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Comparison of blinding effectiveness between sham tDCS and placebo sertraline in a 6-week major depression randomized clinical trial ☆

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HIGHLIGHTS

- We compared blinding integrity of tDCS vs. placebo-pill in a 6-week, parallel, factorial randomized clinical trial in 102 patients with major depression.
- Participants correctly guessed tDCS and sertraline allocation groups beyond chance; nonetheless, it was mainly associated with clinical response and to a lesser extent with adverse effects.
- Although tDCS blinding is comparable to placebo-pill, further studies can improve it by designing parallel (vs. crossover) trials and avoiding subjects' awareness of skin reddening, which more often occurs in the active arm.

ABSTRACT

Objective: To compare blinding integrity and associated factors for transcranial direct current stimulation (tDCS) vs. placebo-pill, the gold standard blinding method.
Methods: Parallel trial. Depressed participants were randomized to verum/placebo sertraline and active/sham tDCS (2 mA, 30-min 10-daily sessions and two additional, fortnight sessions) over 6 weeks. Blinding was assessed in completers ($n = 102$) and in a random subgroup ($n = 35$) of raters and participants, in which we also inquired to qualitatively describe their strongest guessing reason.
Results: Participants and raters presented similar performance for predicting treatment assignment at endpoint, correctly guessing tDCS and sertraline beyond chance. Nevertheless, clinical response was associated with correct prediction and tDCS non-responders failed to predict the allocation group. For tDCS, "*trouble concentrating*" was inversely associated with correct prediction. "*Skin redness*" was more reported for active-tDCS, but did not predict the allocation group. The qualitative reasons for raters' guessing were not associated with correct prediction, whereas for participants clinical response and adverse effects were directly and inversely associated with correct prediction, respectively.
Conclusion: Blinding integrity of tDCS and sertraline were comparable and mainly associated with efficacy rather than blinding failure.
Significance: TDCS blinding can be improved by adopting parallel designs and avoiding subjects' awareness of skin redness.

1. Introduction

Blinding is a cornerstone method of reducing bias in modern randomized, controlled trials (RCTs) as it keeps participants and/or researchers unaware of the allocation group. Lack of researchers' blinding can make them more prone to treat, behave and evaluate subjects in a biased way (Boutron et al., 2007; Brunoni et al., 2010).

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In fact, the failure of blinding participants can increase treatment non-adherence and placebo response (Noseworthy et al., 1994; Turner et al., 2012). Blinding integrity in placebo-controlled trials involves two main aspects – allocation concealment, which is less complicated to achieve, and a placebo as similar as possible to the experimental treatment. Notwithstanding, placebo (sham) for non-pharmacological trials is usually very challenging and instigates researchers to develop novel and "creative" sham procedures (Boutron et al., 2007; Fregni et al., 2010).

Particularly, development of reliable methods of sham stimulation has been a challenge for the field of non-invasive brain stimulation. For instance, for repetitive transcranial magnetic stimulation (rTMS), which has been used in clinical research for almost 20 years, sham stimulation is still not straightforward (for a review see Berlim et al., 2013; Brunoni and Fregni, 2011). Conversely, the sham method of transcranial direct current stimulation (tDCS) has been usually considered reliable or at least better than rTMS sham, since active tDCS *per se* has no auditory artifact and less local skin sensations compared with rTMS, which can be mimicked using a brief period of stimulation prior to the simulated procedure. This method has been used from the earliest tDCS studies hitherto and was formerly evaluated by Gandiga et al. Gandiga et al. (2006) who described minimal rates of adverse effects (AEs) and discomfort between active vs. sham tDCS and that none of the subjects or investigators were able to distinguish between stimulation groups, therefore concluding that "*tDCS can be used in the setting of strict double-blind sham controlled randomized trials*". In agreement, further studies found that the rate of common AEs were non-statistically different in the active vs. sham groups (Brunoni et al., 2011; Poreisz et al., 2007). In fact, although other sham tDCS methods were described, such as not using an initial stimulation period, maintaining a very low-dose current (0.1 mA) during the stimulation session, and discharging small electric pulses during the sham period (Brunoni et al., 2012; Nitsche et al., 2008), the procedure validated by Gandiga et al. Gandiga et al. (2006) is used in most tDCS trials.

