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A Systematic Review on the Acceptability and Tolerability of Transcranial Direct Current Stimulation Treatment in Neuropsychiatry Trials

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation investigated as a treatment for several neuropsychiatric disorders. Notwithstanding tDCS-induced adverse events (AEs) are considered to be low and transient, systematic review analyses on safety and tolerability of tDCS derive mostly from single-session studies.
Objective: To investigate the tolerability (rate of AEs) and acceptability (rate of dropouts) of tDCS.
Methods: Systematic review and meta-analysis of tDCS randomized, sham-controlled trials in healthy or neuropsychiatric adult samples from the first date available to March 9, 2016. We only included parallel studies performing at least 5 tDCS sessions. An adapted version of CONSORT guidelines for reporting harms outcomes was used to evaluate AE reporting.
Results: Sixty-four studies (2262 participants) were included. They had a low risk of publication bias and methodological bias for the items assessed. Dropout rates in active and sham tDCS groups were, respectively, 6% and 7.2% (OR = 0.82 [0.59–1.14]). However, almost half of studies reported no dropouts and only 23.4% reported its reasons; when reported, the most frequent reasons were AEs and protocol violation. A tolerability meta-analysis was not performed, as most studies did not report AEs. The quality of AEs reporting was also limited, particularly in smaller studies and stroke studies.
Conclusions: Although overall dropout rate was low and similar in active and sham groups, studies did not adequately describe AEs. An updated questionnaire and guidelines for assessment of AEs in tDCS trials are proposed in order to standardize the reporting of AE in the field.

Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique based on the application of a weak, direct electric current over the scalp, thereby modifying brain activity and inducing neuroplasticity according to the montage of the apparatus and stimulation parameters [1]. This method has been increasingly used in the treatment of several psychiatric and neurologic disorders [2] as it presents appealing characteristics for use in clinical practice, such as ease of use, portability and low cost.

From a clinical perspective, not only efficacy of a given intervention but also its tolerability and acceptability are critical aspects. A single session of tDCS seems to be well-tolerated; with side effects that are usually mild and short-lived [3]. However, repeated tDCS (tDCS applied over several days, as in clinical trials) studies have not sufficiently explored the impact of adverse events (tolerability) in treatment discontinuation (acceptability). For instance, although tDCS is a technique usually considered to be devoid of serious adverse events (AEs), reports of treatment-emergent mania have been described in depression clinical trials [4]. Also, AEs might increase and tolerability decreases with repeated sessions. For

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instance, it is conceivable that the risk of skin burn increases with the number of sessions, as reported in some studies (e.g. Refs. 5 and 6), as small lesions in one session may lead to subsequent increased risk in the subsequent sessions. Finally, it is also possible that mild AEs, e.g. tingling, become easier to be detected with repeated sessions and thus may affect blinding. The rate and frequency of AE can also vary according to current intensity/density, session duration, electrode positioning, clinical characteristics, and other factors; such information is important to be collected in order to design controlled trials and better sham methods. Although some studies report safety especially related to a single session of tDCS, there has been no recent assessment of tolerability and acceptability of tDCS associated with repeated sessions.

Therefore, our aim was to perform a systematic review and meta-analysis to investigate the tolerability and acceptability of tDCS in clinical trials. Acceptability was measured as the percentage of participants that dropped out of the study due to all causes (i.e., attrition rate). Tolerability herein refers to the rate of AEs. Our hypotheses were that active and sham arms would present similar acceptability and tolerability rates. Moreover, as our earlier meta-analysis evaluating AEs in tDCS studies (mostly single-session) found that almost half of 209 included tDCS studies did not describe AEs [3], we aimed to verify whether AEs are adequately reported in tDCS clinical trials. To this end, we used the CONSORT (Consolidated Standards of Reporting Trials) guideline [7] and the specific CONSORT guidelines for harms reporting (hereby referred as CONSORT-harms) [8]. These guidelines were proposed due to the consequences of poor-quality reporting of randomized clinical trials (RCTs) and aim to standardize and improve the reporting of these trials, particularly regarding their design, randomization and blinding methods, statistical analysis, and outcome reporting. The CONSORT-harms are an extension of the original CONSORT guidelines to improve reporting of AEs in RCTs.

Methods

Study selection

A systematic review and meta-analysis according to the recommendations of the Cochrane group was conducted, and the present report follows PRISMA guidelines [9]. Two authors (LVMA and FG) performed independent systematic reviews and data extraction. Discrepancies were resolved by consensus with the corresponding author (ARB) consulted if necessary.

For the literature search, we screened the PubMed/MEDLINE database using keywords corresponding to tDCS, RCTs, and the investigated conditions. We also contacted experts in the field and looked for references in recent published tDCS reviews (Table 1). Finally, we also searched EMBASE, Google Scholar and ISI Web of Knowledge databases.

We screened for references from the first date available to March 9, 2016. We adopted the following inclusion criteria: (1) manuscripts written in English; (2) randomized, sham-controlled, parallel trials; (3) studies reporting dropouts and adverse effects, or that provided data upon request; (4) original articles that reported tDCS effects in adults (≥18 years old); (5) trials with an intervention of at least 5 sessions of tDCS over 2 weeks (i.e., 5 sessions applied at least every other weekday); (6) parallel studies.

Data extraction

The following variables were extracted according to a structured checklist previously elaborated by the authors: (1) metadata (i.e. authorship, publication date, region etc.); (2) demographics (sample size, age, percentage of females); (3) methods (study design, clinical condition, rating scale); (4) characteristics of the tDCS protocol (intensity of the current; time period of stimulation; current

Table 1
Table chart of the included studies.

