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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

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were respectively positioned over the F3 and F4 areas, corresponding to the left and right dorsolateral prefrontal cortex (EEG 10–20 system). We employed Chattanooga Ionto (Chattanooga Group) devices, which deliver a constant, fixed current by varying the voltage output as resistance changes and interrupting the current whether the resistance is too high. These devices also display an initial, automatic 30-s fade-in phase. Two certified nurses delivered all tDCS sessions. They were previously trained by the study authors in common tDCS procedures, such as preparing the material (e.g., inserting the rubber electrodes in the saline-soaked sponges), positioning the electrodes over the scalp and keeping the sponges humid throughout the stimulation (see DaSilva et al., 2011 for a visualized tDCS session). They were also instructed to adopt the same procedures for both sham and active stimulation. They were also trained to manipulate the tDCS device outside of the patient eyesight, particularly when it was turned off. Their interaction with study participants was minimal as to enhance study blinding.

2.3. Blinding methods: sham tDCS and placebo pill

The sham procedure consisted in an initial 30-s ramp-in phase (0.067 mA/s), 30 s of active stimulation and a ramp-out phase of 15 s (0.13 mA/s). The electrode position and all the other procedures to set up including electrode moisture, checking the contact were identical. The display of the device was kept outside subjects vision field as the device was turned off without subjects noticing.

For the pharmacological intervention, we used placebo pills. All verum/placebo pills had the same size, color and taste and were manufactured by certified pharmacists.

2.4. Blinding assessment

At week 6, blinding integrity was assessed in 102 participants by asking them to guess the received treatment and to rate the confidence of their guess on a Likert scale, from 1 (“not sure at all”) to 5 (“completely sure”). We did not assess blinding in 18 patients due to early trial withdrawal ($n = 17$) and patient’s refusal to report ($n = 1$).

After studies casting doubt on sham tDCS efficacy, we extended data collection on blinding efficacy in the last 35 participants of our study (from March to September 2011). These additional data corresponds to: (1) assessment on blinding guessing for both participants and rates; (2) assessment on blinding not only at week 6, but also week 2 and 4; (3) assessment for both raters and participants for the reason underlying their guessing. Their answers were further divided in two main categories: “reasons associated with AEs (or lack of)” (e.g., descriptions such as “*I think it was sham because I did not feel anything*” or “(...) *because the participant described itching*”) and “reasons associated with clinical symptoms” (eg., descriptions such as: “(...) *because I am not feeling better*”, “*I think it was active based on the clinical response*”). Other descriptions (e.g. “*I know it is active tDCS because I have faith*”) were classified in “other reasons”. If they could not provide an answer at all, no answer was computed. Finally, we used only their strongest guessing reason (i.e., the reason that they were most confident that explained their guessing) for further analyses. In fact, in only 17 (out of 350, 4.8%) occasions they described guessing reasons that would fit in more than one category.

2.5. Raters

Two board-certified psychiatrists with experience in clinical research (ARB and LV, two 30 years-old males) were the blinded raters responsible for guessing the allocation group. Participants were instructed to avoid discussing the treatment experience with the raters. Therefore, the raters’ guessing was based solely on their clinical impression from their interaction with subjects. The raters performed their blinding guessing before the participants; therefore there was no contamination of patients’ blinding guessing on the evaluation of the raters.

2.6. Adverse effects

AEs were collected using a tDCS questionnaire assessing the most common AEs related to tDCS, according to a previous systematic review (Brunoni et al., 2011) and the study of Poreisz et al. Poreisz et al. (2007) who summarized data from 567 tDCS sessions among several studies.

For each AE, we asked whether the participant experimented such effect following tDCS. For AE rating, we took a conservative approach, considering a positive AE whether the subject reported that he/she had at least “mild” AEs that could be as least “possibly” associated with the stimulation. Even though, most patients described no AEs (Brunoni et al., 2013). Also, although for ethical reasons the consent form had to inform that some AEs would might occur, this information was not further detailed as to not compromise blinding (Ambrus et al., 2012; Palm et al., 2013).

We evaluated the individual influence of each AE on blinding by assessing those that were reported at week 2 in >20% of sample and those who were significantly more frequent in one group. Therefore, AEs that had a low frequency and were not statistically different between groups, such as “neck pain” (14% vs. 6% in sham and active tDCS, $p = 0.2$) and “tingling” (16% vs. 7.8%, $p = 0.23$) were not analyzed. This procedure was used to input only the most frequent AEs in the regression models.

