BJPsych | The British Journal of Psychiatry (2016) 208, 522–531. doi: 10.1192/bjp.bp.115.164715

Review article

Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data

André R. Brunoni, Adriano H. Moffa, Felipe Fregni, Ulrich Palm, Frank Padberg, Daniel M. Blumberger, Zafiris J. Daskalakis, Djamila Bennabi, Emmanuel Haffen, Angelo Alonzo and Colleen K. Loo

Background
Transcranial direct current stimulation (tDCS) is a non-pharmacological intervention for depression. It has mixed results, possibly caused by study heterogeneity.

Aims
To assess tDCS efficacy and to explore individual response predictors.

Method
Systematic review and individual patient data meta-analysis.

Results
Data were gathered from six randomised sham-controlled trials, enrolling 289 patients. Active tDCS was significantly superior to sham for response (34% *v.* 19% respectively, odds ratio (OR) = 2.44, 95% CI 1.38–4.32, number needed to treat (NNT) = 7), remission (23.1% *v.* 12.7% respectively, OR = 2.38, 95% CI 1.22–4.64, NNT = 9) and depression improvement (*B* coefficient 0.35, 95% CI 0.12–0.57). Mixed-effects models showed that, after adjustment for other predictors and confounders, treatment-resistant depression and higher tDCS 'doses' were, respectively, negatively and positively associated with tDCS efficacy.

Conclusions
The effect size of tDCS treatment was comparable with those reported for repetitive transcranial magnetic stimulation and antidepressant drug treatment in primary care. The most important parameters for optimisation in future trials are depression refractoriness and tDCS dose.

Declaration of interest
Z.J.D. has served on the advisory board for Sunovion, Hoffmann-La Roche Limited and Merck, and received speaker support from Eli Lilly.

Transcranial direct current stimulation (tDCS) is a novel non-pharmacological intervention consisting of administering direct, weak electric currents into the brain using electrodes placed on the scalp; these currents are able to induce neuromodulatory changes in cortical activity beyond the period of stimulation.[1] tDCS has been intensively investigated for the treatment of neuropsychiatric disorders in the past 15 years,[1] particularly major depression. Its antidepressant effects are premised on findings of relative left dorsolateral prefrontal cortex (DLPFC) underactivity (i.e. prefrontal dysfunction as indicated by reduced regional blood flow or glucose metabolism of the left DLPFC) that could be restored through anodal stimulation of this area, thus ameliorating depressive symptoms.[2] Randomised, sham-controlled clinical trials (RCTs) conducted hitherto have presented mixed results regarding its efficacy. Although recent meta-analyses suggest some efficacy when measuring depression symptoms using a continuous outcome[3–5] these meta-analyses were limited in their results as they used an aggregate data approach.[6] We aimed therefore to perform an individual patient data (IPD) meta-analysis. In contrast to aggregate data meta-analysis, an IPD approach uses the raw data of each participant collected from each study. IPD is more accurate in estimating the efficacy of an intervention as aggregate data meta-analyses present only summary estimates of efficacy. IPD meta-analysis is also superior to the aggregate data approach for obtaining predictors of treatment outcome, as the characteristics of each patient are assessed instead of the mean and frequency values obtained in the traditional aggregate data meta-analysis. Our objectives were twofold: (a) to provide precise estimates of tDCS efficacy based on continuous (depression improvement) and categorical (response and remission rates) outcomes and (b) to identify variables associated with tDCS efficacy.

Method

Systematic review

We first performed a systematic review according to the recommendations of the Cochrane Collaborative group and PRISMA guidelines.[7] The first two authors independently searched the literature and screened the search results. Differences were resolved by consensus. We also contacted experts in the field for unpublished articles and checked reference lists from recent systematic reviews. Our search was performed using MEDLINE, EMBASE, Web of Knowledge and Scopus databases (for the search strategy, please check the online supplement). We searched from the first date available until 1 January 2015. We only included randomised, sham-controlled trials with at least ten patients per arm (i.e. initial tDCS studies were not included) in which IPD were available. Case reports, series of cases, non-controlled trials, trial protocols, systematic reviews and meta-analyses were excluded.

Quality assessment

Methodological quality of each trial was assessed using two recognised checklists: (a) the Cochrane risk of bias tool[8] that evaluates studies on the basis of selection, performance, detection, attrition and reporting biases and; (b) the PEDro scale, in which ten criteria are used for internal validity.[9] The PEDro cut-offs are 9–10 (excellent); 6–8 (good); 4–5 (fair) and below 4 (poor).[9] If the information was unclear, the first and/or the last authors of each RCT were contacted to request additional data.

Outcome measures

Outcome measures were:

(a) clinical response, defined as ⩾50% improvement from baseline to end-point depression scores;

(b) remission, defined as Montgomery–Åsberg Depression Rating Scale (MADRS) ⩽10, Hamilton Rating Scale for Depression (HRSD)-17 ⩽7, HRSD-21 ⩽8 and HRSD-24 ⩽9, according to standardised criteria,[10–12] at end-point. This approach was used because even studies using the same scale differed regarding the remission cut-off point;

(c) depression improvement, estimated as the difference in *z*-scores (that was used for standardising depression symptoms and improvement across the studies, which used different scales) from baseline to end-point;

(d) acceptability (number of participants who dropped out in the active and sham groups at end-point).

Whether a study used more than one depression scale, we used the scale correspondent to the primary outcome. Moreover, when a study did not specify whether the MADRS or the HRSD was used as the primary outcome scale, we defined *a priori* that the HRSD scale would be used to calculate the outcome measures (response, remission and effect size). In fact, we could not use the same scale for our analyses because no single scale was unanimously used in all studies. For crossover (within-participants) RCTs, we considered only the data from the parallel (between-participants) phase. Finally, analyses were performed in the intention-to-treat samples, using the last observation carried forward for imputing missing data, which were considered to be missed at random.

Predictor variables – multivariate analysis

As one of the objectives of this trial, we assessed potential predictor (independent) variables. The main dependent variable was clinical response since it is more straightforward to interpret than depression improvement. Compared with remission, there were more patients presenting clinical response (hence, greater statistical power) and also remission presented heterogeneity of cut-offs. However, we also analysed depression improvement and remission separately. The collected predictor variables are described in the online supplement.

Data analysis

Baseline variables were described using mean and standard deviation for continuous variables and rates for categorical variables. Accordingly, values across groups were compared using one-way ANOVAs or the χ^2 test respectively. For the outcome measures we performed an IPD, aggregate data ('one-stage') meta-analysis. Although both 'one-stage' and 'two-stage' IPD meta-analyses are commonly used, we chose the one-stage analysis as being more suitable for exploring predictors of response (for reviews, see Simmonds *et al*[6] and Debray *et al*[13]). The effect size was measured in terms of odds ratios (ORs) for response and remission and difference in *z*-scores for assessing depression improvement. The *z*-score was used for standardising depression symptoms and improvement across the studies, which used different scales. The *z*-score of each participant was obtained at study baseline and end-point by subtracting the group mean from the individual depression score and then dividing by the group standard deviation. Finally, we estimated the number needed to treat (NNT) based on the odds ratios for response and remission. NNT is a measurement used to assess and compare the effectiveness of clinical interventions; the higher the NNT, the less effective one intervention is. In our study, NNT represents the number of patients with clinical depression it is necessary to treat (i.e. to receive active tDCS) for one additional patient to experience response or remission. NNT provides a value that is relative to the control.

Analyses were performed in Stata 12 using the commands *xtmixed, xtmelogit* and *ipdforest*, according to the recommendations of a recent guideline for performing IPD one-stage meta-analysis in Stata.[14] The variance–covariance structure was considered to be independent; this structure allows a distinct variance for each random effect within a random-effects equation and assumes all covariances to be zero. These analyses were used to estimate the effect size of active *v.* sham tDCS and to graph the forest plots.

For categorical and continuous outcomes, mixed-effects logistic and linear regression models were respectively used with 'study' as a random-effects variable and 'tDCS' (active/sham) nested in the variable 'study'. 'Study' contained six categories that are not ordinal and therefore were dummy coded to be included in the model. The study of Brunoni *et al*[15] was the reference group for this model since it contained the largest number of patients and provided the best power for comparisons. For the logistic regression of response, we had to collapse the studies in order to avoid non-convergence as the number of events was low – therefore the studies of Palm *et al*[16] and Blumberger *et al*[17] were collapsed into one meta-study. For the same reason, for the logistic regression of remission the studies of Palm *et al*,[16] Blumberger *et al*[17] and Bennabi *et al*[18] were collapsed into one meta-study.

To identify predictors of improvement, response and remission, we ran several univariate analyses, initially using only one predictor variable at a time, although forcing the variable 'study' into all models because it is potentially an important confounder, even though it may not necessarily be a significant predictor of response. The predictor analyses were only performed in patients receiving active tDCS (i.e. excluding the sham group). Predictors that were measured in all studies and presented a $P<0.1$ were further included in the multivariate analyses, in which initially all significant ($P<0.1$) predictors were imputed and then successively removed if they were not significant at a two-tailed P threshold of 0.05 (stepwise backward method); best fits were chosen based on the Wald statistics. Finally, to assess acceptability, we compared drop-out rates between active and sham tDCS using the random-effects odds ratio.

Results

Overview

Our MEDLINE search initially retrieved 116 potentially eligible studies. Of those, 107 were excluded based on their title and abstract and the other two after a full study assessment, as they did not match the eligibility criteria. Also, one reference was excluded because individual data were not available. Finally, six RCTs were included in our analysis.[15–20] We did not identify any studies in the other databases that were not also found in the MEDLINE search (see online supplement).

Study description and quality assessment

Table 1 describes the main eligibility criteria of the included studies; the risk of bias is shown in the online supplement. All trials were considered to be of low bias risk according to the Cochrane risk of bias tool and achieved maximum scores on the PEDro scale.