Condition(s)	Keyword(s)	Ref obtained	Excluded after reading title/abstract	Full-text assessed	Excluded (after assessing full-text)	Included	Other sources	Total
Schizophrenia	"schizophrenia"	19	14	5	1	4	1 [10]	5
Depression	"depress*"	148	137	11	2	9	0	9
Substance abuse disorders	smoking OR tobacco OR cannabis OR marijuana OR alcohol OR cocaine OR crack	64	53	11	7	4	0	4
Anxiety disorders, PTSD, OCD and Eating disorders	anorexia OR bulimia OR "binge eating" OR "obsessive compulsive" OR "anxiety" OR "PTSD" OR "post-traumatic stress disorder"	54	54	0	0	0	0	0
Healthy volunteers	"healthy[ti]"	52	50	2	1	1	1 [11]	2
Epilepsy	"epilepsy" OR "seizure" OR "convuls*"	26	21	4	3	1	0	1
Fibromyalgia	"fibromyalgia"	15	10	5	2	3	0	3
Migraine	"migraine" OR "headache"	28	24	4	4	0	0	0
Tinnitus	"tinnitus"	15	11	4	1	3	0	3
Multiple Sclerosis	"multiple sclerosis"	12	9	3	0	3	0	3
Movement disorders	"Dystonia" OR "Parkinson's" OR "Parkinson" OR "ataxia"	24	19	5	3	2	0	2
Neurodegenerative disorders	"Alzheimer" OR "Alzheimer's" OR "Dementia" OR "Mild Cognitive Impairment" OR "Neurodegenerative"	23	18	5	2	3	0	3
Stroke	"stroke"	166	102	64	43	21	0	21
Pain	"Chronic pain" or "neuropathic pain"	70	57	13	5	8	0	8
Total		**715**	**579**	**135**	**74**	**61**	**0**	**64**

The table shows the number of references obtained when the syntax ("tDCS" OR "brain polarization" OR "electric stimulation" OR "Electric Polarization" OR "direct current") AND ("randomized" OR "randomised") AND ("sham" OR "placebo") AND each keyword(s) were searched in PubMed/MEDLINE in March 9, 2016. "Ref obtained" describes all references obtained, the following columns describe the number of references that were excluded after reading title/abstract, that were full-text assessed and that were excluded after this step. In a few cases, additional references were obtained from other sources, such as the reference lists of recent articles and reviews (e.g. Refs. 2, 4, and 12–19). Main causes of exclusion after reading title/abstract were: (a) other study designs (case reports, series of cases, non-controlled trials, absence of a sham group); (b) other methods of brain stimulations; (c) studies in animals; (d) other types of publications, such as systematic reviews, meta-analysis and editorial; (e) duplicated data; (f) studies in children and adolescents; (g) other reasons. Main causes of exclusion after assessing the full-text were: (a) single-session studies; (b) trials that performed less than 5 days of tDCS in 2 weeks; (c) trials that performed tDCS in a frequency lower than every other day.

density; number of sessions); (5) number of individuals in each group (active and sham); (6) acceptability (rates of treatment discontinuation for all causes) in the active and sham tDCS groups at study endpoint and in which moment of the study the dropouts had occurred; (7) AEs as reported by the included studies.

Outcome measures

Our primary outcomes were acceptability and tolerability of tDCS. For the secondary outcomes, we verified whether clinical and demographic variables influenced the primary outcomes.

Quality assessment

We assessed methodological quality of each trial using the Cochrane risk of bias tool. The following biases were assessed: (1) randomization; (2) allocation; (3) control group/sham method; (4) blinding of participants and personnel; (5) blinding of raters (Supplementary Material S2). We also verified whether the studies adopted the CONSORT guideline [7].

CONSORT guidelines for harms reporting

In order to verify whether AEs were adequately reported in the included articles, we used the CONSORT-harms [8]. This guideline contains 10 recommendations for adequate reporting of AEs. Based on these initial recommendations (as some recommendations describe more than one procedure), we adapted the guideline to a checklist containing 11 items (Supplementary Material S1) Data were extracted independently by two authors (LBR and ARB) and disagreements were resolved by consensus.

Statistical analysis

All analyses were conducted with Stata 12 (Statacorp, College Station, TX, USA). We used the most protracted follow-up date in each trial. We calculated a pooled estimate of the odds ratios (OR) in the individual studies using a random-effect model according to the Mantel and Haenszel method. For studies that presented zero events in one or both arms, we used a continuity correction of 0.5 [20]. This approach is employed as the OR is the proportion of two odds (events/no-events) and if one cell presents "zero" events, the calculation is not possible. However, such approach tends to be conservative as it incorporates trials where no events were observed [21]. Therefore, we: (1) also calculated the risk difference (RD, which is the difference between the risks of presenting the event in the active compared to the sham group), as it can be calculated even when there are no events in either group and (2) performed another meta-analysis excluding studies with zero events.

All results are presented with the 95% confidence interval (95% CI). For each analysis, heterogeneity was assessed using the chi-squared-based Q test and I-squared index (I^2) [22]. Funnel plot and the Egger test were used to assess the potential presence of publication bias and sensitivity analysis verified the influence of each study on the net results by sequentially excluding one study at a time. Finally, meta-regressions and subgroup analyses were used to explore the influence of each clinical and demographic variable on the outcome – only one variable was meta-regressed at a time.

Meta-analysis of tDCS tolerability was not performed due to the low number of studies fully reporting adverse outcomes. Therefore, for this outcome, we explored the quality of AE reporting according to a checklist based on CONSORT-harms. For each article, we estimated the percentage of the items attended. After that, we performed one-way analyses of variance (ANOVAs) tests or single linear regressions to explore the association of quality of AE reporting with other variables collected from the included studies.