Nevertheless, results from other studies casted doubt on the reliability of the standardized sham method. Ambrus et al. Ambrus et al. (2010), Ambrus et al. Ambrus et al. (2012) observed that tDCS perception threshold is lower (i.e., tDCS is more perceivable) than transcranial random noise stimulation, and also that experienced investigators were able to correctly identify between active vs. sham tDCS. Current dose (1 mA vs. 2 mA) seems to be, in fact, associated with active tDCS detection (Ambrus et al., 2010; Dundas et al., 2007; Palm et al., 2013). O'Connell et al. O'Connell et al. (2012) found that investigators and subjects were able to distinguish between a 2 mA active vs. sham tDCS session, especially during the crossover phase when the second session was active. They also reported higher frequency of skin redness (60%) for active tDCS. Palm et al. Palm et al. (2013), also using a 2 mA protocol, reported that investigators (but not subjects) correctly guessed the type of stimulation based on skin redness. In addition, in a recent systematic review of 209 tDCS studies, we found similar rates of AEs (such as tingling, itching, discomfort and others) for both active and sham tDCS in a range of 20–40%. Nevertheless, we also found that only 56% of the studies mentioned adverse effects in the results section and, of those, only 7% systematically assessed and described each AE separately. Given the relatively high rates of such effects, we concluded that tDCS AEs are underreported (Brunoni et al., 2011).

However, such observations refer mainly to single-session, crossover tDCS studies, when the same subject receives both interventions. Differently, although tDCS clinical trials use a parallel design, which theoretically could protect more against unblinding; these trials apply repeated, daily tDCS sessions for several days or weeks, increasing the chance of break in blinding. In addition, by assessing a clinical population, correct blinding guessing can be associated with the improvement of the condition under study. Specifically for major depression, eight RCTs were conducted hitherto. One is the one being reported in this article and for the remaining seven articles, three of them did not assess blinding (Boggio et al., 2008; Fregni et al., 2006a; Fregni et al., 2006b) and four assessed (Loo et al., 2010; Blumberger et al., 2012; Loo et al., 2012; Palm et al., 2012). All of these four articles reporting blinding assessment showed integrity of blinding – although, interestingly, only one reported significant clinical effects of tDCS.

Considering the importance of blinding in clinical research and the increasing use of tDCS as a clinical intervention, it is crucial to determine whether sham tDCS methods are adequate or, conversely, if novel methods should be developed. Therefore, the aim of this report is to investigate further whether the blinding of a large RCT using tDCS for depression was adequate and sought for the factors associated with blinding integrity.

2. Methods

2.1. Overview

The present study uses data from the SELECT-TDCS (*Sertraline vs. Electric Therapy for Treating Depression Clinical Study*) trial – for a complete description of its design and results see (Brunoni et al., 2013) and (Brunoni et al., 2011). In short, this was a factorial, randomized, double blind study in which 120 participants with major depression were randomized to receive active/sham tDCS and verum/placebo sertraline pill. The trial was approved by the local Institutional Review Board and the National Ethics Committee and registered in clinicaltrials.gov (NCT01033084). The study was reported according to the 2008 CONSORT (Consolidated Standards of Reporting Trials) recommendations (Boutron et al., 2008), which was the most recent CONSORT guideline when the trial was conceived.

All participants provided written, informed consent. They were 18–65 years-old adults with unipolar depression per DSM-IV criteria (APA, 2000). Only those with moderate-to-severe depression and without other psychiatric diagnoses (except for anxiety disorders whether in comorbidity with the primary diagnosis) were enrolled. Two certified psychiatrists screened the participants using the Portuguese-translated version of the Mini International Neuropsychiatric Interview (MINI) Amorim, 2000; Sheehan et al., 1998 and assessed depression severity with the Portuguese version of the Montgomery–Asberg depression rating scale (MADRS) (C, 2000). Clinical response was defined as >50% MADRS improvement from baseline to endpoint. Prior to trial onset, participants were washed out for all psychiatric drugs except for benzodiazepines that were allowed to remain at low doses (up to 20 mg/day of diazepam-equivalents), a similar approach also used in other large rTMS trials (George et al., 2010; O'Reardon et al., 2007).

The trial duration was 6 weeks, divided in an initial acute treatment phase (first 2 weeks), in which ten daily active/sham tDCS were delivered from Monday to Friday, and two follow-up tDCS sessions every fortnight. Verum/placebo sertraline treatment (fixed 50 mg/day dose) started and ended simultaneously with tDCS.

The blinding assessment was planned before study onset, which began in March 2010 and therefore comprises the entire sample. After publication of reports casting doubt on the efficacy of Gandiga et al. Gandiga et al. (2006) sham tDCS method, we aimed to investigate this issue further by also assessing blinding on weeks 2 and 4 (i.e., after the 10th tDCS and 11th tDCS sessions) and on the clinical investigators ("raters") in the remaining of the sample.

2.2. Interventions

For each active tDCS session, we applied a direct current of 2 mA/25 cm^2 (0.8 A/m^2) for 30 min. The anode and the cathode