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ARTICLE

Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis

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Abstract

Transcranial direct cranial stimulation (tDCS) is a promising non-pharmacological intervention for treating major depressive disorder (MDD). However, results from randomized controlled trials (RCTs) and meta-analyses are mixed. Our aim was to assess the efficacy of tDCS as a treatment for MDD. We performed a systematic review in Medline and other databases from the first RCT available until January 2014. The main outcome was the Hedges' *g* for continuous scores; secondary outcomes were the odds ratio (ORs) to achieve response and remission. We used a random-effects model. Seven RCTs (n=259) were included, most with small sample sizes that assessed tDCS as either a monotherapy or as an add-on therapy. Active *vs.* sham tDCS was significantly superior for all outcomes (g=0.37; 95% CI 0.04–0.7; ORs for response and remission were, respectively, 1.63; 95% CI=1.26–2.12 and 2.50; 95% CI=1.26–2.49). Risk of publication bias was low. No predictors of response were identified, possibly owing to low statistical power. In summary, active tDCS was statistically superior to sham tDCS for the acute depression treatment, although its role as a clinical intervention is still unclear owing to the mixed findings and heterogeneity of the reviewed studies. Further RCTs with larger sample sizes and assessing tDCS efficacy beyond the acute depressive episode are warranted.

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Key words: Major depressive disorder, meta-analysis, non-pharmacological therapies, systematic review, transcranial direct current stimulation.

Introduction

Transcranial direct cranial stimulation (tDCS) is a novel technique based on the application of a weak electrical current over the scalp through two electrodes – the anode, which facilitates neuronal depolarization, and the cathode, which leads to neuronal hyper-polarization (Nitsche et al., 2008; Brunoni et al., 2012b). Recently, several open-label and sham-controlled clinical trials applied daily tDCS sessions for the treatment of major depressive disorder (MDD). Theoretically, tDCS might induce depression improvement through anodal stimulation over the left dorsolateral prefrontal, inducing excitability-enhancing effects over this area, which is hypoactive during the acute depressive episode (Brunoni et al., 2012a).

However, randomized clinical trials (RCTs) have shown mixed results regarding tDCS as a treatment for MDD, according to two recent meta-analyses: whereas Kalu et al. (2012) initially observed improvement of depressive symptoms; the meta-analysis of Berlim et al. (2013), which included one additional trial (Blumberger et al., 2012) found no significant difference between active *vs.* sham response. In fact, these meta-analyses used distinct methodological approaches, chiefly the effect size measure, which was based on depression scores in one meta-analysis (Kalu et al., 2012) and response/remission rates in another (Berlim et al., 2013). Moreover, these studies displayed relatively large confidence intervals, which might reflect the heterogeneity of tDCS trials as well as the low number of studies and sample size (total of 176 (Kalu et al., 2012) and 200 (Berlim et al., 2013) participants addressed), therefore highlighting the need of novel trials. Finally, we recently published results of a randomized, sham-controlled trial enrolling 120 patients with MDD

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(Brunoni et al., 2013) and to the best of our knowledge, these results have not been included in tDCS meta-analyses yet.

Therefore, considering that meta-analyses synthesize the best clinical evidence of an intervention, this meta-analysis was performed to: (1) update the best available evidence for tDCS, with the addition of another randomized clinical trial, therefore increasing the total sample size evaluated and (2) address the mixed findings from previous meta-analyses by assessing both continuous (depression score change) and categorical (response and remission rates) effect size outcomes. This meta-analysis is relevant considering the burden and importance of MDD, which is one of the most disabling conditions worldwide (Eaton et al., 1997) and the potential benefits of tDCS as a non-invasive, affordable, simple intervention with a low rate of adverse effects (Brunoni et al., 2011).

Methods

A systematic review and meta-analysis according to the recommendations of the Cochrane group was conducted, and the present report follows PRISMA guidelines (Liberati et al., 2009). Two authors (PS and ARB) performed independent systematic reviews and data extraction. Discrepancies were resolved by consensus.

Literature review

We screened the MEDLINE database using the key words:

- regarding tDCS: (1) 'Transcranial stimulation'; (2)'tDCS'; (3) 'Brain Polarization'; (4) 'Electric Stimulation'; (5) 'Electric Polarization'; (6) 'non invasive brain stimulation'; (7) 'NIBS'; AND
- regarding depression: (8) 'depressive disorder'; (9) 'depression' and (10) 'depressive episode' AND
- regarding randomized clinical trials: (11) ('randomized controlled trial' [PT] OR ((randomized[TIAB] OR randomized[TIAB]) AND controlled[TIAB] AND trial [TIAB]))

The Boolean terms were imputed: [(1) OR (2) OR (3) OR (4) OR (5) OR (6) OR (7)] AND [(8) OR (9) OR (10)] AND (11). We searched from the first randomized, controlled-study of Fregni et al. (2006b) to January 31, 2014.

