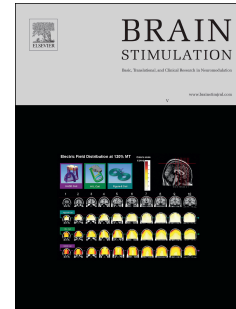


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Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016

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Highlights

- Claims on the safety of tDCS are based on inaccurate data.
- Clinical trials fail in reporting methods applied to identify adverse effects.
- The frequency and the adverse effects observed are also not consistently reported.
- Appropriate methods and transparent report are needed in reviews on the safety of tDCS.

Dear editor:

Last year, Bikson and colleagues attempted to collate data to inform the safety of the transcranial direct current stimulation (tDCS), an electrical brain stimulation technique that has been used to treat of neurological problems and psychiatric disorders. The review was qualified as an evidence-based review and the authors concluded that the review was able to “consolidate evidence on the safety of tDCS” (1).

The study based its conclusions on the analysis of serious adverse effects and irreversible brain damage in animal models (1), as well as human trials published in English before 2013. The studies were searched in one database, PubMed, with the key word “transcranial direct current stimulation”.

We recognise the authors attempt to aggregate evidence regarding the safety of tDCS. However, we are concerned about the several and important limitations in the design of this review which might invalidate it as an evidence-based piece. These limitations comprise both its methodological design and the theoretical concepts adopted.

In regards to the methods, this safety update is inconsistent with the fundamentals of an evidence-based review, also known as a systematic review (2). Evidence-based guidelines recommend the construction of highly sensitive searches to allow the retrieval of all relevant studies (3). Sensitive searches should combine free-text and subject headings and they should be used to retrieve relevant studies indexed in different databases. Searches limited to only one database and one keyword are highly susceptible to publication bias. When considering adverse effects, an even more broad range of databases and free-text and subject headings may be searched to avoid biases (4). The language limit of the search to the English language might or might not be another source of bias (5, 6). Nevertheless, the authors should be transparent when reporting the number of retrieved studies and the results of the screening process (7, 8). For instance, the reader should be able to make a judgment of the size and direction of the bias by acknowledging the number of studies not considered for inclusion because of the language of the publication.

The type of study to be included in a systematic review is another aspect of an evidence-based review to be taken under careful consideration. Different clinical questions require data from different study designs. Accurately searching for data on adverse effects may require an even more careful approach and the consideration of the pros and cons of including either randomised and non-randomised trials, as well as unpublished studies. As much as 95% of the information regarding adverse events remains

unpublished and information of higher complexity in regards to harms may be found in unpublished versions of the same published study (9). The review reported by Bikson et al. (1) neglect all these essential aspects of an evidence-based research focused on safety. In fact, the paper referred loosely to “trials” as the study design included in the review and do not mention any attempt to search for unpublished data. The meaning of the terminology “trials” is unclear as it may correlate with different types of study designs, from small short-term non-randomized studies to large, multicentre randomized trials with long-term evaluation of thousands of participants. Failing in approaching the unpublished literature seriously threatens the validity of the review results.

Another critical aspect is related to the assessment of the risk of bias toward the null hypothesis of no effect. What was measured, who measured it, and when it was measured may define if an adverse effect can, or will, be appropriately detected or not. Lack of proper or rigorous measurement methods to detect adverse effects does not mean safety as even serious events could have been missed. Similarly, outcome reporting bias, or the neglecting in reporting an outcome, can seriously influence the results of any review focusing on harmful outcomes (10). Studies may fail to provide full and transparent reporting of adverse effects and the fact that they are not reported does not mean they didn't happen. For instance, our group performed a systematic review of randomised clinical trials of tDCS in stroke survivors and the results demonstrated that the majority of the trials suffer from poor reporting. Information on the methods applied to collect data on adverse effects, the frequency and the specific adverse effects observed is largely not transparently reported (Table 1). Our results are consistent with another review showing that 40.7% of the studies assessing treatment with tDCS in stroke patients fail to mention whether adverse effects were measured or not and whether they occurred or not (11). Therefore, the conclusion that there are no reports of serious adverse effects associated to tDCS could better represent an “absence of evidence of harms” rather than “evidence of absence of harms” (12).

The concept of safety applied in this review is another matter of concern. Safety is the “substantive evidence of an absence of harm” (13). Evidence of safety should then be understood as evidence of the absence of the totality of all possible adverse consequences of an intervention or, alternatively, evidence that the beneficial effects of an intervention outweigh its possible adverse consequences. The authors of the quoted evidence-based review opted to evaluate safety based only on serious adverse effects with published data allowing the assessment of causality. There are two misconceptions here. Firstly, by definition, an adverse effect is an event for which there is a reasonable possibility of a causal relation (13). Therefore, a definitive prove of causality is not necessary and, in fact, may not be reached

in the majority of the cases. Secondly, mild or moderate adverse effects may significantly reduce patient's quality of life and their willingness in adhering to treatment. Therefore, safety should not be related only to serious events, and the ultimate decision on which an adverse effect is tolerable or not should rely on the patient.

High quality research should provide evidence for an improved informed and shared clinical decision. Unfortunately, the terminology evidence-based has become popular. This may be dangerous as flawed research may claim to provide definitive clinical answers without an appropriate appraisal of the quality and accuracy of the data. We regret to conclude that, ultimately, declaring tDCS a safe technique in face of the limitations of the published review could do more harm than good to patients undergoing treatment.

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Table 1 Reporting of data related to adverse effects in randomised controlled trials of treatment of stroke patients with transcranial direct current stimulation (tDCS) - data are from a systematic review with searches at The Cochrane Central Register of Controlled Trials (CENTRAL), PEDRo and Biosis Preview databases updated until November 2014.

Author, year of publication ^a	Assessment methods of adverse effects	Data on frequency of adverse events?	Nº of tables/graphs describing adverse effects
Bologini 2011	Questionnaire administered at end of each session tDCS	No	0
Danzl 2013	NR	No	0
Edwards 2009	NR	No	0
Gandinga 2006	Visual analogical scale applied in each session and ranging from 1 (no discomfort) to 10 (extreme discomfort/pain)	No	0
Geroin 2011	NR	No	0
Khedr 2013	NR	No	0
Kim 2010	NR	No	0
Kumar 2011	NR	No	0
Lee 2014	NR	No	0
Lindenberg 2010	NR	No	0
Nair 2011	NR	No	0
Polanowska 2013	NR	No	1
Rossi 2013	NR	No	0
Viana 2014	NR	No	0
Wu 2013	NR	No	0
Yang 2012	NR	No	0
You 2011	NR	No	0
Ang 2012	No	No	0
Fusco 2014	NR	No	0
Park 2013	NR	No	0
Polanowska 2013	NR	No	0
Shigematsu 2013	NR	No	0

Wilkinson 2014	Charts with daily record of adverse effects taken before and during the sessions	Yes	1
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NR: not reported.

^a The detailed list of references can be obtained through contacting authors.

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