Results

Literature search

Out of 715 initially retrieved references, 64 RCTs (n = 2262 participants) were included (Table 1)

Characteristics and quality assessment of included RCTs

Studies were generally small (M = 35.7 SD = 24.4 subjects) and gender was balanced. The mean (SD) age of participants was 52.4 (14.1) years. Most studies (77.5%) employed 2 mA currents, used 20-min protocols (61.2%) and performed 10 (38.8%) or less than 10 (44.9%) sessions (Tables 2 and 3).

Quality assessment revealed that most studies presented a low risk of randomization bias (59.3%), allocation concealment bias (56.2%), blinding of participants bias (92.1%), and blinding of raters bias (82.8%). Most studies (83.6%) adequately described the sham method (Supplementary Material S2). Only 5 studies reported using the CONSORT guidelines [49,76,77,81,83] and 5 studies, while not reporting the use of the CONSORT guidelines in the text, used the CONSORT flowchart [68,70,72,75,85].

Acceptability

There were 76 out 1262 (6%) and 69 out of 952 (7.2%) participants that dropped-out of the studies in the active and sham groups, respectively. This difference was not statistically significant (OR = 0.82 [0.59–1.14], p = 0.25), and between-study heterogeneity was low ($\chi^2 = 13.11$, p = 1, $I^2 = 0\%$) (Fig. 1). The funnel plot showed that studies were distributed evenly around the center of the plot, suggesting a low risk of publication bias (Supplementary Material S3). The Egger test was also not significant (p = 0.59). Moreover, sensitivity analysis found that the exclusion of no particular study from the analysis seemed to influence the outcome (data not shown).

Analysis performed using RD (0.000 [–0.017 to 0.017], p = 0.99) also indicated that active and sham treatments were equally acceptable. Importantly, there were 32 (50.8%) reporting zero dropouts. These studies had lower sample sizes than non-zero-cell studies (mean, SD of 29.4 (14.7) vs. 41.2 (29.4), respectively, p = 0.048). They did not differ in other characteristics such as mean age, gender, study region, clinical diagnosis and others. Dropout rates when excluding zero-cell studies were 11.36% and 13.5% for active and sham groups, respectively. This difference was not statistically significant (OR = 0.81 [0.56–1.18], p = 0.28).

As only 15 studies (23.4%) reported the reasons for dropouts, we were not able to perform a meta-analysis, but only a descriptive analysis of the data. The frequency was similar when considering AEs (4.1% vs. 3.7%), protocol violation (3.5% vs. 0.9%), inefficacy (0.3% vs. 0.5%) and other reasons (3.2% v. 3%), respectively to sham and active groups. (Supplementary Material S4)

We performed subgroup analyses regarding clinical diagnosis. We found no differences in acceptability for analyzed groups: pain (OR = 0.65 [0.3–1.44]); stroke (OR = 0.89 [0.44–1.81]); major depression (OR = 0.74 [0.4–1.35]); other neurologic disorders (OR = 0.93 [0.34–2.57]) and other psychiatric conditions (OR = 0.95 [0.38–2.38]). Also, meta-regressions revealed that sample size, age, percentage of females, current, treatment duration, current density, and number of sessions did not significantly influence acceptability (p's > 0.37).

Table 2
Characteristics of the included studies (neurologic disorders).