We also looked for study references in retrieved articles and reviews, particularly the references of the meta-analysis of Kalu et al. (2012) and Berlim et al. (2013). Finally, we also looked for randomized controlled trials by contacting specialists on the field and searching the website 'clinicaltrials.gov' for additional trials.

Eligibility criteria

We adopted the following inclusion criteria: (1) manuscript written in English, Spanish or Portuguese (in fact all retrieved articles were written in English); (2) randomized, sham-controlled trials; (3) studies that provided data (on the manuscript or upon request) for our outcomes, i.e. mean (standard deviation (S.D.)) depression scores and response and remission rates. We excluded case reports and series of cases, non-controlled trials and trials assessing other conditions than major depression disorders or other interventions than tDCS.

Data extraction

The following variables were extracted according to a structured checklist previously elaborated by the authors: (1) metadata (i.e. authorship, publication date etc.); (2) demographics (sample size in each group, age, gender); (3) depression characteristics (baseline depression scores; use of antidepressants; degree of refractoriness; scales, interviews and checklists used for depression diagnosis and assessment of severity); (4) characteristics of the tDCS technique (electrode size; intensity of the current; time period of stimulation; anode and cathode positioning; number of sessions); (5) methods (randomization protocol; sham method; blinding assessment; number of drop-outs) and (6) acceptability (drop-out rates of the active and sham tDCS groups at study endpoint).

The primary outcome was based on depression scores (continuous outcome) and the secondary outcomes were categorical – the odds ratio of achieving response/remission. Importantly, the Cochrane Collaboration considers that both outcome measures are appropriate in a meta-analysis, not particularly recommending one type of analysis over the other (Higgins and Green, 2011). Although categorical outcomes are more readily interpretable than continuous outcomes, our choice for the primary outcome considered that all included studies were based on continuous outcomes; thus we judged that a continuous effect size would better synthesize the studies enrolled. A second point is that all studies enrolled used response/remission outcomes as secondary, thus exploratory and possibly not adequately powered for a correct interpretation. In addition, continuous measures have greater sensitivity (although lower specificity) to detect changes in outcomes. As we expected that the total sample size enrolled would be low, we defined the continuous outcome as primary as to increase the power of our analyses.

The following data were extracted:

a) for continuous outcomes, the meta-analysis was performed on endpoint depression scores. Since studies used more than one depression scale, we extracted data corresponding to the study definition of the primary outcome. When one study reported depression scores in more than one timepoint we used the scores correspondent to the longest time period prior to blinding breaking.
b) for categorical outcomes, we extracted endpoint remission and response rates for each group. All studies

defined response as >50% depression improvement (from baseline to endpoint), although different depression scales were used such as the MADRS (Fregni et al., 2006a; Loo et al., 2010, 2012; Brunoni et al., 2013) and the HAMD 17 items, 21 items, (Boggio et al., 2008; Blumberger et al., 2012; Palm et al., 2012). For remission, we used the definition each study provided: Fregni et al. (2006a) and Palm et al. (2012) did not describe the criteria used; Boggio et al. (2008) and Blumberger et al. (2012) used scores lower than 8 in the HAMD; Loo et al. (2010) and Brunoni et al. (2013) used MADRS $\leqslant 10$ and Loo et al. (2012) used MADRS <10.

It should be underscored that the studies of Fregni et al. (2006a, b) used the same dataset therefore only the study that used the largest, latest database was included. Also, Boggio et al. (2008) randomized patients into three groups: active tDCS over the left DLPFC, active tDCS over the occipital stimulation and sham tDCS. Here, defining whether the 'active occipital stimulation' should be considered 'active' or 'sham' tDCS is challenging, since the authors defined this group as an 'active control'. In fact, Kalu et al. (2012) meta-analysis considered occipital stimulation in the control group and Berlim et al. (2013) meta-analysis considered occipital stimulation in the active group. Since this issue is controversial, in this present study we opted for not including the occipital group in further analyses. In addition, for Palm et al. (2012) we used two different datasets according to current intensity: they were labeled 'Palm-1' and 'Palm-2 mA' to refer to the comparison of active 1 and 2 mA *vs.* sham tDCS, respectively. Finally, for the study of Brunoni et al. (2013) two separate datasets were considered in two different analyses, since the author used a factorial design, randomizing patients to four groups (sham tDCS/placebo, sham tDCS/sertraline, active tDCS/placebo and active tDCS/sertraline). In the main analysis, hereby referred as 'Brunoni-group', we compared active tDCS/placebo *vs.* sham tDCS/placebo. In another analysis ('Brunoni-factor') we compared participants receiving active tDCS (active tDCS/placebo and active tDCS/sertraline) *vs.* sham tDCS (sham tDCS/placebo and sham tDCS/sertraline).