Table 1 Summary of the included studies[a]

	Palm *et al* (2012)[16]	Brunoni *et al* (2013)[15]	Loo *et al* (2012)[20]	Loo *et al* (2010)[19]	Blumberger *et al* (2012)[17]	Bennabi *et al* (2015)[18]
Design	RCT, crossover	2-arm RCT (tDCS, drug)	RCT	RCT	RCT	RCT
Clinicaltrials.gov (NCT)	00667680	01033084	00763230	00256438	01078948	01428804
Start date	Mar 2007	Mar 2010	Sep 2008	Jan 2006	Feb 2008	N/A
End date	Nov 2008	Feb 2011	Feb 2011	Dec 2008	Oct 2010	N/A
Main inclusion criteria	MDD	MDD, low suicide risk, antidepressant-free	MDD	MDD, ⩾3 years	Non-psychotic MDD	Refractory MDD
Depression cut-off	HRSD-24 ⩾18	HRSD-17 ⩾17	MADRS ⩾20	MADRS ⩾20	HRSD-17 ⩾21	MADRS ⩾25
Bipolar disorder	Allowed	Excluded	Allowed	Excluded	Excluded	Excluded
Main exclusion criteria	Other Axis I disorders, suicidality, neurological disorders	Other Axis I disorders, any Axis II disorders, neurological disorders	Other Axis I disorders, failure of ECT, neurological disorders	Other Axis I disorders, failure of ECT, neurological disorders	Other Axis I, any Axis II, neurological disorders, use of ACV	Neurological disorders, use of FGA, failure of ECT
Age range, years	36–79	18–65	23–78	19–65	24–62	30–81
Primary outcome measure	HRSD-24	MADRS	MADRS	MADRS	HRSD-17	HRSD-21
Intention-to-treat analysis	Yes	Yes	Yes	Yes	Yes	Yes
Sample size, *n*	22	120	60	40	24	23
Stimulation characteristics						
Device	Eldith DC	Chattanooga Ionto device	Eldith DC	Eldith DC	CX-6650	Eldith DC
Masking	Double-blind	Double single-blinded	Double-blind	Double-blind	Double-blind	Double-blind
Anode	F3	F3	pF3	F3	F3	F3
Cathode	RSO	F4	F8	RSO	F4	RSO
Number of sessions/frequency	10/once a day	12/once a day	15/once a day	5/every other day	15/once a day	10/twice a day
Weeks of stimulation	2	2 (+ 2 sessions every other week)	3	2	3	1
Current density, A/m^2	0.29/0.57	0.80	0.57	0.29	0.57	0.57
Current, mA	1–2	2	2	1	2	2
Session duration, min	20	30	20	20	20	30
Total charge, C	12–24	43.2	36	6	36	36
Total charge density, C/m^2	3248/6857	17280	10285	1714	10285	10285

RCT, randomised clinical trial; tDCS, transcranial direct current stimulation; MDD, major depressive disorder; HRSD, Hamilton Rating Scale for Depression; MADRS, Montgomery–Åsberg Depression Rating Scales; ECT, electroconvulsive therapy; ACV, anticonvulsant drugs; FGA, first-generation antipsychotic;
F3 or pF3, left dorsolateral prefrontal cortex; F4, right dorsolateral prefrontal cortex; F8/RSO, right supraorbital area.
a. For all studies, sham method consisted of a brief (5–60 s), initial period of active stimulation, followed by no stimulation during the rest of the session.

Table 2 Clinical and demographic characteristics of the included studies at baseline

	All patients (*n* = 289)	Palm *et al* (2012)[16] (*n* = 22)	Brunoni *et al* (2013)[15] (*n* = 120)	Loo *et al* (2012)[20] (*n* = 60)	Loo *et al* (2010)[19] (*n* = 40)	Blumberger *et al* (2012)[17] (*n* = 24)	Bennabi *et al* (2015)[18] (*n* = 23)
Women, *n* (%)[a]	180 (62.3)	14 (63.6)	82 (68.3)	28 (46.7)	22 (55.0)	20 (83.3)	14 (60.9)
Age, years: mean (s.d.)[a]	47.2 (13.4)	57.1 (11.6)	42.3 (12.7)	48.2 (12.4)	47.3 (11.3)	47.3 (10.7)	60.8 (13.3)
Characteristics of depression							
Age at onset, years: mean (s.d.)[a]	31.6 (14)	42.2 (12.4)	30.6 (13.2)	28.3 (12.4)	31.5 (14.1)	21.5 (12)	42.1 (13.5)
Bipolar disorder, *n* (%)[a]	11 (3.8)	2 (9.1)	0	8 (13.3)	0	0	1 (4.3)
Melancholic, *n* (%)	100 (34.6)	4 (18.2)	31 (25.8)	31 (51.7)	17 (42.5)	2 (8.3)	15 (65.2)
Atypical, *n* (%)[a]	81 (28.0)	1 (4.5)	58 (48.3)	N/A	N/A	2 (8.3)	2 (8.7)
Treatment-resistant depression, *n* (%)[a]	149 (51.6)	21 (95.5)	45 (37.5)	24 (40)	13 (32.5)	100	23 (100.0)
Failed trials, mean (s.d.)[a]	2.3 (2.4)	3.6 (1.8)	1.8 (2.3)	1.7 (1.9)	1.5 (1.9)	4.2 (2.3)	5.1 (1.8)
Past episodes, mean (s.d.)	5.5 (7.8)	7.9 (6.3)	5.3 (8.8)	N/A	N/A	5.4 (7.3)	4.2 (2.4)
Duration of current depressive episode, weeks: mean (s.d.)[a]	23.4 (36.9)	8.3 (12.3)	15.8 (18)	44.3 (61.1)	18.7 (16.5)	46.8 (54.1)	9.9 (6.2)
Anxiety disorder, *n* (%)[a]	123 (42.6)	5 (22.7)	70 (58.3)	9 (15.0)	21 (52.5)	5 (20.8)	13 (56.5)
Severe depression, *n* (%)	160 (55.4)	21 (95.5)	68 (56.7)	30 (50.0)	17 (42.5)	13 (54.2)	11 (47.8)
Treatments of the current depressive episode							
Psychotherapy, *n* (%)[a]	86 (29.8)	22 (100)	12 (10.0)	N/A	N/A	N/A	15 (65.2)
Electroconvulsive therapy use, *n* (%)[a]	12 (4.1)	6 (27.3)	2 (1.7)	0	0	4 (16.7)	0
Repetitive transcranial magnetic stimulation use, *n* (%)[a]	5 (1.7)	0	1 (0.8)	0	0	0	4 (17.4)
Tricyclic antidepressants, *n* (%)[a]	27 (9.3)	13 (59.1)	0	7 (11.7)	4 (10.0)	3 (12.5)	0
Selective serotonin reuptake inhibitors, *n* (%)[a]	66 (22.8)	16 (72.7)	0	12 (20.0)	11 (27.5)	4 (16.7)	23 (100)
Serotonin–noradrenaline reuptake inhibitors, *n* (%)[a]	35 (12.1)	2 (9.1)	0	19 (31.7)	5 (12.5)	9 (37.5)	0
Anticonvulsants, *n* (%)[a]	8 (2.8)	3 (13.6)	1 (0.8)	0	0	0	4 (17.4)
Antipsychotics, *n* (%)[a]	47 (16.3)	18 (81.8)	0	11 (18.3)	6 (15.0)	1 (4.2)	11 (47.8)
Benzodiazepines, *n* (%)[a]	56 (19.4)	10 (45.5)	23 (19.2)	1 (1.7)	0	8 (33.3)	14 (60.9)

N/A not available.
a. Variables in which groups were significantly different at baseline ($P < 0.01$).

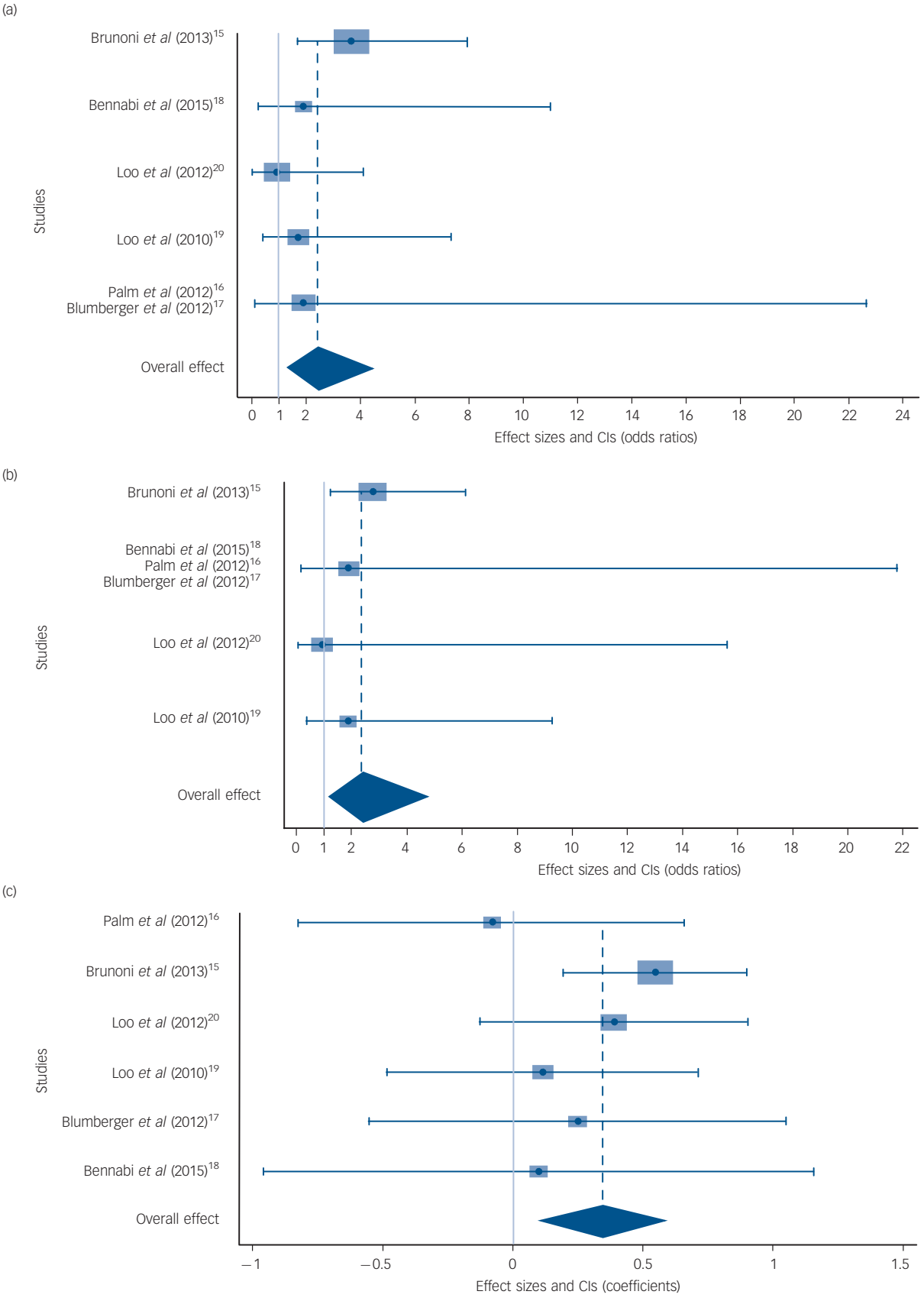


Fig. 1 Individual patient data meta-analysis comparing active *v.* sham transcranial direct current stimulation (tDCS) in terms of (a) response; (b) remission and (c) depression improvement.