2.7. Statistical analysis

Descriptive results are described using mean (SD) and frequencies when appropriate. Statistical analyses were performed with Stata 12 (STATA, College Station, US). We used the χ^2 test or the Fisher’s exact test to explore whether tDCS and sertraline blinding guessing was beyond chance for patients ($n = 102$) and raters ($n = 35$) and paired t-tests to compare the rate of their guessing according to the Likert scale. We also ran univariate and multivariate logistic regressions exploring the factors associated with “correct blinding guessing” (i.e., participants who correctly guessed their allocation group). The factors were clinical response, high guessing confidence (scores 4 or 5 on the Likert scale) and AEs. All variables are binary and were analyzed in both univariate and multivariate regression models. A two-tailed p value <0.05 was considered statistically significant. Secondary analyses were performed according to the tDCS group as to explore specific guessing predictors for active/sham tDCS. The logistic regression analyses were only performed for the blinding integrity from participants ($n = 102$) as we considered that the raters assessed a relatively low number of participants ($n = 35$) to provide adequate power to perform our models.

3. Results

The sample characteristics are summarized in Table 1.

3.1. Blinding integrity

3.1.1. Participants

For the subgroup of 35 participants in which data from weeks 2 and 4 were collected, neither sertraline nor tDCS use was guessed beyond chance at week 2. However, at week 4 sertraline but not tDCS use was guessed beyond chance. At week 6, the 102 completers guessed beyond chance both sertraline and tDCS use (Table 2);

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Table 1
Characteristics of the sample.

	tDCS			Sertraline		
Factors	Active	Sham	*p*	Verum	Placebo	*p*
Demographics						
Female/Male	42 / 11	27 / 22	**<0.01**	33 / 17	36 / 16	0.72
Age (SD)	41.4 (12)	44.9 (13)	0.16	40 (12)	45 (12)	0.09
Depression						
Baseline (SD)	31.3 (5.8)	30.3 (6.2)	0.47	30.8 (5.6)	30.6 (6.4)	0.91
Endpoint (SD)	14.5 (9.2)	21.6 (10.8)	**<0.01**	15.6 (10.4)	20.3 (10.4)	**0.02**
Clinical response	30 (56.6%)	14 (28.5%)	**<0.01**	27 (54%)	17 (32%)	**0.03**
Adverse effects (AE)						
Sleepiness	22 (44%)	13 (27%)	0.07	15 (30%)	20 (40%)	0.33
Itching	19 (38%)	11 (22.5%)	0.09	17 (35%)	13 (26%)	0.35
Trouble concentrating	10 (20.5%)	12 (24.5%)	0.63	8 (16%)	14 (29%)	0.15
Headache	9 (18%)	8 (16%)	0.79	7 (14%)	10 (20%)	0.42
Skin redness	12 (25%)	4 (8%)	**0.03**	8 (16%)	8 (16%)	1
Correct guessing						
Total	44 (83%)	18 (37%)	**<0.01**	29 (58%)	39 (75%)	0.07
Clinical response subgroup	29 (97%)	4 (29%)	**<0.01**	18 (67%)	15 (88%)	0.11
No clinical response subgroup	15 (65%)	14 (40%)	0.06	11 (48%)	24 (69%)	0.11

"Depression" refers to baseline and endpoint scores in the Montgomery–Asberg depression rating scale. Clinical response is >50% depression improvement from baseline to endpoint. SD is standard deviation. Significant *p* values are in bold.

Table 2
Distribution of guessing among participants and raters.

Participants	Device			Pill		
	Correct group			Correct group		
Guessed group	*Sham tDCS*	*Active tDCS*	χ^2 or "e" (*p*)	*Placebo*	*Sertraline*	χ^2 or "e" (*p*)
Week 2						
Sham tDCS/Placebo Pill	3	4	–	12	8	2.3
Active tDCS/Sertraline	16	12	(0.67)	6	9	(0.2)
Week 4						
Sham tDCS/Placebo Pill	5	6	0.5	14	6	–
Active tDCS/Sertraline	14	10	(0.48)	4	11	(**<0.01**)
Week 6						
Sham tDCS/Placebo Pill	18	9	5.1	39	21	11.4
Active tDCS/Sertraline	31	44	(**0.03**)	13	29	(**<0.01**)
Raters	Device			Pill		
Week 2						
Sham tDCS/Placebo Pill	10	6	0.8	12	7	2.29
Active tDCS/Sertraline	9	10	(0.37)	6	10	(0.13)
Week 4						
Sham tDCS/Placebo Pill	14	5	4.6	11	6	3.44
Active tDCS/Sertraline	6	10	(**0.03**)	6	12	(0.06)
Week 6						
Sham tDCS/Placebo Pill	13	8	1.23	13	6	3.8
Active tDCS/Sertraline	6	8	(0.26)	5	11	(**0.02**)