Study	N	Age (years)	Gender	Region	Current (mA)	Duration (min)	Number of sessions	% AE items reported	Drop-out rate (active)	Drop-out rate (sham)
Stroke										
Bolognini [23]	14	46.7	64.28	Italy	2	40	10	27.3	0.00	0.00
Hesse [24]	96	64.9	38.54	Germany	2	20	30	27.3	1.56	0.00
Kim [25]	20	57.8	27.77	Korea	2	20	10	27.3	15.38	0.00
Lee [26]	64	61.3	43.75	Korea	2	20	15	0	7.14	9.09
Lindenberg [27]	20	55.8	25	USA	1.5	30	5	0	0.00	0.00
Shigematsu [28]	20	65.8	35	Japan	1	20	10	0	0.00	0.00
Wu [29]	90	47.6	24.44	China	1.2	20	20	18.2	0.00	0.00
You [30]	33	66.6	42.85	Korea	2	30	10	18.2	33.33	41.67
Geroin [31]	30	62.7	23.33	Italy	1.5	7	10	0	0.00	0.00
Khedr [32]	40	58.3	35	Egypt	2	25	6	0	0.00	0.00
Rossi [33]	50	68.2	48	Italy	2	20	5	18.2	0.00	0.00
Fusco [34]	14	58.4	54.54	Italy	1.5	10	10	0	28.57	14.29
Sattler [35]	20	65	30	France	1.2	13	5	0	0.00	0.00
Yang [36]	16	71	37.5	Korea	1	20	10	0	11.11	14.29
Kumar [37]	14	74.9	50	USA	2	30	5	9	0.00	0.00
Yun [38]	45	62.7	55.5	Korea	2	30	15	9	0.00	0.00
Mortensen [39]	16	63.1	43.7	Denmark	1.5	20	5	63.6	0.00	12.50
Picelli [40]	30	62.5	26.66	Italy	2	20	10	18.2	0.00	0.00
Rocha [41]	21	58.43	28.57	Brazil	1	09 ou 13	12	0	0.00	0.00
Chang [42]	24	62.8	37.5	Korea	2	10	10	0	0.00	0.00
Meinzer [43]	40	23.9	60	Germany	1	20	5	45.4	0	0
Fibromyalgia										
Fregni [44]	32	53.4	100	Brazil	2	20	5	63.6	4.55	0.00
Valle [45]	41	54.8	100	Brazil	2	20	10	27.3	0.00	0.00
Fagerlund [46]	50	48.6	93.7	Norway	2	20	5	91	4.00	4.00
Neurodegenerative disorders										
Benninger [47]	25	64	36	USA	2	20	8	9	0.00	0.00
Khedr [48]	34	69.7	44	Egypt	2	25	10	9	0.00	0.00
Suemoto [49]	40	80	62.5	Brazil	2	20	6	63.6	10.00	0.00
Doruk [50]	18	61	33.3	USA	2	20	10	45.4	0.00	0.00
Chronic pain										
Souto [51]	20	51.95	75	Brazil	2	20	5	72.3	0.00	20
Kim [52]	72	61.5	58.33	Korea	2	20	5	36.4	16.67	16.67
Volz [53]	20	37.5	65	Germany	2	20	5	36.4	0.00	0.00
Brietzke [54]	28	55.21	25	Brazil	2	20	5	9	7.00	14.00
Oliveira [55]	32	24.65	90.62	Brazil	2	20	5	0	0.00	0.00
Luedtke [56]	135	44.49	46.66	UK	2	20	5	36.4	0.00	0.00
Choi [57]	24	56.9	57.14	Korea	2	20	5	45.4	6	25
Soler [58]	40	45	22.5	Spain	2	20	10	45.4	5	10
Multiple sclerosis										
Mori [59]	20	41.15	60	Italy	2	20	5	0	0.00	0.00
Iodice [60]	20	42	75	Italy	2	20	5	9	0.00	0.00
Mori [61]	19	44.8	57.89	Italy	2	20	5	0	0.00	0.00
Tinnitus										
Shekhawat [62]	40	59.2	10	New Zealand	2	20	5	9	0	0
Teismann [63]	34	44.1	.	Germany	2	30	5	0	8.70	0.00
Forogh [64]	22	48.22	36.36	Italy	2	20	5	9	0.09	0.09
Primary progressive aphasia										
Cotelli [65]	16	66.9	63	Italy	2	25	10	0	0.00	0.00
Epilepsy										
Li [66]	37	44.6	38.9	USA	2	20	5	54.5	4.50	14.20

Table shows the sample size (N), mean age, percentage of females (gender), study region, current intensity, duration, number of sessions, percentage of adverse events reported according to a 11-item checklist elaborated according to CONSORT-harms [8], and the drop-out rate in active and sham groups of each study.

Tolerability

Some RCTs described different tDCS AEs; however, most studies did not mention AEs (n = 14); reported "no AEs" (or similar terms); or did not numerically describe AEs. In the remainder, there was a large variation of AE frequency across studies – e.g., skin redness varied from 5% [71] to 96% [75] (Table 4). For these reasons, we were unable to use meta-analytic techniques to evaluate tDCS tolerability.

According to our 11-item checklist based on CONSORT-harms, studies complied with only 23.5% (SD = 24) of the recommendations. One-way ANOVA revealed a significant difference between study diagnosis, with stroke studies complying significantly less ($p < 0.05$) (11.7% SD = 15) than depression (31.3% SD = 28) and pain (42.1% SD = 26.4) studies. Linear regressions revealed that larger studies and with more females were associated to a higher percentage of items attended ($p < 0.01$) and no association with publication year, age, current, current density, treatment duration, number of sessions, and total dropout rate ($p's > 0.1$). We also compared studies that presented low risk of bias in all criteria evaluated according to the Cochrane recommendations (n = 30) vs. other studies (n = 34), finding that the former presented a higher percentage of items attended than the latter (M = 30% SD = 26 vs. M = 17 SD = 21, respectively, $p = 0.02$).

Discussion

This systematic review included all available tDCS RCTs performed in adult samples that used a parallel design and applied at

Table 3
Characteristics of the included studies (psychiatric disorders/healthy volunteers).

Study	N	Age (years)	Gender	Region	Current (mA)	Duration (min)	Number of sessions	% AE items reported	Drop-out rate (active)	Drop-out rate (sham)
Schizophrenia										
Fitzgerald [67]	24	23.2	37.5	Australia	2	20	15	27.3	0.00	0.00
Brunelin [68]	30	38	26.66	France	2	20	10	0	0.00	0.00
Frohlich [69]	26	41.69	15.38	USA	2	20	5	36.4	0.00	0.00
Gomes [10]	15	38.5	26.67	Brazil	2	20	10	0	0.00	12.50
Smith [70]	37	45	24.4	USA	2	20	5	72.3	26.32	16.67
Major depressive disorder										
Boggio [71]	40	49.4	67.5	Brazil	2	20	10	45.4	0.00	0.00
Blumberger [72]	24	47.3	83.33	Canada	2	20	15	54.5	15.38	9.09
Fregni [73]	18	46.4	61.11	Brazil	1	20	5	0	0.00	0.00
Loo [74]	40	47.3	55	Australia	1	20	5	36.4	5.00	20.00
Loo [75]	64	48.2	46.44	Australia	2	20	15	45.4	21.21	16.13
Brunoni [76]	120	42	68	Brazil	2	30	18	81.8	11.67	16.67
Brunoni [77]	40	44	29.72	Brazil	2	30	10	9	40.00	58.82
Segrave [78]	27	40.4	37.0	Australia	2	24	5	0	5.56	0.00
Bennabi [79]	24	60	62.5	France	2	30	10	9	8.33	0.00
Substance dependence										
Boggio [80]	27	27.2	27	Brazil	2	20	5	27.3	15.38	14.29
Klauss [81]	35	44.8	3	Brazil	2	13	5	9	5.88	5.56
Conti [82]	13	29	15.4	Brazil	2	20	5	0	14.29	50.00
Batista [83]	36	30.4	0	Brazil	2	20	5	54.5	0.00	0.00
Healthy volunteers										
Martin [84]	60	22.66	42.30	Australia	2	30	10	36.4	14.29	12.00
Meinzer [11]	40	23.9	60	Germany	1	20	5	45.4	0.00	0.00