Forest plot graphically illustrating the comparative efficacy of active with sham tDCS. For each study the relative strength of treatment effects is represented, the square represents the relative weight of each study, the vertical bar is the 95% confidence interval. The rhombus represents the overall effect. Values >1 and >0 *v.* <1 and <0 represent positive and negative effects of active *v.* sham tDCS for categorical and continuous outcomes respectively.

Main outcomes

Data from 289 patients were analysed. Their distribution across the six studies was significantly different for almost all baseline clinical and demographic variables (Table 2). The between-study heterogeneity was addressed as the variable 'study' was forced into all models.

Active tDCS was superior to sham for response (34% *v.* 19% respectively; OR = 2.44, 95% CI 1.38–4.32, $P = 0.002$), remission (23.1% *v.* 12.7% respectively, OR = 2.38, 95% CI 1.22–4.64, $P = 0.002$) and depression improvement ($\beta = 0.347$, 95% CI 0.12–0.57, $P = 0.002$). The NNTs for response and remission were, respectively, 7 (95% CI 4.04–20.7) and 9 (95% CI 5.2–63). The I^2 of all models were $\leqslant 2.5\%$, which are indicative of low heterogeneity (Fig. 1).

Predictors of clinical response

The variables 'use of psychotherapy', 'number of past episodes' and 'atypical depression' were not included in the predictor models because not all studies collected these data. Also, we could not explore the interaction between number of weeks of stimulation and frequency of sessions because of collinearity. The following predictors achieved the significance threshold in the univariate analyses and were included in the multivariate analyses: female gender, bipolar disorder, treatment-resistant depression and the tDCS characteristics session duration, number of sessions and tDCS dose (Tables 3 and 4).

In the multivariate analyses, the first models included the abovementioned predictors – although, for tDCS, each variable was imputed in a different model since they are redundant. In these first analyses, number of sessions was not significant, although session duration and tDCS dose were. Also, gender was not a significant predictor in both models and the variable bipolar disorder was excluded because of collinearity (caused by the low number of cases). Therefore, the final multivariate model for response included the variables treatment-resistant depression (Table 3) and tDCS dose/session duration (Table 4).

Predictors of remission and depression improvement

The only significant univariate predictors of remission were treatment-resistant depression, melancholia, session duration and tDCS dose (online supplement). It was not possible to identify a multivariate model for remission, since non-convergence was detected in most models, as the number of events was still low even after collapsing the studies.

For depression improvement, severe depression, treatment-resistant depression, bipolar depression, female gender, use of antidepressant drugs, sertraline augmentation, number of sessions and tDCS dose were significant univariate predictors in the linear model (online supplement). For the multivariate analyses, number of sessions/tDCS dose were analysed separately. Also, sertraline augmentation/use of antidepressant drugs were analysed separately as they presented complete separation (i.e. in the study in which sertraline was augmented to tDCS, patients were antidepressant free; whereas there was no drug augmentation in studies in which patients were using antidepressant drugs). Therefore, the first four models included initially all significant predictors. However, models including use of antidepressant drugs were further excluded since this variable did not achieve significance (P's > 0.27). Also, gender was further excluded in the remaining models because it did not achieve significance (P's > 0.08). Therefore, the final models included bipolar depression, treatment-resistant depression, severe depression, sertraline augmentation and number of sessions/tDCS dose (online supplement).

Table 3 Clinical and demographic variables: univariate and multivariate analyses of predictors of response to transcranial direct current stimulation (tDCS)

	Univariate analysis		Multivariate analysis	
Predictor and comparison	OR (95% CI)	*P*	OR (95% CI)	*P*
Gender, binary: women *v.* men	0.42 (0.17–0.99)	0.048		
Age, continuous	1.00 (0.97–1.03)	0.83		
Age at onset, continuous	0.99 (0.96–1.01)	0.35		
Bipolar disorder, no *v.* yes	6.60 (1.05–41.7)	0.04		
Melancholic, no *v.* yes	1.13 (0.48–2.62)	0.78		
Treatment-resistant depression, <2 *v.* ⩾2 trials	0.39 (0.16–0.97)	0.04		
Model 1			0.39 (0.15–1.00)[a]	0.05[a]
Model 2			0.37 (0.15–0.91)[b]	0.03[b]
Major depressive episode duration, <2 *v.* ⩾2 years	0.43 (0.13–1.45)	0.17		
Anxiety disorder, no *v.* yes	1.03 (0.46–2.3)	0.93		
Severe depression, no *v.* yes	1.38 (0.64–3.0)	0.4		
Electroconvulsive therapy use, no *v.* yes	0.53 (0.05–5.82)	0.61		
Repetitive transcranial magnetic stimulation use,[c] no *v.* yes	–	–		
Therapies, no *v.* yes				
Tricyclic antidepressants use	–	–		
Selective serotonin reuptake inhibitors use	1.40 (0.31–6.5)	0.66		
Serotonin–noradrenaline reuptake inhibitors use	1.53 (0.37–6.37)	0.55		
Antidepressant use	1.20 (0.33–4.4)	0.77		
Anticonvulsant use	3.64 (0.41–31.7)	0.24		
Antipsychotic use	1.45 (0.36–5.9)	0.6		
Benzodiazepines use	0.88 (0.31–2.5)	0.81		
Lithium use	2.03 (0.16–26.0)	0.59		
Sertraline augmentation	1.97 (0.7–5.54)	0.19		
Drug free	0.84 (0.32–2.2)	0.71		

a. Results are from Model 1 that includes treatment-resistant depression and session duration.
b. Results are for Model 2 that includes treatment-resistant depression and tDCS dose.
c. We were not able to analyse repetitive transcranial magnetic stimulation (rTMS) use as a predictor due to the low number of patients that received rTMS.

Table 4 Transcranial direct current stimulation (tDCS) characteristics: univariate and multivariate analyses of predictors of response to tDCS[a]

Predictor and comparison	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Cathode position, RSO *v.* F4	0.83 (0.05–15)	0.9		
Session duration, 20 min *v.* 30 min	13.44 (2.89–62.2)	0.001	16 (1.6–162)[b]	0.02[b]
Current dose, 1 mA *v.*2 mA	1.42 (0.28–13.1)	0.98		
Number of weeks of stimulation				
1 week	Reference			
2 weeks	1.71 (0.48–6)	0.4		
3 weeks	1.42 (0.06–33)	0.82		
Number of sessions, continuous (5–15)	1.44 (0.95–2.18)	0.09		
tDCS dose				
<36 C or <10285 C/m^2	Reference		4.9 (1.2–20.1)[c]	0.03[c]
36 C or 10285–14400 C/m^2	4.8 (0.53–42)	0.16		
43.2 C or 17280 C/m^2	27.4 (1.5–481)	0.024		

RSO, right supraorbital area; F4, right dorsolateral prefrontal cortex.
a. Number of sessions and number of weeks of stimulation are different variables because there were studies performing tDCS sessions once daily, twice daily or on alternated days. Please refer to the main text for details.
b. Results are from Model 1 that includes treatment-resistant depression and session duration.
c. Results are for Model 2 that includes treatment-resistant depression and tDCS dose.

Acceptability

The drop-out rates between active (10.1%) and sham (12.2%) groups were not significantly different (OR = 0.78, 95% CI 0.33–1.82; $P = 0.57$) (online supplement).

Discussion

Main findings and comparison with findings for other treatments

In this first IPD meta-analysis of tDCS as a treatment for acute depressive episodes, we collected data from 289 patients (147 and 142 in the active and sham groups respectively) from six RCTs. We found significant effect sizes of efficacy of active *v.* sham tDCS in terms of depression improvement, response and remission, with overall response and remission rates of active tDCS of 34% and 23% respectively and NNTs of 7 and 9. Our work has some strengths when compared with findings from aggregate data meta-analyses. For instance, using an IPD meta-analytic approach, we were able to provide more precise estimates of effect size than previous aggregate data meta-analyses. This approach also allowed us to use the same operational definition of response and remission for all studies, in contrast to aggregate data meta-analyses that used the definition provided by the study, limiting their generalisability. tDCS was also an acceptable treatment, as the drop-out rates between active and sham groups were not statistically different.

The NNT for response was similar to a Cochrane meta-analysis assessing the efficacy of antidepressant drug treatments in primary care,[21] which observed NNTs for response of 9 and 7 for TCAs and selective serotonin reuptake inhibitors (SSRIs), respectively. Another meta- analysis[22] reviewed 122 antidepressant drug trials published in the past 30 years and observed an NNT of 8 for antidepressant drug treatment in depression. Our findings are also in the same range as a recent active *v.* sham repetitive transcranial magnetic stimulation (rTMS) meta-analysis for depression ($n = 1371$) that found response and remission NNTs of 6 and 8 respectively.[23] In that study, the absolute rates of response and remission in the active group of rTMS (29.3% and 18.6% respectively) were similar to the rates observed in our study on tDCS. The absolute rate of tDCS response was also similar to that observed in the STAR*D trial, a multicentric, pragmatic antidepressant treatment study that enrolled up to 3000 patients.[24] Our findings indicates two potential applications for tDCS in the therapeutic arsenal for depression: in primary care settings and as a non-pharmacological, neuromodulatory therapy for depression. Another aspect corroborating the role of tDCS in primary care is its characteristics of low-cost, ease of use, portability and a benign profile of side- effects.[1] Given these results we discuss below potential factors that can influence response such as patient selection (best responders) and parameters of stimulation based on our multivariate regression models results.

