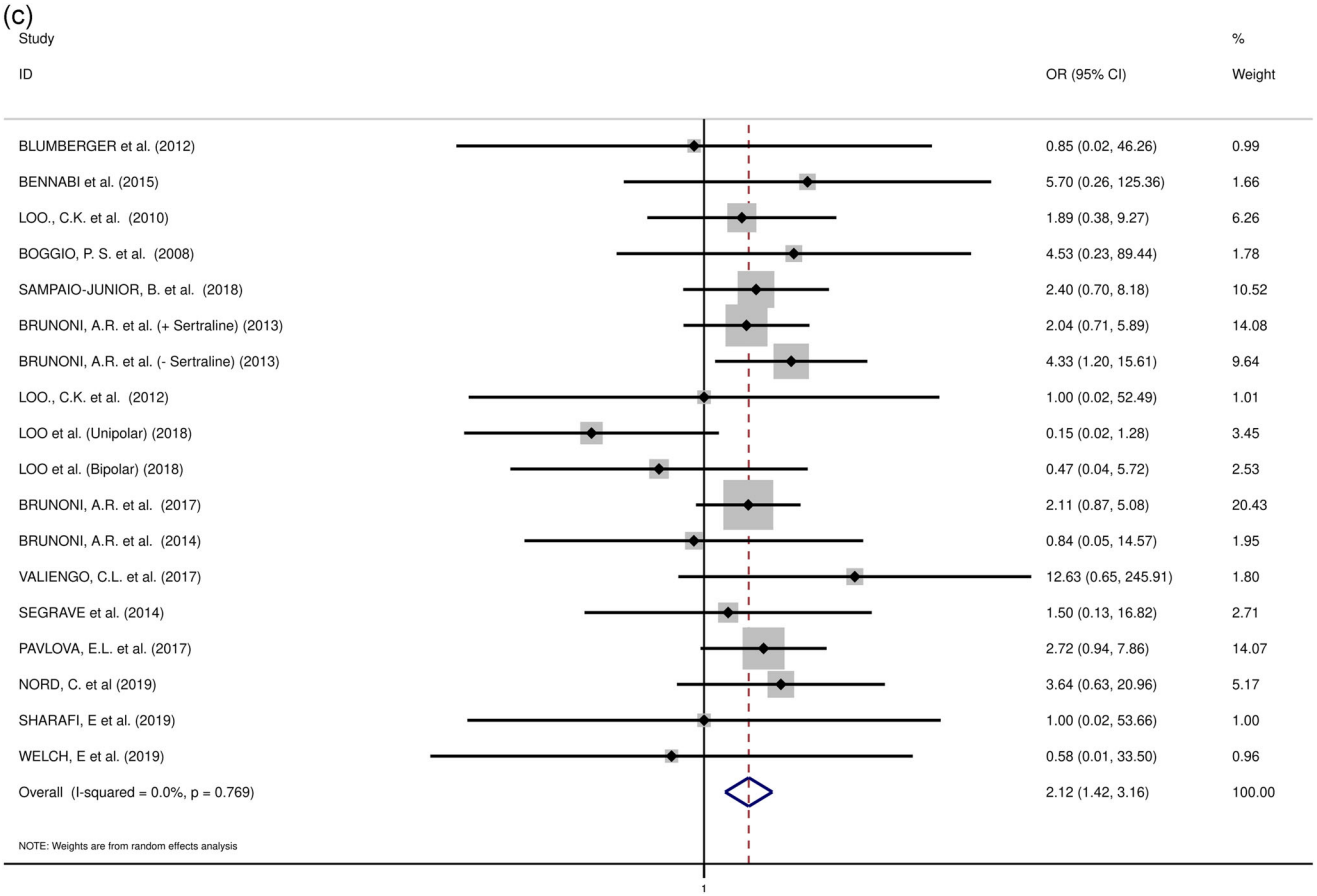

FIGURE 2 Continued

OR for this outcome was 1.01 (95% CI: 0.69–1.48), indicating that dropout rates were similar in both groups (Figure 3a).

3.4 | Funnel plot

The funnel plot for the primary outcome is not suggestive of publication bias as studies were symmetrically distributed (Figure 3b). In accordance, the Egger Test was not suggestive of publication bias ($t = 0.41$, $p = .69$).