Table shows the sample size (N), mean age, percentage of females (gender), study region, current intensity, duration, number of sessions, percentage of adverse events reported according to a 11-item checklist elaborated according to CONSORT-harms [8], and the drop-out rate in active and sham groups of each study.

least 5 stimulation sessions. Quality assessment revealed that studies were of good methodological quality, presenting an overall low risk of bias. Further analyses revealed that there was no indication of publication bias and that no single outlier study influenced our estimates. Meta-analysis on acceptability revealed that active tDCS was as acceptable as sham, since these interventions presented non-significantly different rates of all-cause treatment discontinuation. This finding was confirmed in additional meta-analysis that estimated risk difference, and estimated OR excluding "zero-cell" studies. Also, no particular clinical and demographic variable was associated with our outcome measures. However, we could only provide a descriptive data analysis to the reasons for dropout, as this was reported in only 23.4% of studies. Moreover, we were unable to quantitatively (and reliably) estimate tolerability, as less than one-third of studies fully described AEs. The quality of AE reporting was very low, and, as we discuss below, some study characteristics were associated with worse reporting.

The CONSORT-harms was used as the gold standard for our analysis of AE, i.e., an ideal RCT would have fulfilled all items of this guideline. This approach was used in other reviews and it was found, for instance, that inadequate AE reporting is also an important issue in other interventions such as psychotherapy [87], antiepileptic drugs [88], and finasteride [89]. This approach also has its limitations; for instance, the same weight is given to all items, despite that some of them might be less important than others. Another obvious limitation is that lack of reporting does not necessarily translate to lack of quality; AEs might have been collected and not reported due to limitations in journal space, for instance. Notwithstanding, as we discuss below, we found that reporting of AEs was extremely poor – hence, even considering these limitations, we found evidence that AEs in RCT tDCS trials are underestimated.

Acceptability

The total number of dropouts for any reason was used as a proxy for acceptability. This definition has indeed been adopted in past [90] and recent meta-analyses published in major journals (e.g. Refs. 91 and 92) as well as in Cochrane studies and protocols (e.g., PROSPERO protocol CRD42015025643). Although our employed approach is valid (indeed, some recent meta-analyses only used this approach [91,92]) and can be considered a "hard surrogate outcome", we acknowledge that we only provide a crude composite measurement of acceptability, without being able to explore the specific reasons for discontinuation.

In case of tDCS, other factors such as convenience to go to a medical center on a daily basis needs to be taken into account. As we only enrolled RCTs in our analysis, it is reasonable to assume that a similar proportion of subjects dropped out in each group due to logistic reasons and, therefore, that it is valid the finding that the attrition rate between active and sham groups is comparable. In fact, we performed a descriptive analysis using data from the studies that provided reasons for dropouts, finding a similar frequency of dropouts due to AEs (around 4%). Thus, it is likely that the acceptability rates when considering AEs are in fact lower than those of our approach for estimating this outcome.

Importantly, this meta-analysis presented "zero-cell counts", with almost half of studies reporting no dropouts in both arms. This probably occurred because most studies were pilot trials, which enrolled small samples. Thus, it is possible that the careful and stringent selection of participants excluded those who were more likely to dropout. Accordingly, zero-cell studies enrolled smaller samples than studies reporting dropouts. Also it was not possible to assess whether the number of sessions was associated with a likelihood of no dropouts given the number of studies reporting this variable.

Tolerability

We were not able to compare the frequency of AEs between active and sham groups as less than one third of the trials quantitatively described these AEs. Even in the remaining studies that reported and quantified AEs, a meta-analysis was not possible due to between-study heterogeneity, i.e., not all AEs were reported in all studies and the frequency of an AE (e.g., skin redness) could vary from 5% to 95%. Therefore, we were not able to explore whether tDCS parameters such as current intensity and electrode positioning are associated