Factors influencing response to tDCS

Treatment-resistant depression was unanimously associated with lower tDCS efficacy in all predictor models. This finding had already been found in a larger tDCS trial and its follow-up study,[15,25] although not detected in previous aggregate data meta-regressions, possibly because of lack of power. This finding is in line with outcomes observed for pharmacotherapy,[26] rTMS[27,28] and electroconvulsive therapy,[29] and further ratifies the notion that the optimal use of tDCS would be in primary care and other low-refractory sample settings. Conversely, tDCS protocols targeting refractory samples should be optimised, possibly using higher tDCS doses as its efficacy is lower in such samples.

tDCS dose constituted an important and independent predictor of better efficacy and it was also associated with greater improvement in active *v.* sham groups. The association of higher tDCS doses with treatment efficacy is in keeping with prior clinical trials in the field of non-invasive brain stimulation. For rTMS, for instance, the first studies employed a small number (5–10 days) of sessions, whereas pivotal studies performed 3–6 weeks of sessions.[30] A recent review[31] indicated an association between treatment efficacy of rTMS and more intensive protocols (for example days of stimulation and number of pulses). Nonetheless, previous aggregate data meta-analyses indicated either a lack of association[4] or a non-significant trend for a positive association between tDCS 'dose' and efficacy,[5] probably because this type of analysis is underpowered, compared with IPD meta-analysis, in identifying predictors of outcome.[6]

Importantly, there is no consensus regarding how to measure 'tDCS dose' in RCTs. We therefore employed different approaches,

considering session duration, current dose and number of sessions. When using charge density, a measurement that takes into account all these variables (current, duration and number of sessions), we estimated a tDCS dose that was an independent predictor for both continuous and categorical multivariate analyses. This finding is relevant for clinical application protocols as it indicates that there is an important dose-dependent effect for tDCS. On the other hand, we were not able to investigate the influence of electrode size (and thus the importance of current delivered per area) as only one study used 25 cm^2 (*v.* 35 cm^2) electrodes. In addition, we could not identify whether current dose or number of sessions were more important for determining depression improvement, as neither was significantly associated with the outcome, although a longer session duration (30 *v.* 20 min) was positively associated with clinical response. From a clinical perspective, however, it is possible that increasing the number of sessions is more feasible than increasing current dose and session duration, which might become uncomfortable and tiresome, respectively, for patients. In this context, there should be further investigation of the optimal frequency interval between tDCS sessions – a variable that may be critical in inducing optimal neuroplasticity,[1] and if missing treatment sessions can be replaced at the end of the protocol without harming clinical efficacy, as previously suggested.[32]

We found no interaction between concomitant pharmacotherapy and tDCS efficacy, in comparison with neurophysiological studies (for a review, see Stagg & Nitsche[33]) that showed influence of pharmacotherapy on tDCS effects. However, these studies tested a single drug dose timed with the administration of a single tDCS session in healthy volunteers and measured a surrogate outcome (motor cortical excitability), whereas the RCTs included in our analyses performed tDCS sessions over several days over the prefrontal cortex in participants with depression and with chronic use of pharmacotherapy. Therefore the neurophysiological findings described may not necessarily reflect what is taking place in our sample. Also, although antidepressant drug use was a significant univariate predictor of depression improvement in a previous naturalistic finding in 82 patients with depression,[34] this study was less controlled than the present RCTs and measured outcomes immediately after 5 days of stimulation. Nonetheless, sertraline augmentation was an independent predictor of depression improvement, reflecting the results of Brunoni *et al*[13] that showed that tDCS and sertraline simultaneously combined led to faster, greater depression improvement when compared with groups receiving only sertraline or only tDCS.

Bipolar depression was a univariate predictor of response and a multivariate predictor of depression improvement; however, the overall number of patients with bipolar disorder was low (3.8%) and, in fact, half of the RCTs did not include people with bipolar disorder, limiting the conclusions on tDCS efficacy. This highlights the urgent need for tDCS studies in bipolar disorder. Gender was also a univariate predictor of response. This finding can be explained by reasons such as: (a) all the RCTs used convenience samples – the recruited women could have presented with milder forms of depression than men – as usually women are more prone to spontaneously seek for medical care; (b) different antidepressant effects of tDCS according to gender, as observed in a recent rTMS meta-analysis for depression.[35] Importantly, gender was not a significant predictor after adjustment for other confounders, indicating that the role of gender in determining tDCS efficacy is less important compared with other variables such as depression refractoriness and tDCS dose. Finally, depression severity was an independent predictor of depression improvement. A previous antidepressant meta-analysis also observed that drugs are more effective in more severe depression.[36] Such greater effect can also be a statistical artefact associated with clinical trial design, as there is more room for improvement where baseline severity is high (i.e. regression to the mean).

Acceptability of treatment

We could not measure the frequency of individual adverse effects because this assessment varied among studies and different questionnaires were used. Hence, we used the frequency of drop-out as a proxy of tDCS acceptability, finding that active and sham groups presented similar drop-out rates. This indicates that tDCS is a tolerable and acceptable treatment for acute depression. Also, the collected adverse effects were mild and transient.

Follow-up studies

Our work focused on the efficacy of tDCS during an acute depressive episode. Two of the included RCTs[15,20] assessed relapse rates in tDCS responders during a long-term follow-up of 6 months. Both follow-up studies[25,37] presented similar findings regarding: (a) relapse rates of approximately 50% at the end of the follow-up; (b) treatment-resistant depression was a predictor of relapse and; (c) the decrease in tDCS regimen at month 3 was associated with an increase in relapse rates. Thus, an association between tDCS efficacy with treatment-resistant depression and tDCS dose was also observed in the continuation studies. Also, overall effectiveness of tDCS was poor. Therefore, further maintenance studies could assess whether more intensive tDCS treatment regimens – both in the acute and in the maintenance phases – could be associated with lower relapse rates at follow-up.

Strengths and limitations

Quality assessment revealed that studies used generally similar and acceptable methods of randomisation and masking. Regarding the sham method, the studies that used non-automated tDCS devices either observed that patients were not able to guess between active and sham tDCS[19,20] or found that the sham procedure was as effective as the gold-standard placebo-pill.[38]

We did not observe other types of bias in the included studies, although most of them included small sample sizes and were heterogeneous. This issue was addressed by including the variable 'study' as a random-effects variable.

Only results from the study by Brunoni *et al*[15] were significant when each study was analysed individually (Fig. 1), which is in line with the results observed in the corresponding clinical trials, excluding the continuous outcome of Loo *et al*[20] – significant in the original study (this occurred as different continuous outcomes were used in the original and in the present study – this strategy was employed to obtain an individual standard score). These discrepant findings occurred primarily because of the insufficient sample size that yielded non-significant findings in the original and in the present trials – conversely, the larger study by Brunoni *et al*[15] presented significant findings. This issue was at least partly addressed by the statistical approach of one-stage IPD meta-analysis that assesses the net effect size by pooling data from each participant. Nonetheless, this observation highlights the need for further, larger RCTs for tDCS in the treatment of acute depressive episodes. Another possibility is the different sample characteristics across these studies such as depression refractoriness and use of other medications that could have influenced the efficacy of tDCS. In this context, Nitsche *et al*[39] found that the SSRI citalopram enhanced the effects of anodal tDCS on motor cortical excitability measures. Thus, differences in medication may contribute to variation of antidepressant efficacy and the

pharmacotherapy–tDCS interaction needs to be further investigated in depression.

The studies also used distinct criteria for refractoriness, chronicity, response and remission; these issues were addressed by standardising the same operational criteria for all studies. Finally, IPD data from a potential included study[40] were not available. However, considering that its results were positive, our main results would not change; in fact, its inclusion would probably increase the observed effect size.

Implications

This first IPD meta-analysis expanded evidence that active tDCS is superior to sham tDCS in terms of depression improvement, clinical response and remission for an acute depressive episode. Our findings also suggest that tDCS presents similar efficacy to antidepressant drugs and rTMS, although the total number of studies is still small. Treatment-resistant depression and higher tDCS dosages were negatively and positively, respectively, associated with treatment response in univariate and multivariate models; upcoming trials can be thus optimised according to these parameters. Other variables, such as presence of bipolar disorder, severe depression, sertraline augmentation and female gender were also identified in some models and should be explored in further studies.

André R. Brunoni, MD, PhD, **Adriano H. Moffa**, BS, Interdisciplinary Center for Applied Neuromodulation, University Hospital & Service of Interdisciplinary Neuromodulation, Department and Institute of Psychiatry, Laboratory of Neurosciences (LIM-27), University of São Paulo, São Paulo, Brazil; **Felipe Fregni**, MD, PhD, Spaulding Neuromodulation Center, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, Massachusetts, USA; **Ulrich Palm**, MD, **Frank Padberg**, MD, PhD, Department of Psychiatry and Psychotherapy, Ludwig Maximilian University Munich, Munich, Germany; **Daniel M. Blumberger**, MD, **Zafiris J. Daskalakis**, MD, Temerty Centre for Therapeutic Brain Intervention and Campbell Family Research Institute, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Ontario, Canada; **Djamila Bennabi**, MD, **Emmanuel Haffen**, MD, Department of Clinical Psychiatry, Clinical Investigation Center 1431 Inserm, EA 481 Neurosciences, University Hospital of Besancon and FondaMental Foundation, Créteil, France; **Angelo Alonzo**, PhD, **Colleen K. Loo**, MD, School of Psychiatry, University of New South Wales, Black Dog Institute and St George Hospital, Sydney, Australia

Correspondence: André R. Brunoni, MD, PhD, Interdisciplinary Center for Applied Neuromodulation, Av. Professor Lineu Prestes, 2565, 3o andar, CEP 05508-000, São Paulo (SP), Brazil. Email: brunoni@usp.br

First received 3 Feb 2015, final revision 6 Jul 2015, accepted 12 Jul 2015

Funding

A.R.B. is supported by the following grants: 2013 NARSAD Young Investigator from the Brain & Behavior Research Foundation (Grant Number 20493), 2013 FAPESP Young Researcher from the São Paulo State Foundation (Grant Number 20911-5) and National Council for Scientific and Technological Development (CNPq, Grant Number 470904). A.R.B. also received equipment from the Soterix company. F.P. received grants from neuroConn GmbH, Ilmenau, Germany and Brainsway Inc, Jerusalem, Israel. C.L. has received research grant funding from the Australian National Health and Medical Council and the Stanley Medical Research Foundation, and equipment from the Soterix company. D.M.B. currently receives compensation from: the Centre for Addiction and Mental Health, Toronto, Ontario. D.M.B. also receives research support from the Canadian Institutes of Health Research and the US National Institute of Health (NIH). D.M.B. receives research support and in-kind equipment support from Brainsway Ltd for an investigator-initiated clinical trial and a sponsor-initiated clinical trial. D.M.B. receives in-kind equipment support from Tonika-Magventure for an investigator-initiated study. E.H. and D.B. received a grant from Lundbeck Foundation. Z.J.D. received research and equipment in-kind support for an investigator-initiated study through Brainsway Inc. This work was supported by the Ontario Mental Health Foundation (OMHF), the Canadian Institutes of Health Research (CIHR), the Brain and Behaviour Research Foundation and the Temerty Family and Grant Family and through the Centre for Addiction and Mental Health (CAMH) Foundation and the Campbell Institute.

References

1 Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul* 2012; **5**: 175–95.

2 Brunoni AR, Ferrucci R, Fregni F, Boggio PS, Priori A. Transcranial direct current stimulation for the treatment of major depressive disorder: a summary of preclinical, clinical and translational findings. *Prog Neuropsychopharmacol Biol Psychiatry* 2012; **39**: 9–16.

3 Kalu UG, Sexton CE, Loo CK, Ebmeier KP. Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. *Psychol Med* 2012; **42**: 1791–800.