Quality assessment

We assessed methodological quality of each trial by assessing: (1) methods of randomization – whether the study was correctly randomized and/or the authors reported the randomization method; (2) sham tDCS – how sham tDCS was performed; (3) blinding of raters – whether the studies reported that the study was double-blinded or 'double single-blinded' (i.e. tDCS appliers not blinded although subjects and raters were blinded) according to the sham method; (4) blinding integrity – whether it was assessed and, when assessed, whether blinding integrity was described.

Quantitative analysis

Main outcomes

All analyses were performed using the statistical packages for meta-analysis of Stata 12 for Mac OSX. For the main outcome (depression scores), we initially calculated the standardized mean difference and the pooled S.D. of each comparison. This procedure is convenient when handling with different scales (such as depression scales) since it standardizes the effect sizes across all studies based on the S.D. of each study. The Hedges' g was used as the measure of effect size, which is appropriate for studies of small sample sizes. The pooled effect size was weighted by the inverse variance method and measured using the random-effects model. For the secondary outcomes (response and remission rates), the random-effects odds ratio (OR) was used as the measure of effect size. For acceptability, we also compared the dropout rates between active *vs.* sham tDCS using the random-effects odds ratio.

The primary analysis used data from 'Brunoni-group'. We also performed similar analyses considering the 'Brunoni-factor' dataset.

Quantitative assessment of heterogeneity and bias

Heterogeneity was evaluated with the I^2 (>35% for heterogeneity) and the χ^2 test ($p<0.10$ for heterogeneity). Publication bias was evaluated using Egger's regression intercept test and the funnel plot, which displays confidence interval boundaries to assist in visualizing whether the studies are within the funnel, thus providing an estimate of publication bias whether the studies are distributed asymmetrically and/or fall outside the funnel. Sensitivity analysis, which assesses the impact of each study in the net results by excluding one study at a time, was also performed.

Meta-regression

Meta-regression analyses were performed to evaluate the influence of the following variables in the outcome: age, gender, baseline severity scores, treatment-resistant depression, current density of stimulation, dose of the electric current, number of days, cathode site and current electric charge. Current density (A/m^2) was estimated by dividing the electric current (Amperes, A) by the electrode surface area (square meters, m^2). Current electric charge (Coulombs, C) was estimated by multiplying the electric current by the total time of stimulation (in seconds).

Meta-regression was performed using the random-effects model modified by Knapp and Hartung (2003) method, using only one variable at a time.

Results

Overview

Our systematic review yielded 100 references. Among them, 85 references were excluded after title and abstract

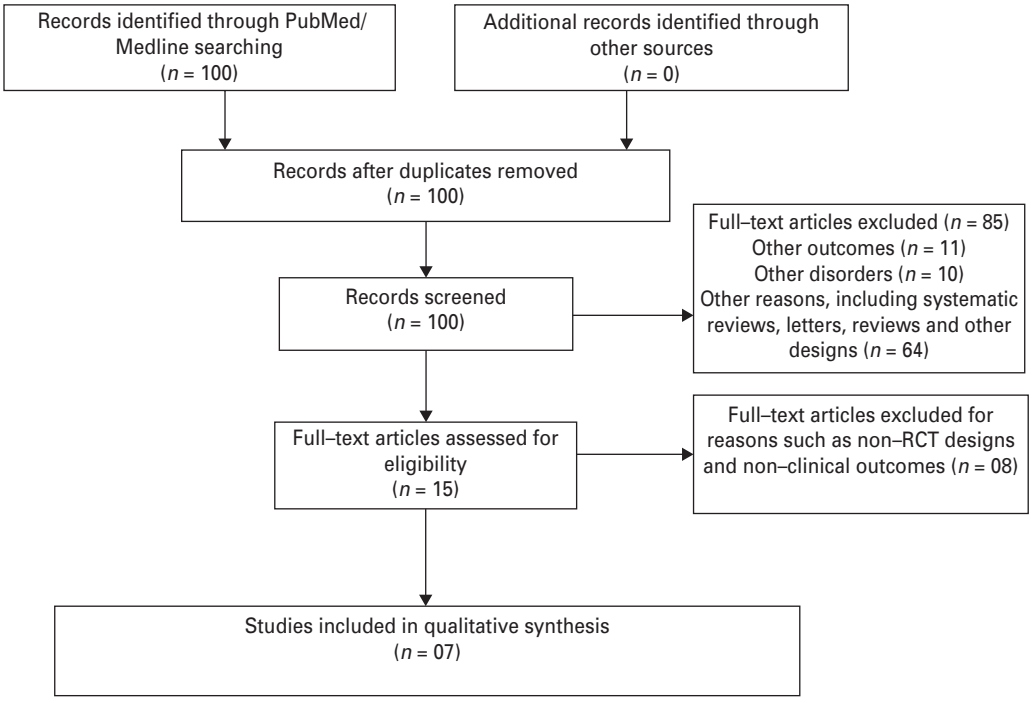

Fig. 1. Flowchart of study selection for our systematic review and meta-analysis. RCT Randomized controlled trials.