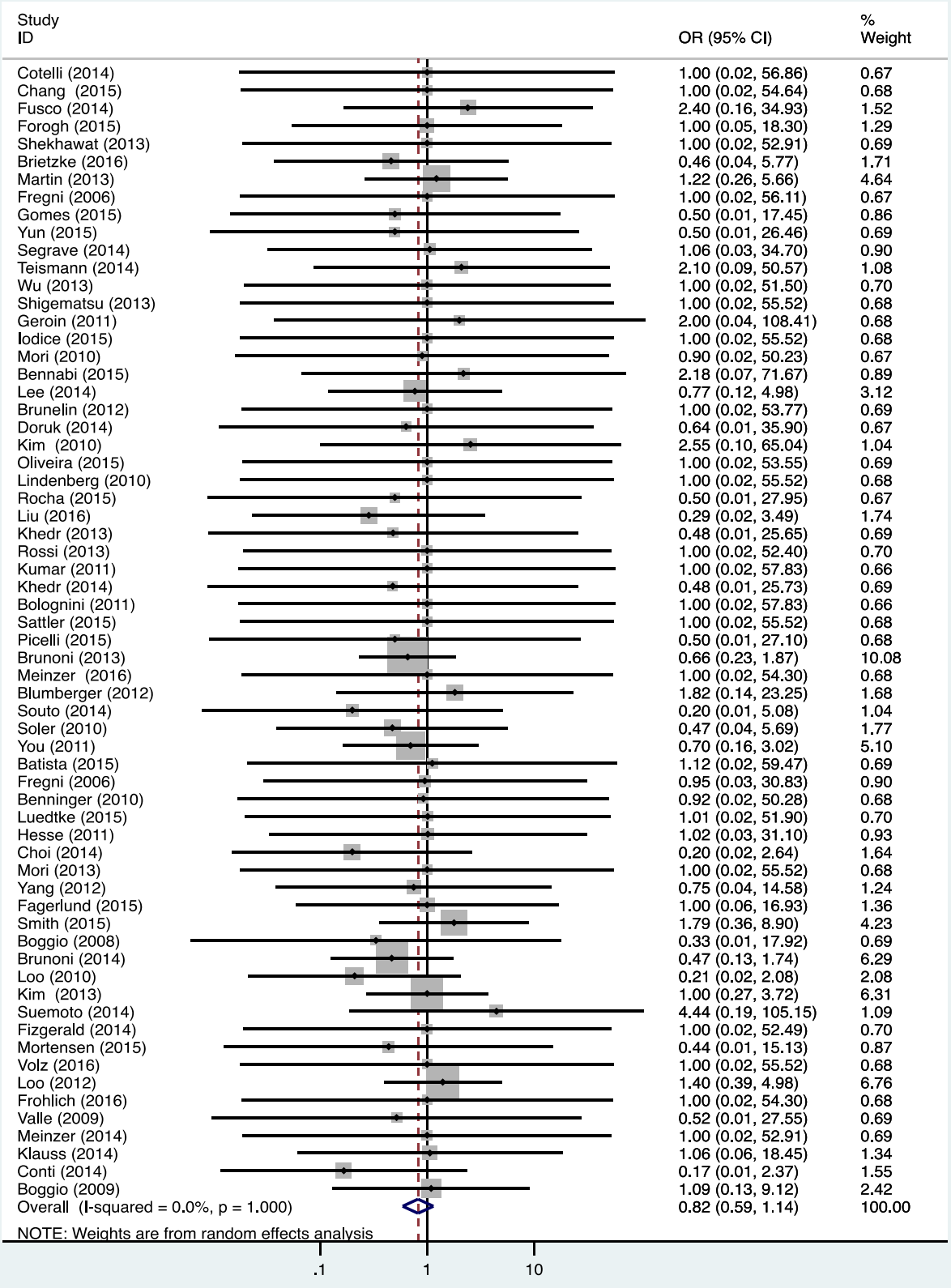

Figure 1. Forest plot of acceptability in tDCS trials. Forest plot showing treatment discontinuation rates (acceptability) between active and sham groups. The diamond at the bottom of the plot summarizes the best-estimate results of the meta-analysis, with the width representing the corresponding 95% CI. Effect sizes are odds ratios (random model), error bars represent 95% confidence interval.

Table 4
Frequency of adverse events reported in each study.

	Itching		Burning		Headache		Fatigue		Sleepiness		Skin redness		Tingling		Pain	
	Active	Sham	Active	Sham	Active	Sham	Active	Sham	Active	Sham	Active	Sham	Active	Sham	Active	Sham
Stroke																
Bolognini [23]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hesse [24]	0	0	0	0	N/A	N/A	0	0	0	0	0	0	12.5	12.5	0	0
Kim [25]	0	0	0	0	N/A	N/A	0	0	0	0	0	0	0	0	0	0
Lee [26]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lindenberg [27]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Shigematsu [28]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Wu [29]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
You [30]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Geroin [31]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Khedr [32]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Rossi [33]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fusco [34]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Sattler [35]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Yang [36]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Kumar [37]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Yun [38]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Mortensen [39]	62.5	12.5	0	12.5	50	12.5	0	0	12.5	12.5	0	0	87.5	50	0	0
Picelli [40]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Rocha [41]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Chang [42]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Meinzer [43]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fibromyalgia																
Fregni [44]	0	0	36.4	20	0	0	36.4	10	0	0	0	0	0	0	0	0
Valle [45]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fagerlund [46]	12.6	17.7	31.9	44.9	15.1	10.2	0	0	55.5	50.8	56.3	68.6	53.8	65.2	15.1	7.6
Neurodegenerative disorders																
Benninger [47]	0	0	0	0	0	0	0	0	0	0	0	0	100%	100%	0	0
Khedr [48]	0	8.6	0	0	8.6	0	0	0	0	0	0	0	0	0	0	0
Suemoto [49]	5	0	75	40	25	15	0	0	65	60	75	55	85	35	0	0
Doruk [50]	0	0	0	0	22	22	0	0	55	55	22	22	50	50	11	11
Chronic pain																
Soler [86]	0	0	0	0	15	0	0	0	0	0	0	0	0	0	0	0
Choi [57]	0	0	0	0	0	16.6	0	0	0	0	0	0	0	0	0	0
Luedtke [56]	0	0	0	0	0	0	0	0	0	0	2.9	0	0	0	0	0
Oliveira [55]	0	0	0	0	0	0	0	0	0	0	6.6	0	0	0	0	0
Brietzke [54]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Volz [53]	70	40	50	50	0	10	0	0	20	0	80	10	80	70	20	0
Kim [52]	5	5	0	0	7.5	0	0	0	0	0	0	0	0	0	0	0
Souto [51]	0	0	20	0	0	0	0	0	20	0	10	0	40	0	0	0
Multiple sclerosis																
Mori [61]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mori [59]	0	0	0	0	0	0	0	0	0	0	10	0	0	0	0	0
Iodice [60]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Tinnitus																
Shekhawat [62]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Teismann [63]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Forogh [64]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Primary progressive aphasia																
Cotelli [65]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Epilepsy																
Liu 2016	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Schizophrenia																
Fitzgerald [67]	6.25	16.7	0	0	4.2	4.2	0	0	0	0	0	0	0	0	0	0
Brunelin [68]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gomes [10]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Smith [70]	20	25	0	0	13	13	7	0	0	6	0	0	0	0	0	0
Frohlich [69]	N/A	N/A	N/A	N/A	.	.	.	.	.	.	.	.	N/A	N/A	.	.
Major depressive disorder																
Boggio [71]	23.3	20	0	0	13.3	10	0	0	0	0	6.6	10.1	0	0	0	0
Blumberger [72]	0	0	0	0	23	0	0	0	0	0	0	0	30.7	36.3	0	0
Fregni [73]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Loo [74]	38.2	35	0	0	35.3	30	0	0	0	0	94.1	60	17.6	40	0	0
Loo [75]	74.1	75.9	45.2	24.1	45.2	34.5	22.6	13.8	0	0	96.8	100	83.9	93.1	6.5	0
Brunoni [76]	37	25	0	0	22	19	0	0	44	29	25	8	13	9	6.5	0
Brunoni [77]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Segrave [78]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Bennabi [79]	0	0	N/A	N/A	0	0	0	0	0	0	N/A	N/A	0	0	0	0
Substance dependence																
Boggio [80]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Klauss [81]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Conti [82]	N/A	N/A	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Batista [83]	0	0	17.6	N/A	0	5.3	0	0	0	0	0	0	70.6	73.7	0	0
Healthy volunteers																
Martin [84]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Meinzer [11]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