4 Berlim MT, Van den Eynde F, Daskalakis ZJ. Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *J Psychiatr Res* 2013; **47**: 1–7.

5 Shiozawa P, Fregni F, Bensenor IM, Lotufo PA, Berlim MT, Daskalakis JZ, et al. Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. *Int J Neuropsychopharmacol* 2014; **17**: 1443–52.

6 Simmonds MC, Higgins JP, Stewart LA, Tierney JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clin Trials* 2005; **2**: 209–17.

7 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009; **6**: e1000100.

8 Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2.* (updated September 2009). The Cochrane Collaboration, 2009.

9 de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust J Physiother* 2009; **55**: 129–33.

10 Keller MB. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. *JAMA* 2003; **289**: 3152–60.

11 Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* 2003; **54**: 573–83.

12 Zimmerman M, Posternak MA, Chelminski I. Implications of using different cut-offs on symptom severity scales to define remission from depression. *Int Clin Psychopharmacol* 2004; **19**: 215–20.

13 Debray TP, Moons KG, Abo-Zaid GM, Koffijberg H, Riley RD. Individual participant data meta-analysis for a binary outcome: one-stage or two-stage? *PLoS One* 2013; **8**: e60650.

14 Kontopantelis E, Reeves D. A short guide and a forest plot command (ipdforest) for one-stage meta-analysis. *Stata J* 2013; **13**: 574–87.

15 Brunoni AR, Valiengo L, Baccaro A, Zanao TA, Oliveira AC, Goulart AC, et al. The sertraline versus electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. *JAMA Psychiatry* 2013; **70**: 383–91.

16 Palm U, Schiller C, Fintescu Z, Obermeier M, Keeser D, Reisinger E, et al. Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind, placebo-controlled study. *Brain Stimul* 2012; **5**: 242–51.

17 Blumberger DM, Tran LC, Fitzgerald PB, Hoy KE, Daskalakis ZJ. A randomized double-blind sham-controlled study of transcranial direct current stimulation for treatment-resistant major depression. *Front Psychiatry* 2012; **3**: 74.

18 Bennabi D, Nicolier M, Monnin J, Tio G, Pazart L, Vandel P, et al. Pilot study of feasibility of the effect of treatment with tdcs in patients suffering from treatment-resistant depression treated with escitalopram. *Clin Neurophysiol* 2015; **126**: 1185–9.

19 Loo CK, Sachdev P, Martin D, Pigot M, Alonzo A, Malhi GS, et al. A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. *Int J Neuropsychopharmacol* 2010; **13**: 61–9.

20 Loo CK, Alonzo A, Martin D, Mitchell PB, Galvez V, Sachdev P. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. *Br J Psychiatry* 2012; **200**: 52–9.

21 Arroll B, Elley CR, Fishman T, Goodyear-Smith FA, Kenealy T, Blashki G, et al. Antidepressants versus placebo for depression in primary care. *Cochrane Database Syst Rev* 2009; **3**: CD007954.

22 Undurraga J, Baldessarini RJ. Randomized, placebo-controlled trials of antidepressants for acute major depression: thirty-year meta-analytic review. *Neuropsychopharmacology* 2012; **37**: 851–64.

23 Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Psychol Med* 2014; **44**: 225–39.

24 Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med* 2006; **354**: 1231–42.

25 Valiengo L, Bensenor IM, Goulart AC, de Oliveira JF, Zanao TA, Boggio PS, et al. The sertraline versus electrical current therapy for treating depression clinical study (SELECT-TDCS): results of the crossover and follow-up phases. *Depress Anxiety* 2013; **30**: 646–53.

26 Trivedi MH, Fava M, Wisniewski SR, Thase ME, Quitkin F, Warden D, et al. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med* 2006; **354**: 1243–52.

27 Fregni F, Marcolin MA, Myczkowski M, Amiaz R, Hasey G, Rumi DO, et al. Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation. *Int J Neuropsychopharmacol* 2006; **9**: 641–54.

28 Lisanby SH, Husain MM, Rosenquist PB, Maixner D, Gutierrez R, Krystal A, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology* 2009; **34**: 522–34.

29 Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry* 2000; **57**: 425–34.

30 George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry* 2010; **67**: 507–16.

31 Lefaucheur JP, Andre-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol* 2014; **125**: 2150–206.

32 Zanao TA, Moffa AH, Shiozawa P, Lotufo PA, Bensenor IM, Brunoni AR. Impact of two or less missing treatment sessions on tdcs clinical efficacy: results from a factorial, randomized, controlled trial in major depression. *Neuromodulation* 2014; **17**: 737–42.

33 Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. *Neuroscientist* 2011; **17**: 37–53.

34 Brunoni AR, Ferrucci R, Bortolomasi M, Scelzo E, Boggio PS, Fregni F, et al. Interactions between transcranial direct current stimulation (tDCS) and pharmacological interventions in the major depressive episode: findings from a naturalistic study. *Eur Psychiatry* 2013; **28**: 356–61.

35 Kedzior KK, Azorina V, Reitz SK. More female patients and fewer stimuli per session are associated with the short-term antidepressant properties of repetitive transcranial magnetic stimulation (rTMS): a meta-analysis of 54 sham-controlled studies published between 1997–2013. *Neuropsychiatr Dis Treat* 2014; **10**: 727–56.

36 Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med* 2008; **5**: e45.

37 Martin DM, Alonzo A, Ho KA, Player M, Mitchell PB, Sachdev P, et al. Continuation transcranial direct current stimulation for the prevention of relapse in major depression. *J Affect Disord* 2013; **144**: 274-8.

38 Brunoni AR, Schestatsky P, Lotufo PA, Bensenor IM, Fregni F. Comparison of blinding effectiveness between sham tDCS and placebo sertraline in a 6-week major depression randomized clinical trial. *Clinical Neurophysiol* 2014; **125**: 298–305.

39 Nitsche MA, Kuo MF, Karrasch R, Wachter B, Liebetanz D, Paulus W. Serotonin affects transcranial direct current-induced neuroplasticity in humans. *Biol Psychiatry* 2009; **66**: 503–8.

40 Boggio PS, Rigonatti SP, Ribeiro RB, Myczkowski ML, Nitsche MA, Pascual-Leone A, et al. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *Int J Neuropsychopharmacol* 2008; **11**: 249–54.

EXTRA CONTENT ONLINE

Data supplement to Brunoni et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. Br J Psychiatry doi: 10.1192/bjp.bp.115.164715

Search strategy

1. MEDLINE (PubMed)

The following syntax was used, yielding 116 results:

((("depressive disorder" OR "treatment-resistant" OR "treatment resistant" OR "major depression")) AND ("direct current" OR "transcranial direct current stimulation" OR "tDCS”))), limited to 01/01/2015.

2. Embase

The following syntax was used, yielding 316 results:

'depressive disorder'/exp OR 'depressive disorder' OR 'treatment-resistant' OR 'treatment resistant' OR 'major depression'/exp OR 'major depression' AND ('direct current'/exp OR 'direct current' OR 'transcranial direct current stimulation'/exp OR 'transcranial direct current stimulation' OR 'tdcs') NOT [1-1-2015]/sd.

3. ISI - Web of Knowledge

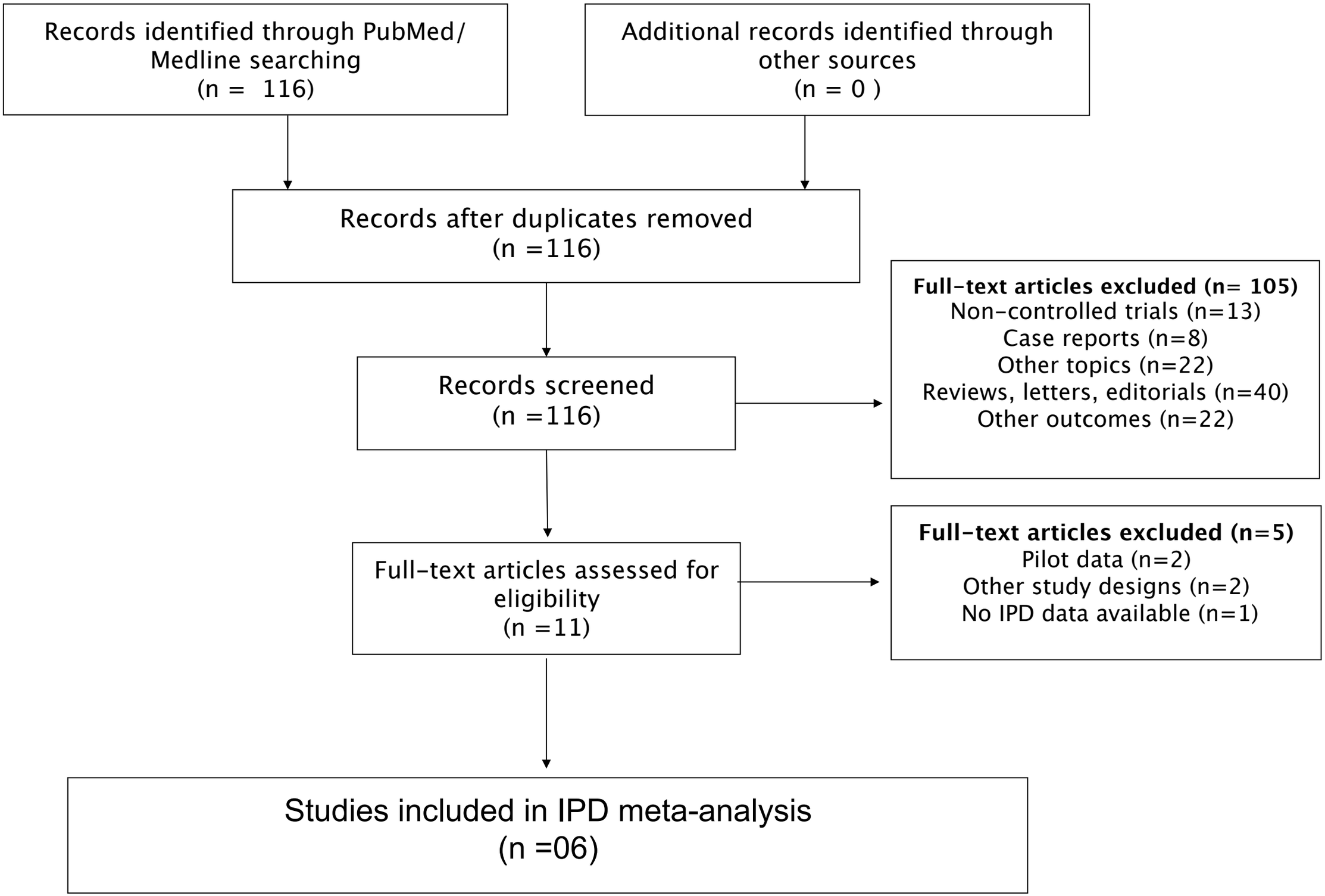
The following syntax was used, yielding 213 results:

TOPIC:(("depressive disorder" OR "treatment-resistant" OR "treatment resistant" OR "major depression") AND ("direct current" OR "transcranial direct current stimulation" OR "tDCS")) **Timespan:** 1864-2014.