review and eight were excluded after assessment of the full-text as they did not match eligibility criteria (Fig. 1). Seven studies (259 patients) were thus included (Tables 1 and 2). The mean age was of 43.62 yr (S.D. = 10) and 58.2% of participants were women. Patients presented a moderate degree of treatment-resistant depression, with a mean of 2.16 (S.D. = 1.7) previous antidepressant trials. Three trials, considering 'Brunoni-factorial' assessed patients without concomitant antidepressant use (Fregni et al., 2006a; Boggio et al., 2008; Brunoni et al., 2013), whereas the other four evaluated tDCS as an 'add-on' (augmentation) intervention to pharmacotherapy. All studies placed the anode over the left dorsolateral prefrontal cortex (DLPFC) – F3 area, according to the EEG 10/20 system. Cathode was positioned either in contralateral cortex (F4) or over the right supraorbital area. One study used current charge of 1 mA (Fregni et al., 2006a), one study assessed both intensities (Palm et al., 2012) and the other five used 2 mA. Regarding charge density, i.e. the amount of electric charge per surface area, studies used either 0.28 A/m^2 (Fregni et al., 2006b; Loo et al., 2010; Palm et al., 2012), 0.57 A/m^2 (Boggio et al., 2008; Blumberger et al., 2012; Loo et al., 2012) or 0.8 A/m^2 (Brunoni et al., 2013). Regarding total charge used, measured in Coulombs (C) – defined as the amount of electrical charge that 1A transports in 1 s – trials varied from 1680 to 17 280 C. (Table 1)

Quality assessment revealed that all studies were randomized. In all studies, sham tDCS was performed using a procedure in which a simulated session is preceded by a brief active stimulation period, although this period ranged from 5 s (Fregni et al., 2006b) to 60 s (Brunoni et al., 2013). Finally, all studies reported that raters were blinded to the treatment applied.

Primary and secondary outcomes

According to our primary outcome, we calculated the effect size for endpoint, continuous outcomes (as above mentioned, here the 'Brunoni-group' dataset is considered). We found that active *vs.* sham tDCS was significantly superior (Hedges' $g = 0.37$; 95% CI 0.04–0.7). (Fig. 2*a*)

For our secondary outcomes, we calculated the effect size for endpoint, continuous outcomes using the 'Brunoni-factor' dataset. We found that active tDCS *vs.* tDCS was significantly superior (Hedges' $g = 0.40$; 95% CI 0.07–0.73) (Fig. 2*b*).

For response rates, the pooled ORs were 1.63 (95% CI 1.26–2.12) and 1.66 (95% CI 1.32–2.10) respectively for the 'Brunoni-group' and the 'Brunoni-factor' datasets (Supplementary Fig. 2). For remission rates, both the 'Brunoni-group' and 'Brunoni-factor' datasets showed that active tDCS *vs.* significantly superior to sham tDCS, with ORs of 2.5 (95% CI 1.26–2.499) and 2.5 (95% CI 1.23–5.08), respectively (Supplementary Fig. 3).

Quantitative assessment of heterogeneity and bias

Heterogeneity was not significant in our meta-analysis ($I^2 = 35.3\%$ and $p = 0.15$ for the χ^2 test). In addition, the risk of publication bias was not significant according to the Egger's regression intercept test ($p = 0.43$). Accordingly, the funnel plot revealed that studies were evenly