This table shows the percentage of adverse events (AEs) reported by the included studies. Studies where a dot (".") is showed are those in which AEs or similar terms (e.g., side effects) were not mentioned in the paper. There are 14 studies that did not mention AEs at all. Cells that contain zeros ("0") describe those studies that used terms such as "no side effects were reported", "AEs were minimal and well-tolerated" and so on. Most studies fall in that category. Cells that contain N/A describe studies that stated that some subjects presented AEs but did not describe the percentage. Finally, cells containing a number ranging from 0 to 100 describe the percentage of patients that presented a given AE. As it can be seen, only a minority of studies quantitatively reported and described AEs, which hindered us to conduct a meta-analysis of AEs.

to AEs. The issue of inadequate reporting of AEs had already been pointed out by our earlier systematic review of AEs that assessed mostly single-session tDCS studies [3]. In that review, 44% of studies did not report AEs and 20.5% reported "no AEs" (vs. 21.8% and 28%, respectively, in this review).

One possible explanation for the discrepant reports on AEs is, in fact, the definition adopted of an AE. "Adverse event" can be defined as a "harmful or undesirable outcome that occur during of after the use of a drug or intervention but is not necessarily caused by it" [93], which can be ambiguous in deciding on whether a very mild AE should be collected and/or reported. Another issue is passive vs. active surveillance of AEs. In a controlled trial, Bent et al. [94] showed that, during the placebo run-in period, reporting of AEs was much higher in active compared to passive surveillance. Overestimation of AEs is of particular concern in non-controlled trials as there is no control group for comparison of AE frequency.

Nonetheless, part of our findings can also be explained by poor reporting. According to our estimation of quality of AE reporting based on CONSORT-harms [8], the studies generally complied with less than one-fourth of recommendations. Interestingly, better reporting was associated with studies having large sample sizes and low risk of bias. Possibly, smaller, pilot studies are primarily proof-of-concept studies investigating whether tDCS is effective in a particular condition, whereas larger studies, usually done after smaller studies showing positive results, investigate both efficacy and safety. Furthermore, quality of AE reporting was not associated to publication year. This likely occurs because tDCS is considered a "safe" technique, thus making investigators less prone to investigating AEs. However, we only found reporting of CONSORT guidelines [7] in 15% of articles, suggesting that lack of use of reporting guidelines. Though the use of the general CONSORT guidelines would help with reason for dropouts, it does not have specific recommendations to collect and report adverse effect. In this case, the use of CONSORT-harms guidelines would be recommended [8].

Also of note, reporting is even more problematic in stroke studies. Possibly, it is more difficult to assess AEs in these patients due to post-stroke complications. Nevertheless, these complications are, in fact, compelling reasons for a more careful assessment of AEs in these samples. Better reporting was associated to studies with a higher proportion of women. Although one possible explanation is that women better report symptoms than men, this finding should be interpreted with caution as no individual patient data of each study were assessed, since our meta-analysis is based on aggregate data.

Strengths and limitations

A study limitation is that we have not assessed pediatric populations, although tDCS is being increasingly used in child and adolescent disorders such as epilepsy and autism [95]. However, we considered that such patients present very distinct characteristics (e.g., parental consent to participate and attend to a trial) and therefore it would not be appropriate to include these studies in our selection criteria, although this would be an interesting topic for a subsequent study.

Study strengths were the relatively large number of included articles, which were of good methodological quality, and included samples with several neuropsychiatric disorders. This meta-analysis also presented low between-study heterogeneity, providing support to the consistency of our findings. Finally, we found no evidence of publication bias.

