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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.