Each cell represents the absolute number of patients according to the cross-tabulation guessing *vs.* correct group. For raters and participants at weeks 2 and 4, 35 participants were assessed. At week 6 for participants, 102 participants were surveyed. For each distribution the χ^2-test or the Fisher's exact test was calculated (for the exact test only the *p* values are shown). Statistical significant values are in bold.

such results remained significant when performing additional analyses according to whether subjects were asked vs. not asked on blinding at weeks 2 and 4 ($p < 0.05$ for all analyses).

Interestingly, whereas for sertraline and for raters the guessing distribution was relatively even, participants would more frequently guess that they received active than sham tDCS (Table 2). As we further discuss, this could be related to the expectancy of patients in receiving a novel treatment.

At week 6, subjects were moderately confident on their guessing according to the Likert scale for both sertraline ($M = 3.6$ SD = 1.2) and tDCS ($M = 3.8$ SD = 1.2). These rates were not statistically different ($t = 1.05$, $p = 0.3$). Considering the rates 4 and 5 only (almost/absolutely confident on their guessing), sertraline but not tDCS use ($\chi^2 = 9.9$, $p < 0.01$; $\chi^2 = 2.8$, $p = 0.09$, respectively; $n = 62$ for both) was guessed correctly.

3.1.2. Raters

The raters failed to identify the allocation group at week 2. At week 4 they correctly guessed beyond chance for tDCS and a trend-wise for sertraline ($p = 0.06$). At week 6 only the sertraline group was correctly guessed beyond chance (Table 2).

3.2. Qualitative description of blinding integrity

For participants, the two main reasons described for guessing were depression symptoms improvement and AEs; being the

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frequency of depression improvement reason statistically superior to AEs reason for participants at almost all timepoints (Table 2). Interestingly, although frequency of depression improvement reason was in most of the assessments higher than 50% for both groups; for tDCS there was an increase in the frequency of this reason over weeks 4 and 6 (from 52% to 75% and 72%, respectively) as compared with sertraline group in which this reason remained relatively constant (52%, 44% and 54%). In fact at week 6, interestingly, AEs reason was more pronounced for the sertraline group than tDCS group (40% vs. 16%).

For tDCS, raters' guessing reasons were similar than participants' reasons, i.e., mainly based on depression improvement. For sertraline, however, raters' guessing was mainly based in AEs (Table 3).

We also compared whether the distribution of the answers vs. correct guessing occurred beyond chance. For tDCS, we found a significant association for participants at week 2 ($p = 0.01$) but not at weeks 4 and 6 ($p = 0.28$ and 0.14, respectively). At week 2, we found that participants who based their guessing on depression improvement were more likely to correctly guess their allocated group (41% vs. 70% for incorrect and correct guessing, respectively), whereas those who based their guessing on AEs were less likely to perform a correct guess (53% vs. 7%, respectively).

For raters, no significant association was observed at weeks 2, 4 and 6 ($p > 0.33$ for all comparisons) – in other words, the reasons raters provided for their guessing did not correctly guide their choice.

3.3. Quantitative analysis of blinding integrity

We analyzed the AEs that were either reported in more than 20% of the sample or were more frequent in one group.

Table 3
Qualitative description of reasons for blinding guessing for 35 participants.

	tDCS		Sertraline	
	Subjects	Raters	Subjects	Raters
	N	*N*	*N*	*N*
Week 2				
Related to adverse effects	11 (35%)	2 (7%)	12 (41%)	20 (59%)
Related to depression improvement	16 (52%)	27 (90%)	15 (52%)	5 (15%)
Other reasons	4 (13%)	1 (3%)	2 (7%)	9 (26%)
χ^2 (p)	7.03 (**0.03**)	43.4 (**<0.01**)	9.5 (**<0.01**)	10.6 (**<0.01**)
Week 4				
Related to Adverse effects	5 (18%)	4 (17%)	9 (26.5%)	16 (44.5%)
Related to depression improvement	21 (75%)	18 (75%)	15 (44%)	5 (14%)
Other reasons	2 (7%)	2 (8%)	10 (29.5%)	15 (41.5%)
χ^2 (p)	22.3 (**<0.01**)	19 (**<0.01**)	1.8 (0.4)	6.16 (**0.04**)
Week 6				
Related to adverse effects	5 (16%)	1 (5%)	13 (40%)	9 (50%)
Related to depression improvement	23 (72%)	20 (95%)	18 (54%)	9 (50%)
Other reasons	4 (12%)	0	2 (6%)	0
χ^2 (p)	21 (**<0.01**)	36.2 (**<0.01**)	12.2 (**<0.01**)	9 (**0.01**)