Table 1. Clinical and methodological characteristics of each included trial

Study	Demographics				Depression			tDCS				
	N (active/sham)	Age (s.d.)	Gender (%fem)	Scale	Number (s.d.) of failed antidepressant therapies	AD use	Current (mA)	Duration (min/d)	Anode	Cathode	Number of sessions	Current density (A/m^2)
Boggio et al. (2008)	21/10	49 (7.4)	67.5	HAMD	1.6 (1.2)	No	2	20 min	F3	RSO	10	0.57
Loo et al. (2010)	20/20	47.3 (11.3)	55	MADRS	1.3 (1.6)	Yes	1	20 min	F3	RSO	5	0.28
Loo et al. (2012)	33/31	48.2 (12.5)	46.6	MADRS	1.7 (1.2)	Yes	2	20 min	F3	F8	15	0.57
Palm et al. (2012)	11/11	57 (12)	50	HAMD	2.9 (1.6)	Yes	1 or 2	20 min	F3	RSO	10	0.28/0.57
Blumberger et al. (2013)	13/11	42.7 (11.6)	45.6	HAMD	4.2 (2.3)	Yes	2	20 min	F3	F4	15	0.57
Fregni et al. (2006)	9/9	48.2 (10)	NR	MADRS	NR	No	1	20 min	F3	RSO	5	0.28
Brunoni et al. (2013) (group analysis)	30/30	43.7 (13.5)	68.5	MADRS	1.7(2.3)	No	2	30 min	F3	F4	12	0.8
Brunoni et al. (2013) (factor analysis)	60/60	42 (12)	68	MADRS	1.7(2.3)	Yes	2	30 min	F3	F4	12	0.8

s.d.: standard deviation; HAMD: Hamilton Depression Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; F3: left dorsolateral prefrontal cortex (according to the EEG 10/20 system); F4: right dorsolateral prefrontal cortex (according to the EEG10/20 system); F8: right lateral aspect of the supraorbital area (according to the EEG 10/20 system); RSO – right supraorbital area; AD: antidepressant drug. Two different analyses were performed, once at a time, for the Brunoni et al. study. In the 'group analysis' we compared the active-transcranial direct cranial stimulation tDCS/placebo *vs.* sham-tDCS/placebo; whereas in the 'factor analysis' we compared tDCS *vs.* sham-tDCS (regardless of drug use). Please refer to the main text for further details.

distributed in the funnel, with just one small study located marginally at one edge of the funnel (Fig. 3).

The sensitivity analysis showed that the exclusion of one study at a time did not have a significant impact on the results, with resulting effect sizes close to the net effect size (Supplementary Fig. 1). Therefore, no particular study was driving the results of our analysis. We also performed quantitative assessments of heterogeneity and bias for our categorical outcomes. The results were fairly similar to our primary, continuous outcome measure (data not shown).

Meta-regressions

Meta-regression results showed no influence of any assessed variable on the results, such as baseline severity scores ($p=0.66$), session duration ($p=0.74$), charge density ($p=0.55$), current intensity ($p=0.37$), number of days of stimulation ($p=0.94$), total charge ($p=0.67$), cathode site ($p=0.72$), treatment-resistant depression ($p=0.84$) and age ($p=0.94$) were not significant. Meta-regression results of the categorical outcomes displayed similar results (data not shown).

Subgroup analyses

We evaluated the association between days of stimulation and the effect size. A trend ($p=0.09$) was found when comparing $\leqslant$10 d (Hedges' g of 0.37 95% CI −0.22 to 0.96) *vs.* >10 d (Hedges' g of 0.42 95% CI 0.07 to 0.77) – i.e. longer periods of stimulation might be associated with a larger antidepressant response.

We also evaluated the association between total current electric charge (C) and the effect size. This association was not significant ($p=0.09$) although a trend was observed for higher current charges determining larger antidepressant effects (Supplementary Fig. 4).

Acceptability

We found a total of 12 drop-outs in the active group and 15 in the sham group (8.2 *vs.* 11.4%, respectively). The OR was 0.73 (95% CI 0.32 to 1.69), showing that there were no differences in acceptability between active and sham tDCS (Supplementary Fig. 5).

Discussion

In this systematic review we assessed 7 randomized clinical trials ($n=259$) that evaluated the clinical effects of tDCS either as an add-on therapy to pharmacotherapy or as monotherapy in antidepressant drug-free samples. We found that active tDCS was significantly superior to sham tDCS for the treatment of MDD. This result was shown in our main analysis that used continuous effect size measures and corroborated by secondary meta-analyses that used categorical outcomes. The net effect size from our main outcome (Hedges' g of 0.37)