Directions for future studies

The observation that tDCS acceptability does not differ in studies applying <2 vs. 2 mA indicates that, even though tDCS-induced skin sensations increase in higher currents [96], this AE did not seem to impact tDCS acceptability. Likewise, other parameters related to tDCS "dose", such as current density, session duration and numbers of sessions were not associated to acceptability. As a higher tDCS "dose" could be related to increased efficacy according to a recent tDCS depression meta-analysis [97], our findings indicate that future studies can use more intensive tDCS protocols, without necessarily impacting their overall acceptability. However, we could not evaluate whether currents higher than 2 mA could adversely impact acceptability.

Although the lack of adequate reporting of AEs is concerning as it results in underestimation of the true rate of AEs in repeated tDCS trials and also false bias assessment related to blinding due to active treatment associated adverse effects, the solution is not simple. An immediate recommendation as we have previously proposed is the collection and reporting of AEs using a standard questionnaire [3]. However it needs to be considered that adverse effects reporting may be driven by these questionnaires as reported before in antidepressant trials [98]. Another challenge for the collection of AEs in repeated sessions tDCS trials is the association between therapeutic and side effects as shown before [7] and also reported by us in our longitudinal clinical trial [99].

Given these considerations, and taking into account that most tDCS clinical trials in the upcoming years will be phase-II or phase-III, and also that better sham tDCS methods should continue to be developed; we still encourage the active surveillance of adverse effects; however the investigator needs to be aware of these limitations and report the method used when collecting and interpreting AEs. Based on that, we here present an updated questionnaire of AE assessment (Table 5), based on the previous questionnaire presented in our earlier meta-analysis [3], in CONSORT-harms [8], and in the reporting of other AEs observed in more recent studies.

(1) AEs should be assessed as secondary outcomes in trials measuring efficacy as the main outcome, either by passive or by

Table 5
Proposal of a questionnaire for surveying for tDCS adverse effects.

Adverse effect	No	Yes	Severity	Relationship with stimulation
Headache	()	()	1 2 3 4	1 2 3 4 5
Neck pain	()	()	1 2 3 4	1 2 3 4 5
Local pain (anode)	()	()	1 2 3 4	1 2 3 4 5
Local pain (cathode)	()	()	1 2 3 4	1 2 3 4 5
Itching (anode)	()	()	1 2 3 4	1 2 3 4 5
Itching (cathode)	()	()	1 2 3 4	1 2 3 4 5
Scratching (anode)	()	()	1 2 3 4	1 2 3 4 5
Scratching (cathode)	()	()	1 2 3 4	1 2 3 4 5
Tingling (anode)	()	()	1 2 3 4	1 2 3 4 5
Tingling (cathode)	()	()	1 2 3 4	1 2 3 4 5
Burning (anode)	()	()	1 2 3 4	1 2 3 4 5
Burning (cathode)	()	()	1 2 3 4	1 2 3 4 5
Skin redness (anode)	()	()	1 2 3 4	1 2 3 4 5
Skin redness (cathode)	()	()	1 2 3 4	1 2 3 4 5
Somnolence	()	()	1 2 3 4	1 2 3 4 5
Concentration changes	()	()	1 2 3 4	1 2 3 4 5
Fatigue	()	()	1 2 3 4	1 2 3 4 5
Nausea	()	()	1 2 3 4	1 2 3 4 5
Dizziness	()	()	1 2 3 4	1 2 3 4 5
Other effects:				
	()	()	1 2 3 4	1 2 3 4 5
	()	()	1 2 3 4	1 2 3 4 5
	()	()	1 2 3 4	1 2 3 4 5

The patient is asked to describe whether the adverse effect was experienced. If it was experienced, the patient is asked to rate its severity (1 – very mild; 2 – mild; 3 – moderate; 4 – severe) and relationship with tDCS (1 – none; 2 – remote; 3 – possible; 4 – probable; 5 – definite). This questionnaire contains the term "anode" and "cathode" to highlight that AEs can occur differently in these electrodes. When presenting this questionnaire to patients, the terms should be substituted according to the trial (e.g., "left" and "right" electrode). This questionnaire is a general recommendation and can be adapted according to the sample investigated; for instance, adding specific mood questions in trials of mood disorders.

active surveillance (passive surveillance is better to maintain rater blinding but can underestimate the frequency of AEs; if using active surveillance, it is recommended that the rater evaluating AEs to be different from the one assessing efficacy);
(2) the time period of each assessment should be reported;
(3) severity and frequency of symptoms (very mild, mild, moderate or severe) should be estimated according to the total number of sessions in which that AE was reported (e.g. "skin redness was a mild symptom in 85% of tDCS sessions") and reported separately;
(4) any severe, unexpected and/or severe AE should be reported separately.
(5) We recommend the use of the extension checklist for reporting harms outcomes from the CONSORT guidelines (CONSORT-harms).
(6) we encourage trials being designed to measure safety (including side effects) as the main outcome. These trials are costly and difficult to be designed. However, alternative designs such as observational trials are possible. In this case the data from sham-controlled trials are even more important as to detangle the real detrimental effect, if any, of transcranial direct current stimulation.

These recommendations are intended to standardize the assessment of AEs across tDCS clinical trials. We also recommend that the questionnaire or the recommendations should be adapted according to the study sample (e.g., aphasic patients, children etc.). Validation of questionnaires in different cultures is also recommended. Finally, time period of dropout should be systematically reported.

Conclusions

There were no differences in acceptability between active and tDCS groups, showing that commonly used tDCS protocols in clinical trials are well tolerated by neuropsychiatric patients. As most tDCS trials did not adequately reported adverse effects, tolerability (rate of AEs) was not assessed. Therefore, it is unknown whether active tDCS presented more AEs than sham tDCS in clinical trials, which is a concern for safety and blinding issues.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.brs.2016.05.004.

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