4. Scopus

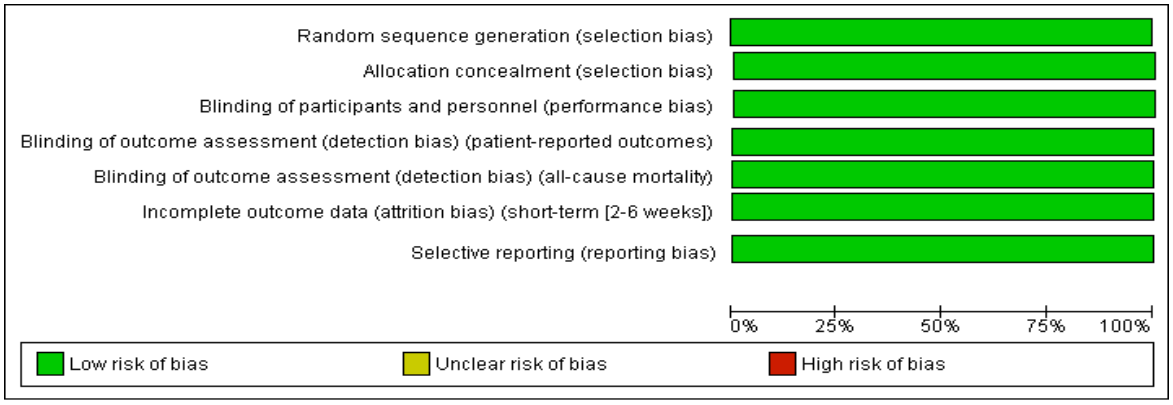
The following syntax was used, yielding 163 results:

TITLE-ABS-KEY ((**"depressive disorder"** OR **"treatment-resistant"** OR **"treatment resistant"** OR **"major depression"**) AND (**"direct current"** OR **"transcranial direct current stimulation"** OR **"tDCS"**)) AND PUBYEAR < **2015**


Records identified through PubMed/ Medline searching (n = 116)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n =116)
Records screened (n =116)
Full-text articles excluded (n= 105)
Non-controlled trials (n=13)
Case reports (n=8)
Other topics (n=22)
Reviews, letters, editorials (n=40)
Other outcomes (n=22)
Full-text articles assessed for eligibility (n =11)
Full-text articles excluded (n=5)
Pilot data (n=2)
Other study designs (n=2)
No IPD data available (n=1)
Studies included in IPD meta-analysis (n =06)

QUALITY ASSESSMENT

A) Quality assessment based on the Cochrane Handbook for Systematic Reviews of Interventions.



1) Bias risk assessment in the study of Loo et al. (2010)

Entry	Judgment	Support for judgment
Random sequence generation (selection bias)	Low risk.	Quote: “Subjects were stratified by age and gender and then randomly assigned to active or sham treatment groups
Allocation concealment (selection bias)	Low risk	Comment: allocation concealment confirmed by the authors
Blinding of participants and personnel (performance bias)	Low risk.	Quote: “with (...) subjects blind to treatment group assignment.”; Quote: “The switching on and off of the current was programmed into the stimulator and did not require intervention by the operator. The machine was placed behind the subjects’ heads so that they were unable to see the readout on the front panel of the stimulator..” Personnel blinding confirmed by the authors
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Low risk.	Quote:" with (...) subjects blind to treatment group assignment."
Blinding of outcome assessment (detection bias) (Mortality)	Low risk.	Quote: "All ratings were conducted by a psychiatrist who was blinded to treatment condition..."
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Low risk.	Quote: “Intention-to-treat last-observation carried-forward scores were used for the analyses" Comment: measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	N/A	Comment: work focused in the efficacy of tDCS during the acute phase of the major depressive episode

Selective reporting (reporting bias)	Low risk.	All clinical rating scales and cognitive tasks listed in Methods were reported.

2) Bias risk assessment in the study of Loo et al. (2012)

Entry	Judgment	Support for judgment
Random sequence generation (selection bias)	Low risk.	Quote: “participants were stratified by gender and age and randomly assigned by a computer-generated random sequence”
Allocation concealment (selection bias)	Low risk.	Quote: “The treatment assignment was indicated by a code on study treatment sheets, which were concealed from raters.”
Blinding of participants and personnel (performance bias)	Low risk	Quote: “ ...participants(...) masked to group allocation." Personnel blinding confirmed by the authors.
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Low risk.	Quote: “"...participants (...) masked to group allocation."
Blinding of outcome assessment (detection bias) (Mortality)	Low risk.	Quote: “"... raters masked to group allocation."
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Low risk.	Quote:" Intention-to-treat last observation-carried-forward scores were used for the analyses". Comment: measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	N/A	Comment: work focused in the efficacy of tDCS during the acute phase of the major depressive episode
Selective reporting (reporting bias)	Low risk.	All clinical rating scales and cognitive tasks listed in Methods were reported.

3) Bias risk assessment in the study of Palm et al. (2012)

Entry	Judgment	Support for judgment
Random sequence generation (selection bias)	Low risk.	Quote: “patients were randomized in two groups.”
Allocation concealment (selection bias)	Low risk.	Quote: “...using a PC-generated random number list”. Concealment confirmed by the authors.
Blinding of participants and personnel (performance bias)	Low risk.	Quote: “double blind”; “Two indistinguishable CE-certified programmable constant current DC-Stimulator were used for active and placebo tDCS. ” Personnel blinding confirmed by authors

Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Low risk.	Quote: “double blind”.
Blinding of outcome assessment (detection bias) (Mortality)	Low risk.	Quote: “rating scales and cognitive tests were administered by experienced raters blind to treatment conditions..."
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Low risk.	Quote: “Twenty patients completed the study, two dropped out because of personal reasons. The data of all 22 subjects were included in the analysis (last observation carried forward)."
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	N/A	Comment: work focused in the efficacy of tDCS during the acute phase of the major depressive episode
Selective reporting (reporting bias)	Low risk.	All clinical rating scales and cognitive tasks listed in Methods were reported.

4) Bias risk assessment in the study of Blumberger et al. (2012)

Entry	**Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk.	Quote: “subjects were randomly assigned using a computer-generated randomization list”
Allocation concealment (selection bias)	Low risk.	Quote: “...with the information stored on a centralized computer .”
Blinding of participants and personnel (performance bias)	Low risk	Quote: “with (...) subjects blind to treatment group allocation.”; Quote: “Only the treating clinician was aware of subjects’ treatment condition."
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Low risk.	Quote: “with (...) subjects blind to treatment group allocation.”
Blinding of outcome assessment (detection bias) (Mortality)	Low risk.	Quote:"...with clinical raters (...) blind to treatment group allocation."
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Low risk.	Quote: “analysis was conducted on an intention to treat basis." Comment: measures of key outcomes were obtained from more than 85% of the subjects initially allocated to groups
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	N/A	Comment: work focused in the efficacy of tDCS during the acute phase of the major depressive episode
Selective reporting (reporting bias)	Low risk	All clinical rating scales and cognitive tasks listed in Methods are reported.

5) Bias risk assessment in the study of Brunoni et al. (2013)

Entry	Judgment	Support for judgment
Random sequence generation (selection bias)	Low risk.	Quote: “A assistant not directly involved in other aspects of the trial performed a 1:1:1:1 permuted block randomization.”
Allocation concealment (selection bias)	Low risk.	Quote: “...the allocation was concealed using a central randomization method.”
Blinding of participants and personnel (performance bias)	Low risk.	Quote: “...patients were blinded to the treatment"; "..., because the nurses were not blinded to the intervention, their interaction with the participants was minimal"
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Low risk.	Quote: " The raters and patients were blinded to the treatment"
Blinding of outcome assessment (detection bias) (Mortality)	Low risk.	Quote: " The raters and patients were blinded to the treatment"
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Low risk.	Quote: "Analyses were conducted in the intention-to-treat sample according to last observation carried forward through the time points. Missing data were considered to be at random" Comment: measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	N/A	Comment: work focused in the efficacy of tDCS during the acute phase of the major depressive episode
Selective reporting (reporting bias)	Low risk.	All clinical rating scales and cognitive tasks listed in Methods were reported.

6) Bias risk assessment in the study of Bennabi et al. (2014).

Entry	Judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Quote: “subjects were randomly assigned using a computer-generated randomization list”
Allocation concealment (selection bias)	Low risk	Quote: “...with the information stored on a centralized computer to receive either active or sham tDCS."
Blinding of participants and personnel (performance bias)	Low risk	Quote: “Predefined codes assigned to either real or sham stimulation were used to start the stimulator and thus allowed for a double-blind study design."
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Low risk	Quote: “double blind”.

Blinding of outcome assessment (detection bias) (Mortality)	Low risk	Quote: "A trained, licensed neuropsychologist blinded to the patients' treatment group conducted a complete neuropsychological test battery ..."
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Low risk	Comment: measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Low risk	Comment: work focused in the efficacy o tDCS during the acute phase of the major depressive episode
Selective reporting (reporting bias)	Low risk	All clinical rating scales and cognitive tasks listed in Methods were reported.

B) Quality assessment based on the PEDro Scale.

PEDro scale	Palm (2012)	Brunoni (2013)	Loo(2012)	Loo(2010)	Blumberger(2012)	Bennabi (2014)
1 (Eligibility)	Y	Y	Y	Y	Y	Y
2	Y	Y	Y	Y	Y	Y
3	Y	Y	Y	Y	Y	Y
4	Y	Y	Y	Y	Y	y
5	Y	Y	Y	Y	Y	Y
6	Y	Y	y	Y	Y	Y
7	Y	Y	Y	Y	Y	Y
8	Y	Y	Y	Y	Y	Y
9	Y	Y	Y	Y	Y	Y
10	Y	Y	Y	Y	Y	Y
11	Y	Y	Y	Y	Y	Y
PEDro total score	**10**	**10**	**10**	**10**	**10**	**10**

Palm et al. (2012)

A1 - p.243, ¶1, ln.1-6: "Twenty-two in- and outpatients of the Department of Psychiatry at the Ludwig-Maximilians University, Munich, Germany (14 female, mean age 57 years, range 36-79), having a major depressive episode (DSM-IV criteria; based on a clinical interview by an experienced psychiatrist) were recruited."