Table 2. Clinical results of each study

Study	Mean baseline depression scores		Mean endpoint depression scores		Response (%)		Remission (%)	
	Sham (s.d.)	Active (s.d.)	Sham (s.d.)	Active (s.d.)	Sham	Active	Sham	Active
Boggio et al. (2008)	21.9 (4.8)	21.1 (4.4)	21.2 (5.4)	13.8 (9.2)	20	38.1	0	23.8
Loo et al. (2010)	28.4 (4.4)	29.2 (4.9)	22.5 (8.1)	23.6 (7.7)	20	30	15	25
Loo et al. (2012)	29.5 (5)	30.4 (6)	24.9 (7.6)	20.6 (7.6)	12.9	12.1	3	3
Palm et al. (2012)	34.6 (5.4)	33 (7.3)	28.2 (8.8)	30.2 (7.4)	9	9	9	9
Blumberger et al. (2013)	24.1 (2.9)	24.9 (3.1)	18.1 (5.5)	18.8 (4.8)	9	7.7	9	7.7
Fregni et al. (2006)	25.9 (4.2)	23.5 (5)	22.5 (13.6)	9.8 (4.8)	0	77.7	–	–
Brunoni et al. (2013) (group analysis)	30.8 (5.3)	30.8 (5.8)	24.7 (8.6)	19.1 (12.2)	16.7	43.3	13.3	40
Brunoni et al. (2013) (factor analysis)	30.7 (5.6)	30.8 (6.4)	23.2 (11.1)	16.1 (10.8)	25	53.3	21.7	43.3

s.d.: standard deviation; NR: not reported. The column 'Depression scores' refers to the depression scale used for the primary outcome, as described in Table 1. All studies defined response as >50% depression improvement (from baseline to endpoint). Remission was defined as the absence of clinically relevant symptoms although different criteria were used in the the studies, as described in the main text. Two different analyses were performed, once at a time, for the Brunoni et al. study. In the 'group analysis' we compared the active-transcranial direct cranial stimulation (tDCS)/placebo *vs.* sham-tDCS/placebo, whereas in the 'factor analysis' we compared tDCS *vs.* sham-tDCS (regardless of drug use). Please refer to the main text for further details.

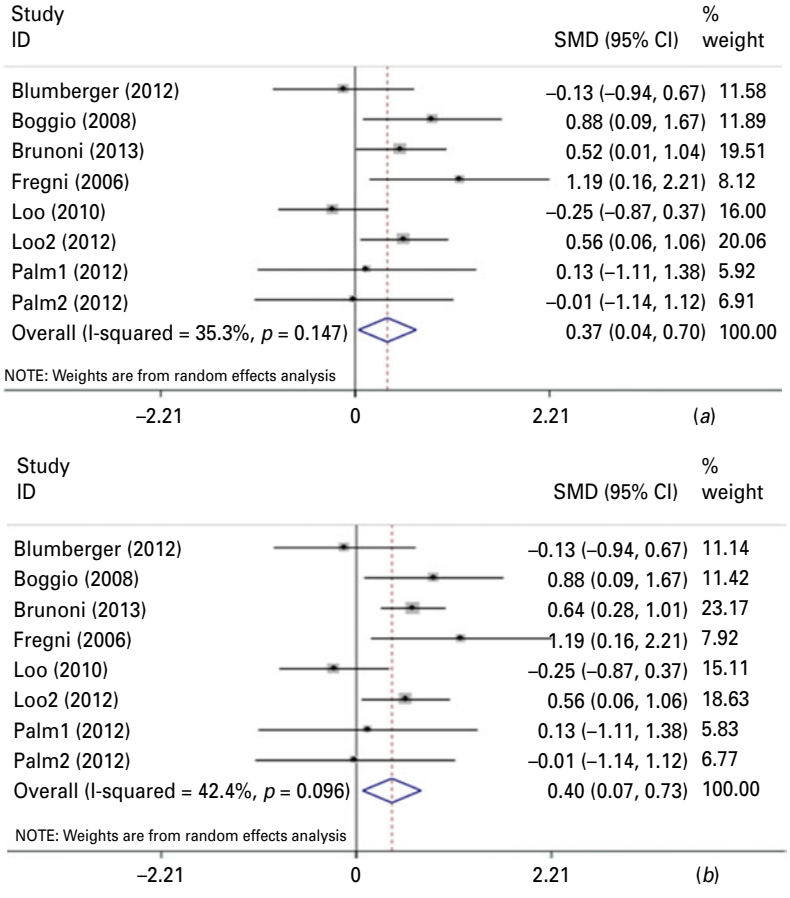

Fig. 2. Forest plot of effect sizes (Hedges' *g*) (*a*) used data from the comparison of active transcranial direct cranial stimulation (tDCS)/placebo *vs.* sham tDCS/placebo in Brunoni (2013); (*b*) used data from the comparison between active and sham tDCS in Brunoni (2013); CI, Confidence interval. The forest plot was used to graphically illustrate the relative strength of treatment effects for each selected study; the vertical line represents the overall effect. Study ID Study identification; SMD Standard mean deviation; CI Confidence interval