3.5 | Metaregression and subgroup analyses

No metaregressed variable was associated with the primary outcome, including treatment characteristics such as current dose and number of sessions (Table 2).

Subgroup analyses revealed that cathode positioning over F4 or over right supraorbital area had a trend to be more effective than the over F8 ($p = .09$). Regarding treatment strategy, tDCS as a monotherapy (i.e., patients were not using antidepressant drugs, either because they were drug-naive or a washout was performed) was more effective than an augmentative therapy (combined with concurrently commenced CCT, CES, or pharmacotherapy) and than tDCS as an add-on therapy (i.e., added on to existing pharmacotherapy). Other subgroup analyses, including treatment-resistant depression and depression diagnosis underlying the depressive episode, did not reveal significant differences between groups (Table 2).

Importantly, most subgroup analyses resulted in lower heterogeneity. Notwithstanding, subgroup analyses were hypothesis-driven based on previous studies, as mentioned above.

3.6 | Sensitivity analysis

Active tDCS was still superior to sham when considering only the RCTs with low risk of bias ($k = 15$, $g = 0.43$, [0.19–0.68], $I^2 = 62.6\%$, 95% CI: 36–79).

3.7 | Cumulative meta-analysis

The cumulative meta-analysis shows that the results first became to present more stable results favoring active tDCS after Salehinejad et al., 2015 with a $g = 0.47$ (95% CI: 0.28–0.67, $n = 439$ participants). Afterward, the effect size was basically unchanged, with small changes in the confidence intervals (Figure 4). The cumulative evidence reached a $g = 0.45$ (95% CI: 0.32–0.57, $n = 1{,}092$ participants).

4 | DISCUSSION

We investigated the effects of tDCS in improving depressive symptoms in 25 datasets ($n = 1{,}092$ patients, 591 in the active group and 501 in the sham group) in this updated aggregated data meta-analysis, which is the largest performed hitherto examining the effects of tDCS in treating depressive episodes. Our main findings were that active tDCS was superior to sham in improving depressive symptoms, yielding higher response and remission rates and lower depression scores at the endpoint. Our results were reproduced in all outcomes, presented no evidence of publication bias, and most studies had low evidence of bias.

Albeit significant for all outcomes, the efficacy of tDCS was modest, showing small to medium effect sizes. For instance, meta-analyses have