A2 - p.243, ¶2, ln. 1-4: "Within a placebo-controlled cross-over design, patients were randomized in two groups (active/sham; sham/active) by the principal investigator (F.P.) using a PC-generated random number list."

A3 – confirmed by authors

A4 - p.247, ¶2, ln. 3-5: "Both groups were comparable in terms of demographic measures, clinical characteristics, and cognitive performance at baseline."

A5 - p.242, ¶2, ln. 5-6: "Patients, raters, and operators were blinded to treatment conditions."

A6 - p.246, ¶1, ln. 4-5: "All operators, tDCS trained MD or PhD students, were blind to treatment conditions."

A7 - p.246, ¶2, ln. 1-3: "The (…) rating scales and cognitive tests were administered by experienced raters blind to treatment conditions."

A8 - p.247, ¶3, ln. 2-4: "The data of all 22 subjects were included in the analysis (last observation carried forward [LOCF])."

A9 - p.247, ¶3, ln. 2-4: "The data of all 22 subjects were included in the analysis (last observation carried forward [LOCF])."

A10 - p.247, ¶3, ln. 4-8: "In the Active/Sham group baseline HAMD scores decreased by 16% during active tDCS and by 8% during sham treatment. In the Sham/Active group HAMD scores decreased by 12% during sham tDCS and by 14% during active treatment."

A11 - p.247, Table 2.

Brunoni et al. (2013)

B1 - p.385, ¶1, ln. 1-6:" We included patients with unipolar, nonpsychotic MDD per *DSM-IV* criteria and confirmed by psychiatrists using the Mini-International Neuropsychiatric Interview. Only those with a 17-item Hamilton Depression Rating Scale score greater than 17, with low suicide risk, and aged between 18 and 65 years were included."

B2 - p.384, ¶5, ln. 14-16:" A research assistant not directly involved in other aspects of the trial performed a 1:1:1:1 permuted block randomization…"

B3 - p.384, ¶5, ln. 16-17:"… the allocation was concealed using a central randomization method."

B4 - p.386, ¶3, ln. 3-4:" The groups were similar in clinical and demographic characteristics at baseline."

B5 - p.385, ¶4, ln. 5-7:" The raters and patients were blinded to the treatment, and contact between participants was avoided to enhance study blinding."

B6- NO

B7 - p.385, ¶4, ln. 5-7:" The raters and patients were blinded to the treatment, and contact between participants was avoided to enhance study blinding."

B8 - p.386, ¶4, ln. 1-2:" Nine patients dropped out within the first 2weeks and 103 patients (85.8%) completed the entire trial."

B9 - p.385, ¶10, ln. 3-5:" Analyses were conducted in the intention-to-treat sample according to the last observation carried forward through the time points."

B10 - p.386, Table 1.

B11 - p.386, Table 1.

Loo et al. (2012)

C1 - p.53, ¶1, ln. 1-7: "Sixty-four participants with a DSM-IV major depressive episode and with a score of >=20 on the Montgomery–Asberg Depression Rating Scale (MADRS) gave informed written consent and were enrolled as out-patients. Diagnosis was based on a structured assessment using the Mini-International Neuropsychiatric
Interview (MINI) and confirmed in a clinical interview by a study psychiatrist."

C2 - p.53, ¶3, ln.1-3: "Participants were stratified by gender and age and randomly assigned by a computer-generated random sequence to active (n = 33) or sham (n = 31) treatment."

C3 - p.53, ¶3, ln. 6-8: "The treatment assignment was indicated by a code on study treatment sheets, which were concealed from raters.

C4 - p.54, ¶3, ln.1-2: "The only significant difference between the active and sham groups at baseline was higher CORE scores for the active group."

C5 - p.53, ¶3, ln. 9-10: "…with participants and raters masked to group allocation."

C6 – blinding confirmed by authors

C7 -p.53, ¶3, ln. 9-10: "…with participants and raters masked to group allocation."

C8 - p.55, Fig. 1

C9 - p.53, ¶7, ln.4-5: "Intention-to-treat last-observation-carried-forward scores were used for the analyses…"

C10 - p.55, Table 2

C11 - p.55, Table 2

Loo et al. (2010)

D1 - p.2, ¶3, ln. 1-9:" Forty subjects with unipolar DSM-IV major depressive episode of up to 3 yr duration and a score >=20 on the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) were enrolled as outpatients. The diagnosis was based on a structured assessment using the MINI (MINI International Neuropsychiatric Interview; Sheehan et al. 1997) and confirmed in a clinical interview by a study psychiatrist…"

D2 - p.2, ¶6, ln. 1-3:" Subjects were stratified by age and gender and then randomly assigned to active or sham treatment groups."

D3 - confirmed by authors

D4 - p.4, ¶4, ln. 1-2:" There were no significant differences between active and sham treatment groups at baseline…"

D5 – blinding of all patients confirmed by authors

D6 – blinding of all therapists confirmed by authors

D7 -p.3, ¶1, ln. 4-6:" All ratings were conducted by a psychiatrist who was blinded to treatment condition…"

D8 - p.3, Fig.1

D9 - p.4, ln. 2-3:" Intention-to-treat last-observation-carried-forward scores were used for the analyses…"

D10 - p.6, Table 2

D11 - p.6, Table 2

Blumberger et al. (2012)

E1 - p.2, ¶5, ln. 5-13:" All subjects had a diagnosis of unipolar Major Depressive Disorder without psychotic features and were experiencing a Major Depressive Episode, as confirmed by the Structured Clinical Interview for the DSM-IV(SCID-IV). Subjects were required to have a score of >=21 on the 17-item Hamilton Rating Scale for Depression (HRSD-17).Subjects were required to meet stage II criteria on the Thase Scale for treatment- resistance (failure to achieve remission or inability to tolerate two trials of an antidepressant from separate classes;"

E2 - p.3, ¶1, ln. 1-4:"… subjects were randomly assigned using a computer-generated randomization list with the information stored on a centralized computer to receive either active or sham tDCS."

E3 – confirmed by authors.

E4 - p.3, ¶8, ln. 1-3:" The subjects' baseline clinical and demographic characteristics are summarized in Table1. There were no clinically important differences between groups."

E5 - p.3, ¶1, ln. 7-8:" … with clinical raters and subjects blind to treatment group allocation."

E6 – blinding confirmed by authors.

E7 -p.3, ¶1, ln. 7-8:" … with clinical raters and subjects blind to treatment group allocation."

E8 - p.4, Fig. 1

E9 - p.3, ¶6, ln. 1-2:" … and the analysis was conducted on an intention to treat basis."

E10 - p.5, Table 2

E11 - p.5, Table 2

Bennabi et al. (2014)

F1-p.2, ¶3, ln. 1-8:" Twenty-four patients (18 females, 6 males, mean 61.8 ± 16.3 years) meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for unipolar depression were recruited from the psychiatric wards of the university hospital of Besançon (France). Patients were required to have a score P25 on the Montgomery

Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and to meat at least stage II treatment resistant criteria (Montgomery and Asberg 1979; Rush et al., 2003)."

F2- p.2, ¶4, ln. 4-7:" Following completion of baseline clinical measures, subjects were randomly assigned using a computer-generated randomization list with the information stored on a centralized computer to receive either active or sham tDCS."

F3- concealment confirmed by authors

F4- p.3, ¶3, ln. 3-11:" Demographic characteristics did not differ across the treatment groups for age ($t21 = 0.09$, $p = 0.93$), gender ($z = 1.33$, $p = 0.09$) or educational level ($t21 = 1.72$, $p = 0.18$). Statistical analyzes revealed no difference at baseline between active and sham stimulations groups in depression severity (HDRS: $t21 = 0.66$, $p = 0.51$; MADRS: $t21 = 1.72$, $p = 0.1$; BDI: $t21 = 0.25$, $p = 0.8$), anxiety level (STAI-A: $t21 = 0.78$, $p = 0.44$: STAI-B: $t21 = 0.25$, $p = 0.81$), psychomotor retardation (SRRS: $t21 = 0.49$, $p = 0.63$) and all cognitive performances (Table 2: $ps > 0.05$)."

F5- p.2, ¶5, ln. 11-13:" Predefined codes assigned to either real or sham stimulation were used to start the stimulator and thus allowed for a double-blind study design."

F6- p.2, ¶5, ln. 11-13:" Predefined codes assigned to either real or sham stimulation were used to start the stimulator and thus allowed for a double-blind study design."

F7- blinding of all assessor confirmed by authors

F8- p.3, ¶3, ln. 12-13:" One patient experienced mania and was subsequently withdrawn from the trial."

F9- confirmed by authors

F10- p.3, ¶2, ln. 1-7:" Concerning our primary outcome (HDRS 21) the mixed model revealed no significant differences between the two groups ($F(2,28) = 0.37$, $p = 0.69$) (Fig. 1a). The score decreased from 40% and 45.6% in active and sham groups respectively. ANCOVA showed no

significant effect of the main factor ‘time’ in both rating scales at T2 (HDRS p = 0.17; MADRS: p = 0.35), T3 (HDRS p = 0.08; MADRS: p = 0.18) or T4 (HDRS p = 0.80; MADRS: p = 0.85).”

F11- p.3, Fig.1.

PREDICTOR VARIABLES

a) *Demographic variables*: gender (binary) and age (years, continuous);

b) *Depression characteristics*: age of onset (years, continuous); bipolar depression (binary); melancholic depression (binary); atypical depression (binary) and presence of any concomitant anxiety disorder (binary). Treatment-resistant depression (<2 vs. ≥2 adequate failed antidepressant trials); recurrent depression (≤5 vs. >5 previous depressive episodes); chronic depression (≤2 vs. >2 years of length of the current depressive episode) and severe depression (MADRS ≤30 vs. >30 or HDRS ≤24 vs. >24 according to the study primary outcome measure) were also handled as binary.

c) *Treatment of the current depressive episode,* in which the binary variables employed were: ECT (electroconvulsive therapy) and rTMS (repetitive transcranial magnetic stimulation) use in the present episode; and concomitant psychotherapy, SSRI (selective serotonin reuptake inhibitor), TCA (tricyclic antidepressant), SNRI (serotonin-noradrenaline reuptake inhibitor), anticonvulsant drug, lithium, antipsychotic and benzodiazepine use. In addition, simultaneous augmentation with sertraline was included as a predictor variable, considering the factorial design of Brunoni et al. (13).

d) *tDCS treatment:* cathode position (F4 vs. right supraorbital area); session duration (binary, 20 vs. 30 min); current dose (binary, 1 vs. 2mA); number of completed sessions (continuous); number of weeks of stimulation (1, 2 or 3 weeks) and the interaction of this variable with frequency of the sessions (every other day; once a day or twice a day); total charge (in Coulombs, C) and total charge density (in C/m^2)[1]. For

[1] Total Charge (C) = Dose (A) * session duration (sec) * number of sessions; Total Charge Density (C/m^2) = Total Charge / electrode size (m^2)

these two last variables, as they were not normally distributed, they were arranged in three groups according to its percentile distribution. Moreover, only Brunoni et al. used 25 cm^2 (vs. 35 cm^2) electrodes, which lead to "total charge" and "total charge density" stratifying into the same subjects. Therefore, we considered "total charge" and "total charge density" representing a "tDCS dose", further classifying this variable into three levels: (i) <36C or <10285 C/m^2; (ii) 36C or 10285 – 14400 C/m^2 and; (iii) 43.2C or 17280 C/m^2.