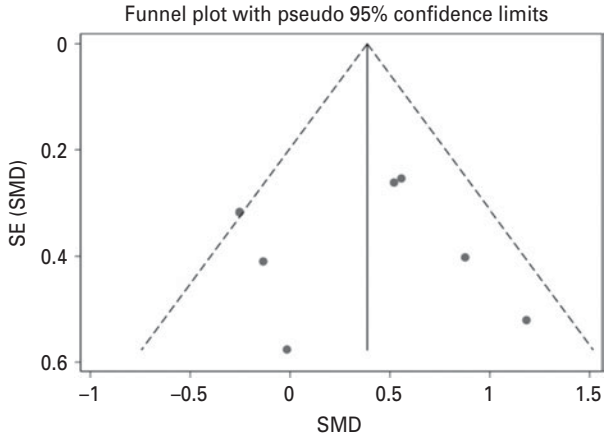

Fig. 3. Begg's Funnel Plot The funnel plot was used to evaluate the existence of publication bias. All studies are within the limits determined by the graphic, indicating low bias. SE Standard error; SMD Standard mean deviation

is indicative of a small to medium effect size. Importantly, we found that between-study heterogeneity and the risk of publication bias were low, and also that tDCS was an acceptable treatment, with similar dropout rates being observed in the active *vs.* sham groups. The effect size hereby found is comparable to those obtained by a recent repetitive transcranial magnetic stimulation (rTMS) meta-analysis (Schutter, 2009) (0.37 *vs.* 0.39, respectively), although it should be underscored that the rTMS meta-analysis reviewed a much larger number of studies than ours. This is reflected in the narrower confidence interval observed in the rTMS meta-analysis (0.25 to 0.54) compared to ours (0.04 to 0.7).

Previous tDCS meta-analyses (Kalu et al., 2012; Berlim et al., 2013) presented different results on the efficacy of tDCS for MDD, possibly owing to methodological discrepancies in the assessment of the primary outcome – Kalu et al. (2012) used a continuous outcome and found positive results whereas Berlim et al. (2013), which included the study of Blumberger et al. (2012) and used categorical outcomes, did not reveal a difference between active *vs.* sham tDCS. It should be underscored, though, that the non-significant results of the meta-analysis by Berlim et al. (2013) could have occurred owiong to the relatively low sample size addressed, since their results were marginally significant. In the present study, we analyzed both continuous and categorical (response and remission rates) measures as outcomes, all results showing that active tDCS was significantly superior to sham tDCS in depression treatment. It is important to underscore that response and remission rates represent more clearly clinical significance than continuous measures, although we opted to the latter as the measure of the primary outcome, as previously discussed. Nonetheless, future meta-analyses, whether pooling data from a larger number of tDCS clinical trials for depression, should attempt to report categorical primary outcomes, in accordance to meta-analyses from rTMS and antidepressant drug trials that focus on categorical definitions of remission.

Another characteristic of our meta-analysis is that we analyzed separately two datasets of Brunoni et al. (2013) study. This is because these authors employed a factorial design, presenting results for both the comparison of active tDCS/placebo *vs.* sham tDCS/placebo and active *vs.* sham tDCS groups (regardless of antidepressant use). We used 'Brunoni-group' as the main outcome as to compare the effects of active *vs.* sham tDCS, although similar results with the 'Brunoni-factor' analysis were found. Importantly, we did not analyze separately the group active-tDCS/sertraline from the Brunoni et al., study – this group presented the largest depression improvement in that study, being superior to all other groups (active-tDCS/placebo, sham-tDCS/sertraline, sham-tDCS/placebo). This group was not analyzed separately in the meta-analysis because it differs from the active tDCS groups from all other clinical trials, in which tDCS was either used as a monotherapy or as an add-on treatment in patients who were already taking antidepressant drugs (i.e. both active and sham groups in those trials were already on pharmacotherapy for several weeks in the beginning of the study) – conversely, the active-tDCS/sertraline group from Brunoni et al., had both interventions starting *simultaneously*, which might explain the faster, larger response observed. In this context, there is evidence showing that tDCS has its largest effects when associated with other interventions – for instance, Bolognini et al. (2011) showed that active tDCS associated with constraint-induced movement therapy (CIMT) presented larger behavioral and functional gains (*vs.* sham tDCS associated with CIMT) in patients with motor impairment after stroke, whereas, in another study with healthy volunteers, Bolognini et al. (2010) showed that active tDCS (*vs.* sham) over the posterior parietal cortex associated with a multisensory visual field exploration training enhanced the training-induced behavioral improvement. Indeed, in a case report of treatment-resistant depression, D'Urso et al. (2013) reported evidence of synergistic effects between tDCS and cognitive-behavior therapy (CBT). Also considering the portability of the device, future tDCS trials could consider to explore the effects of tDCS with CBT aiming to enhance the clinical efficacy of the technique for major depression.