The table describes the frequency of the described reasons for the guessing of raters and subjects, classified in "related to adverse effects", "related to depression improvement" and other reasons (please see the main text). We also show the Pearson's χ^2 and p values of the comparison of the observed frequency vs. an evenly distributed frequency. For instance, at week 2 (tDCS/subjects), we performed the χ^2 comparing the observed distribution (11, 16, 4 subjects) vs. a theoretical, evenly distributed frequency (10.33 subjects per group). The total sum varies because participants/raters did not answer to the questionnaire whether they could not describe their guessing reasons.

Table 4
Univariate and multivariate logistic regressions of factors associated with correct blinding guessing of participants.

Independent variable	Univariate regression		Multivariate regression	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Gender	0.47 (0.2–1.1)	0.08	0.62 (0.22–1.7)	*0.3*
Clinical response	3 (1.3–7)	**0.01**	2.7 (0.84–6.47)	**0.048**
High guessing confidence	0.88 (0.4–2)	0.77	0.57 (0.2–1.6)	0.27
Adverse effects				
"Sleepiness"	0.96 (0.4–2.2)	0.92	1.1 (0.37–3)	0.87
"Itching"	2.24 (0.8–5.7)	0.09	2.4 (0.8–6.5)	0.09
"Trouble concentrating"	0.28 (0.1–0.75)	**0.01**	0.22 (0.05–0.93)	**0.03**
"Headache"	0.93 (0.3–2.7)	0.89	1.16 (0.47–10.1)	0.81
"Skin redness"	1.5 (0.5–4.9)	0.44	0.46 (0.35–4.6)	0.64
Active tDCS only				
Gender	0.9 (0.15–5.1)	0.9	0.75 (0.06–8.2)	0.28
Clinical response	15.4 (1.7–135)	**0.01**	13.8 (1.1–166)	**0.04**
High guessing confidence	2.2 (0.5–9)	0.29	0.28 (0.02–3.7)	0.33
Adverse effects				
"Sleepiness"	0.8 (0.16–3.4)	0.41	2.1 (0.13–29)	0.57
"Itching"	5.2 (0.6–46)	0.13	9.15 (0.5–167)	0.13
"Trouble concentrating"	0.17 (0.03–0.87)	**0.03**	0.06 (0.01–5)	0.22
"Headache"	0.28 (0.05–1.5)	0.14	2.89 (0.05–115)	0.57
"Skin redness"	0.96 (0.16–5.7)	0.97	0.57 (0.05–8)	0.67
Sham tDCS only				
Gender	0.67 (0.2–2.2)	0.52	0.7 (0.15–3.1)	0.64
Clinical response	0.6 (0.15–2.3)	0.45	0.33 (0.05–1.62)	0.17
High guessing confidence	0.48 (0.14–1.6)	0.22	0.28 (0.06–1.32)	0.1
Adverse effects				
"Sleepiness"	0.4 (0.1–0.8)	**<0.01**	0.43 (0.08–2.5)	0.35
"Itching"	0.98 (0.2–3.9)	0.97	0.56 (0.1–3)	0.51
"Trouble concentrating"	0.26 (0.05–1.3)	0.11	0.08 (0.01–0.82)	**0.03**
"Headache"	1.9 (0.4–8.9)	0.4	4.24 (0.36–39)	0.2
"Skin redness"	0.54 (0.05–5.7)	0.61	0.13 (0.01–3.1)	0.16

Clinical response is >50% depression improvement from baseline to endpoint. "High guessing confidence" describes participants who described to be almost/completely sure on their guessing. Significant p values are in bold.

Importantly, since the gender distribution was significantly different between active vs. sham tDCS, this variable was analyzed in our regression models. We found that whereas for sertraline there was a non-significant trend for higher rate of correct guessing when receiving placebo; participants receiving active vs. sham tDCS guessed more correctly their allocation (83% vs. 37%, $p < 0.01$). Further univariate and multivariate logistic regressions (Table 4) revealed that clinical response was directly associated with correct guessing and the AE "*trouble concentrating*" was inversely related to correct guessing – i.e., participants who correctly guessed their tDCS allocation group presented greater depression improvement whereas incorrect guessing was associated to reporting the AE "*trouble concentrating*" with increased frequency. In addition we found that incorrect guessing in the sham tDCS group was associated with increased frequency in reporting the AEs "*sleepiness*" (in the univariate regression) and "*trouble concentrating*" (in the multivariate model) (Table 4).