Supplementary Table – Univariate analyses of predictors of remission and depression improvement (difference in z-scores) to tDCS.

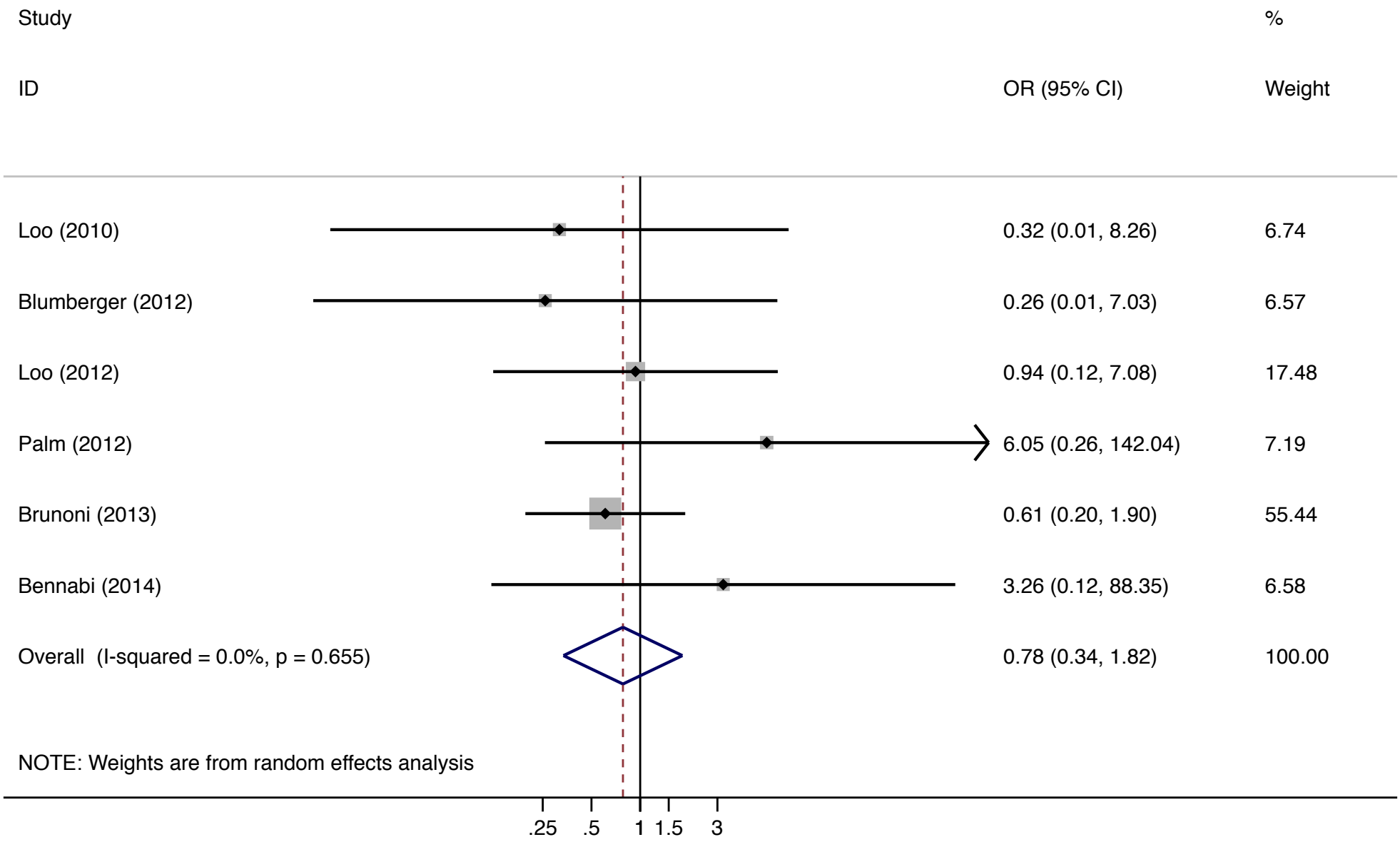
		Remission		Difference in z-scores	
Predictor	Comparison	OR	*p*	β (SE)	*p*
Clinical and demographic variables					
Gender (binary)	Fem vs. Male	0.5 (0.18-1.35)	0.17	-0.34 (0.16)	0.03
Age (continuous)	Continuous	0.99 (0.96-1.02)	0.51	<0.01 (<0.01)	0.91
Age of onset	Continuous	1 (0.96-1.03)	0.96	<0.01 (<0.01)	0.37
Bipolar disorder	No vs. Yes	--	--	0.98 (0.36)	<0.01
Melancholic	No vs. Yes	0.43 (0.17-1.05)	0.06	-0.17 (0.16)	0.29
TRD	<2 v ≥2 trials	0.4 (0.15-1.11)	0.08	-0.42 (0.17)	0.02
MDE duration	<2 v ≥ 2 y	0.28 (0.06 - 1.35)	0.11	-0.33 (0.2)	0.11
Anxiety Disorder	No vs. Yes	0.89 (0.36 - 2.1)	0.78	0.21 (0.16)	0.2
Severe depression	No vs. Yes	1 (0.43 - 2.37)	0.98	0.52 (0.15)	<0.001
ECT use	No vs. Yes	--	--	0.39 (0.36)	0.28
rTMS use	No vs. Yes	--	--	-0.75 (0.56)	0.17
Therapies					
TCA use	No vs. Yes	--	--	-0.16 (0.34)	0.96
SSRI use	No vs. Yes	1.3 (0.23 - 6.8)	0.78	0.4 (0.27)	0.13
SNRI use	No vs. Yes	2.05 (0.38 - 10.9)	0.4	0.15 (0.23)	0.52
AD use	No vs. Yes	1.56 (0.3 - 8.1)	0.59	0.4 (0.22)	0.06
ACV use	No vs. Yes	--	--	0.42 (0.5)	0.41
AP use	No vs. Yes	1.37 (0.19 - 9.7)	0.75	0.33 (0.28)	0.22
BZD use	No vs. Yes	0.6 (0.2 - 2.1)	0.47	-0.24 (0.25)	0.33
Lithium use	No vs. Yes	--	--	0.07 (0.42)	0.86
Sertraline augmentation	No vs. Yes	1.16 (0.41 - 3.3)	0.78	0.46 (0.23)	0.04
Drug free	No vs. Yes	1.33 (0.45 - 3.9)	0.6	-0.32 (0.2)	0.11
TDCS characteristics					
Cathode Position	RSO vs. F3	1.17 (0.1 - 13.6)	0.89	0.28 (0.28)	0.32
Session duration	20m vs. 30m	7.8 (1.2 - 51.5)	0.03	0.11 (0.27)	0.67
Current dose	1mA vs. 2mA	0.96 (0.09 - 10.4)	0.98	0.05 (0.55)	0.93
Number of weeks of stimulation	1 week	Ref			Ref
	2 weeks	0.75 (0.6 - 9.6)	0.83	0.28 (0.28)	0.32
	3 weeks	0.05 (0.01 - 1.31)	0.08	0.16 (0.36)	0.64
N of Sessions	Continuous (5 to 15)	1.05 (0.83 - 1.33)	0.64	0.21 (0.05)	<0.001
TDCS dose	Low	Ref		Ref	
	Medium	0.46 (0.1 - 1.83)	0.27	1.03 (0.46)	0.02
	High	5.5 (1.8 - 16.4)	<0.001	1.7 (0.43)	<0.001

OR, odds ratio; CI, confidence interval; SE, standard error; TRD, treatment-resistant depression; MDE, major depressive episode; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin-noradrenaline reuptake inhibitors; AD, antidepressant; tDCS, transcranial direct current stimulation; Ref, reference. Number of sessions and number of weeks of stimulation are different variables because there were studies performing tDCS sessions once daily, twice daily or in alternated days. Please refer to the main text for details.

Supplementary Table – Multivariate analyses of predictors of depression improvement to tDCS.

Variable	Difference in z-scores		
	β	SE	p
Model 1. Bipolar disorder, TRD, severe depression, sertraline augmentation and number of sessions.			
Bipolar Disorder	0.77	0.3	0.01
TRD	-0.51	0.14	<0.001
Severe Depression	0.55	0.13	<0.001
Sertraline augmentation	0.45	0.19	0.03
N of sessions	0.21	0.04	<0.001
Wald = 88.1 (p<0.001)			
Model 2. Bipolar disorder, TRD, severe depression, sertraline augmentation and tDCS dose.			
Bipolar Disorder	0.81	0.3	0.02
TRD	-0.48	0.14	0.001
Severe Depression	0.51	0.13	0.02
Sertraline augmentation	0.48	0.19	0.01
TDCS "dose"	0.78	0.18	<0.001
Wald = 85.9 (p<0.001)			

TRD, treatment-resistant depression.


Study
ID
OR (95% CI)
%
Weight
Loo (2010)
0.32 (0.01, 8.26)
6.74
Blumberger (2012)
0.26 (0.01, 7.03)
6.57
Loo (2012)
0.94 (0.12, 7.08)
17.48
Palm (2012)
6.05 (0.26, 142.04)
7.19
Brunoni (2013)
0.61 (0.20, 1.90)
55.44
Bennabi (2014)
3.26 (0.12, 88.35)
6.58
Overall (I-squared = 0.0%, p = 0.655)
0.78 (0.34, 1.82)
100.00
NOTE: Weights are from random effects analysis
.25
.5
1
1.5
3

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4/5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5/6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7/8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9/10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10/11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11/12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12/15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16/17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data

André R. Brunoni, Adriano H. Moffa, Felipe Fregni, Ulrich Palm, Frank Padberg, Daniel M. Blumberger, Zafiris J. Daskalakis, Djamila Bennabi, Emmanuel Haffen, Angelo Alonzo and Colleen K. Loo

BJP 2016, 208:522-531.
Access the most recent version at DOI: 10.1192/bjp.bp.115.164715