Treatment-resistant depression was not identified as a predictor of response, in contrast with studies showing that interventions, such as pharmacotherapy (Trivedi et al., 2006), rTMS (Fregni et al., 2006d; Lisanby et al., 2009) and ECT (Sackeim et al., 2000) performed poorer in treatment-resistant samples. Interestingly, the trials of Boggio et al. (2008), Loo et al. (2012) and Brunoni et al. (2013) also reported a low/moderate degree of treatment resistance and significant effects of active tDCS, whereas the trials of Palm et al. (2012) and Blumberger et al. (2012) clearly reported a high degree of treatment resistance and non-significant effects of active *vs.* sham tDCS.

This might indicate that our meta-regression was underpowered to identify an association of treatment-resistant depression with clinical improvement. Indeed, meta-regressions are usually underpowered to identify predictors of response (Lambert et al., 2002), as no individual patient data are assessed.

The same issue might explain the lack of association between the number of tDCS sessions and clinical improvement. In fact, when this variable is assessed as a binary variable (i.e. $\leqslant$10 tDCS sessions *vs.* >10 tDCS sessions) in subgroup analysis there was a trend (p=0.09) suggesting that patients performing >10 tDCS sessions presented a superior improvement. This trend (p=0.09) was also observed for current electric charge, with higher charges associated with greater antidepressant effects. Nonetheless, further tDCS trials are needed to investigate the amount of tDCS sessions necessary to achieve optimal clinical response.

The included studies were also heterogeneous regarding the concomitant use of pharmacotherapy. For instance, only the studies of Boggio et al. (2008), Fregni et al. (2006a, b) and Brunoni et al. (2013) enrolled antidepressant-free patients at baseline – in all other studies, antidepressant drugs were being used at stable doses at trial enrollment. Moreover, all studies allowed the concomitant use of other psychotropics, notably benzodiazepines. Although it would be desirable to perform a complete washout of all pharmacotherapy regimens to assess the efficacy of tDCS as a monotherapy, this cannot always be performed for several reasons, such as ethical concerns of clinical deterioration prior to study entry. Although this issue might have lead to an overestimation of the impact of tDCS, it should be noted that doses were stable for several weeks at study entry and randomly distributed between active *vs.* sham groups.

Here, we should take into account the several studies assessing the impact of pharmacotherapy in tDCS-elicited cortical excitability (for a review see Stagg and Nitsche (2011)) – for instance, anodal tDCS effects are enhanced with the acute administration of citalopram (Nitsche et al., 2009), and initially delayed but later enhanced and longer after the acute administration of lorazepam (Nitsche et al., 2004). However, it is important to underscore that the transferability of the findings of these pharmacological studies, although revealing regarding the mechanisms of action of tDCS, is limited as these studies were conducted in healthy subjects after the acute administration of a single dose of a pharmacological drug. Other factors such as the underlying neuropsychiatric disorder, the concomitant use of medications and the application of daily tDCS for several days play an important role in clinical studies. In fact, a study in Parkinson's disease has shown that tDCS impact on cortical excitability is fundamentally different than studies in healthy subjects (Fregni et al., 2006c). To conclude, the impact of the association of different pharmacological drugs with daily, repeated tDCS sessions in depression must be evaluated in sham-controlled and open studies by assessing individual patient data regarding pharmacotherapy use and clinical outcome, along with other clinical variables that might influence treatment outcome.

Our meta-analysis is limited by the total number of trials enrolled and the total number of subjects evaluated (n=259), which were low. In fact, the effect size hereby found was small to medium (0.37) and significant; although the confidence interval range was relatively large, with the lower limit (0.04) close to non-significance. In addition, no randomized, controlled trials explored the effects of tDCS at the medium- and long-term range; therefore we could provide no information regarding its effectiveness beyond the acute treatment phase. Also, owing to the low total sample size and lack of statistical power, it was not possible to identify predictors of tDCS response. All together, theses issues highlight the need of further tDCS studies in order to elucidate its role for major depression.

Conclusion

Active tDCS was statistically superior to sham tDCS in the treatment of MDD, with a medium, significant effect size in both continuous (depression score change) and categorical (response and remission) outcomes. TDCS was also an acceptable intervention, with similar dropout rates in the active *vs.* sham groups. However, given the mixed results of previous trials and meta-analyses and the relatively small number of trials, there is not enough evidence to perform immediate treatment suggestion of tDCS in daily clinical practice; physicians and psychiatrists should therefore still rely on established interventions for depression treatment (such as pharmacotherapy and rTMS), whereas the results of larger, ongoing further phase III trials assessing broader samples are not yet available for clarifying the potential impact of tDCS in the treatment of MDD.

Supplementary material

For supplementary material accompanying this paper, visit http://dx.doi.org/10.1017/S1461145714000418

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Statement of Interest

All authors report no biomedical financial interests or potential conflicts of interest.

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