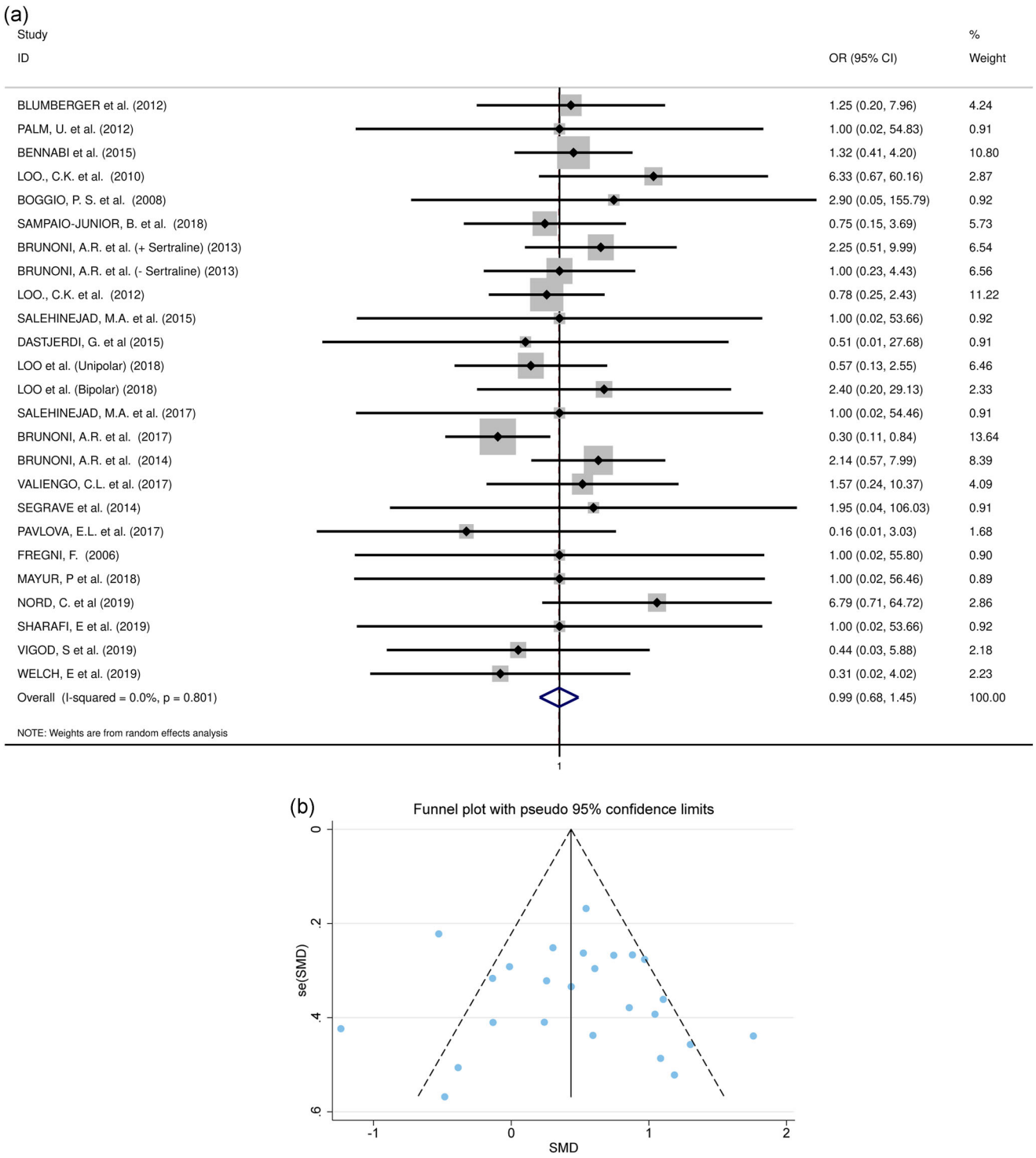

FIGURE 3 Forest plot of (a) acceptability, according to the dropout rates (OR), (b) funnel plot. OR, odds ratio

TABLE 2 Results of metaregression and subgroup analyses

Univariate metaregression	Coef (B)	% CI	*p*
Clinical and demographic variables			
% Females	0.007	−0.01 to 0.03	.41
Age, years	−0.01	−0.04 to 0.02	.51
Depression characteristics			
Duration of current episode, months	−0.03	−0.14 to 0.08	.58
Treatment characteristics			
Current density (mA/cm^2)	−0.13	−0.72 to 0.44	.63
Number of sessions	0.007	−0.05 to 0.07	.23
Total charge delivered	−0.004	−0.02 to 0.01	.64
Methodological characteristics			
Total sample size (n)	−0.0004	−0.009 to 0.008	.93
Dropouts (n)	−0.01	−0.05 to 0.02	.49
Subgroup analyses[a]			
Cathode positioning			
F4 (*k* = 12)	0.69	0.38 to 1.00	Ref
F8 (*k* = 6)	−0.48	−1.05 to 0.09	*.09*
right SO (*k* = 5)	−0.002	−0.60 to 0.60	.99
Treatment strategy			
Monotherapy (*k* = 8)	0.76	0.38 to 1.14	Ref
Add-on (*k* = 8)	−0.87	−1.55 to −0.19	**.015**
Augmentation (*k* = 9)	−0.55	−0.97 to −0.12	**.015**
Treatment-resistant depression			
Yes (*k* = 16)	0.57	−0.78 to 1.36	.84
No (*k* = 3)	0.83	−0.79 to 0.96	
Diagnosis			
Unipolar (*k* = 19)	0.40	0.07 to 0.73	Ref
Bipolar (*k* = 2)	0.66	−0.35 to 1.67	.19
Poststroke depression (*k* = 1)	0.23	0–1.18 to 1.65	.73
Pregnancy depression (*k* = 1)	0.71	−0.93 to 2.36	.38

Note: We metaregressed only one variable at a time due to the relatively low number of available randomized clinical trials. Current density is the current intensity divided by electrode size; total charge delivered was obtained by multiplying current density, session duration and number of sessions. K represents the number of datasets analyzed. SO, supraorbital; Ref, reference.
Significant values were considered as $p < .05$. Bold values denote significant results. Italic values denote trend for significant results.
[a]*p* represents the results of the metaregression.

shown that the efficacy of antidepressant drugs is higher (Arroll et al., 2009; Undurraga & Baldessarini, 2012). Notwithstanding, tDCS was a safe and well-tolerated intervention, in line with the extant literature (Aparicio et al., 2016; Moffa et al., 2017) and in contrast to pharmacotherapy that presents side effects that usually limit its use (Carvalho, Sharma, Brunoni, Vieta, & Fava, 2016). In fact, although some initial reports have suggested that tDCS could induce treatment-emergent mania (Baccaro, Brunoni, Bensenor, & Fregni, 2010; Borrione, Moffa, Martin, Loo, & Brunoni, 2018; Brunoni, Valiengo, et al., 2011), a recent meta-analysis showed that this risk is not superior to sham (Brunoni, Moffa, Sampaio-Junior, Galvez, & Loo, 2016).

Another noninvasive neuromodulatory intervention is repetitive transcranial magnetic (rTMS). Several modalities of rTMS for depression have already been approved for clinical use worldwide (Brunoni, Sampaio-Junior, et al., 2018). The technique is safe, although associated with a small risk of seizures according to the stimulation parameters, and seems to present superior response and remission rates than tDCS (Baeken et al., 2019). Nonetheless, tDCS has not been directly compared with rTMS, and a network meta-analysis did not provide evidence that rTMS would be superior to tDCS (Mutz et al., 2019). In fact, tDCS presents other advantages compared with rTMS, such as the possibility of home use and self-administration, and lower costs (Brunoni, 2019). These characteristics are particularly appealing when using tDCS for longer periods as maintenance treatment (Alonzo et al., 2019; Aparicio et al., 2019).

Risk of bias assessment revealed that almost 60% of RCTs had an overall low risk of bias. Nonetheless, issues detected among studies include: (a) deviations in the study protocol as compared with the preregistered protocol; (b) the absence of study preregistration; (c) insufficient details regarding sham and blinding procedures. The first two issues have been improving over time with the previous publication of the study protocol before the publication of its main results, as it has been done for some RCTs included in this meta-analysis (Alonzo et al., 2016; Brunoni et al., 2015; Pereira Junior Bde et al., 2015) and for upcoming large RCTs (Bajbouj et al., 2018; Padberg et al., 2017). The latter issue is important particularly considering that the sham procedure commonly used in RCTs has been challenged as ineffective regarding blinding (Greinacher, Buhôt, Möller, & Learmonth, 2019; Turi et al., 2019). However, these studies asked participants to guess the assigned group after a single session, and these results might not necessarily be translated to RCTs with patients who guess based not only on the skin sensations but also considering their clinical improvement.

Metaregression results in aggregate data meta-analysis should be interpreted with caution, particularly when averages of patient characteristics are covariates (Thompson & Higgins, 2002). For instance, although treatment-resistant depression was not associated with the outcome, there was substantial interstudy variability in treatment resistance in trials that did not use treatment resistance as an entry criterion.

Subgroup analyses also should be interpreted with caution, mainly because they were performed post hoc and might be explained by unknown variables. Regarding treatment strategy, results showed that tDCS as an add-on therapy to existing drug use and as an augmentative therapy were not superior to sham. Although these results are in contrast to previous literature findings (Brunoni, Valim, & Fregni, 2011; Sathappan et al., 2019), they could be explained by the underpowered included studies in this meta-analysis.

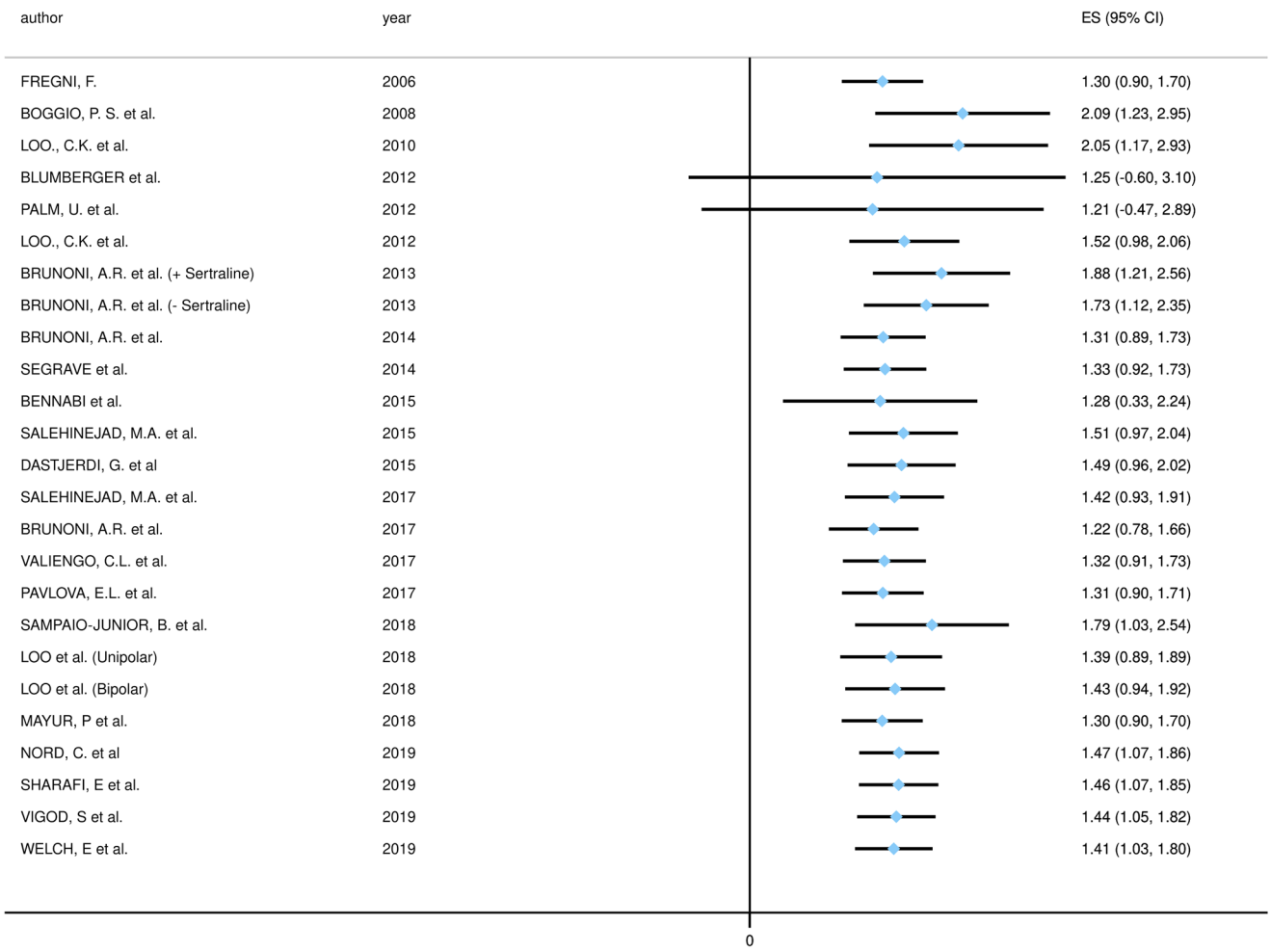

FIGURE 4 Cumulative meta-analysis, showing the resulting point-effect meta-analytic estimates when an additional randomized clinical trial is added, in a chronological order

Results of cumulative meta-analysis showed that the effect size of active versus sham tDCS has been stable for at least 5 years. Interestingly, the effect size obtained in this meta-analysis of 0.46 (0.22–0.70) is remarkably similar to an earlier meta-analysis performed in 2014 that showed a Hedges' g of 0.37 (0.04–0.7), although the confidence intervals were wider (Shiozawa et al., 2014). Therefore, additional RCTs performed during this timeframe, which totaled 11 trials and more than 600 patients, essentially narrowed the CI of the effect size, as the point-estimate remained unchanged. This suggests that the efficacy of tDCS, under the parameters currently employed, is relatively established and associated with modest effects. It should be highlighted that despite variation in some parameters, the design and procedures of tDCS trials for MDD did not substantially vary over time. For instance, all studies employed anodal tDCS over the left DLPFC, current intensities between 0.5 to 2.5 mA, and 5 to 20 tDCS sessions. Therefore, the cumulative meta-analysis reveals, on one hand, that the clinical effects of tDCS in depression have been stable over the last 10 RCTs conducted and, on the other hand, that such effects are modest and new, groundbreaking approaches are warranted to further improve tDCS effects.

In this context, one approach could be identifying biomarkers for a better tDCS response. For instance, recent ancillary analyses of large RCTs indicated that better baseline scores in attention tasks (Martin et al., 2018) and larger left prefrontal cortex volume (Bulubas et al., 2019) predict tDCS antidepressant response. On the other hand, peripheral baseline plasma biomarkers (Brunoni, Padberg, et al., 2018) and the Val66Met BDNF polymorphism (Loo et al., 2018) are not associated with tDCS effects. Thus, future trials should comprehensively explore neuroimaging and neuropsychological biomarkers to identify possible predictors of tDCS response. Finally, changing the parameters of stimulation—for instance, employing high doses or using focal tDCS variants such as smaller electrode sizes or "high-definition" tDCS, could increase clinical effects; although evidence from neurophysiological studies in this aspect have been mixed (Esmaeilpour et al., 2018; Gordon et al., 2018).

It is also likely that extending the treatment period beyond 4 weeks may be required to observe the full effects of tDCS.

This parallels the development of rTMS, with early trials employing a 1-to-2-week treatment period, while later trials extended the placebo-controlled period to 6 weeks (O'Reardon et al., 2007).

4.1 | Strengths and limitations

As study strengths, this is the largest meta-analysis evaluating the efficacy of tDCS in depression to date. We employed a rigorous assessment of study eligibility and quality and employed additional meta-analytical techniques (sensitivity analyses, metaregressions, assessment of publication bias, additional model using fixed-effects) that did not change our results, strengthening our findings. Finally, most studies presented low risk of bias.

Study limitations include: (a) we performed an aggregate data meta-analysis, which has poorer performance than individual patient data meta-analysis, especially for identifying moderators of the outcome (Riley, Lambert, & Abo-Zaid, 2010); (b) the quality and sample size of the included studies were heterogeneous, which reflected in the large heterogeneity identified in the primary outcome—nonetheless, we used meta-analytic techniques to explore the source of heterogeneity and performed analysis for specific subgroups (e.g., including studies with only low risk of bias); (c) we could not assess the prolonged effects of tDCS (follow-up phase) as RCTs evaluating its effects for depression were generally conducted only over a few weeks. To the best of our knowledge, only four studies have evaluated the effects of tDCS in a maintenance phase for more than 3 months. These studies were open-label trials and presented distinct relapse rates, ranging from 25% to 50%, which might be related to the number of sessions and to the tDCS application regimen in the follow-up phase (Alonzo et al., 2019; Aparicio et al., 2019; Martin et al., 2013; Valiengo et al., 2013); and (d) on average, the sample size of the included studies is small (<50 subjects per arm), which is a common feature of NIBS studies even for other clinical conditions (Lefaucheur et al., 2019, 2014, 2017).

5 | CONCLUSION

Results of this meta-analysis enrolling more than 1,000 participants showed that active tDCS was clinically superior and as tolerable as sham in all outcomes. Moreover, no evidence of publication bias was found. Results remained significant when limited to studies with low risk of bias. Notwithstanding, subgroup analyses showed that tDCS as monotherapy was superior to sham, but not as an add-on therapy to ongoing, concurrent pharmacotherapy, and tDCS applied concomitantly with other therapies. In addition, cumulative meta-analysis showed that tDCS effects in depression have been stable over the last 14 RCTs (>600 patients), which suggests that further replication RCTs are not a priority. However, besides tDCS efficacy was only modest, highlighting the need of further RCTs designed to increase its efficacy, such as biomarker-guided RCTs, the present results should be interpreted with caution, considering the several above mentioned study limitations.

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CONFLICT OF INTERESTS

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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