4. Discussion

We hereby evaluated the blinding integrity in the SELECT-TDCS (Brunoni et al., 2013), a randomized, factorial (2 × 2) controlled trial for major depression that used two interventions: verum/pla-

cebo sertraline pill and active tDCS vs. a standardized sham tDCS method in which a brief stimulation session precedes a simulated session to mimic AEs and keep participants and investigators unaware of the allocation group. Our main findings were: (1) the blinding assessment of a pharmacological (sertraline) and a non-pharmacological (tDCS) intervention presented overall similar results; (2) blinded raters were not different than participants in correct guessing the allocation group; though participants were generally more accurate in their guessing; (3) although AEs (but, notably, not skin redness) were associated with correct guessing, the main factor associated with correct guessing was clinical response; and (4) correct guessing of treatment allocation increases over time at least in the context of two treatments in which active intervention is associated with positive clinical outcome. These findings are further discussed.

4.1. Methodological considerations

An important strength of our results is that we had a concomitant pharmacological treatment; thereby we were able to compare the 2 mA tDCS sham method against the placebo-pill (the gold standard approach). In fact, we found that, although participants correctly guessed tDCS use beyond chance, this also occurred for the pharmacotherapy – indeed, for the "high confidence" guessers, only pharmacotherapy use was guessed beyond chance. Of note, 50 mg of sertraline has less AEs than higher doses, which further corroborates the good quality of tDCS blinding since even with a low sertraline dose patients and raters were not able to distinguish it from sham tDCS. In the participants who were also assessed at other timepoints only sertraline use at week 4 was correctly guessed beyond chance, whereas raters correctly guessed tDCS use only at week 4 and sertraline use only at week 6. In addition, the immediate, post-tDCS AEs, which are a significant threat to blinding breaking and thus study validity was not the main factor for correct guessing in our study – indeed, guessing of sertraline was associated more with the reason of AEs than tDCS. Taken together, these findings indicate the blinding of tDCS can be considered at least as reliable as of a pharmacological therapy for depressed patients.

We assessed blinding by asking participants and raters to guess their allocation group, similarly than other tDCS studies assessing blinding (Gandiga et al., 2006; O'Connell et al., 2012; Palm et al., 2013). Even though, the latest, 2010 CONSORT guidelines eliminated text on blinding assessment (Schulz et al., 2010), reflecting the fact that in RCTs testing for blinding does not *de facto* reflect blinding validity, but rather on "hunches" on efficacy (Sackett, 2007) – in agreement, we found that responders were more accurate in identifying that they received active tDCS and at week 2 guessing based on clinical improvement correctly predicted the allocation group. Interestingly, guessing based on (the presence or absence) of AEs was associated with statistically worse guessing. This means that, for the sham group, our sham procedure adequately mimicked the common adverse tDCS effects and/or, for the active group, these AEs were mild and well tolerated. Although this may contrast the recent results of the study of O'Connell et al. O'Connell et al. (2012) in which guessing of active tDCS was superior compared to sham tDCS in a sample of healthy subjects after a single session of tDCS; several considerations need to be made in order to integrate both findings that we believe go in the same direction. First, for the crossover phase of the study of O'Connell et al., guessing was much superior when active tDCS was administered after sham tDCS. Second, those subjects had a lower level of confidence in the first vs. the second session when they compared both treatments. Finally, in the context of daily, repeated sessions in a parallel trial, participants might be much more sensitive to the suggestion of sham tDCS method as shown in our results. Taken together, blinding of tDCS seems to be adequate in parallel designed clinical trials in which several sessions are administered as shown in our results in which blinding is comparable between sham tDCS and placebo pill.

In addition, we assessed blinding in other timepoints and for raters in approximately one-third of the sample, and therefore, such analyses might have been underpowered. Another potential concern is whether asking repeatedly on blinding could have lead to break of blinding. Nevertheless, in additional analyses we found that this did not occur in our study. Finally, participants were more prone to respond (not necessarily correctly) that they received active rather than sham tDCS (for instance, at week 6 only 27% guessed to sham tDCS). This did not occur for sertraline and for raters' guessing, which presented a more even distribution of guessing. Here, one possibility is that patients had increased expectancy that they would receive tDCS, since they volunteered to a trial in which tDCS was tested. Therefore, patients could have associated depression improvement to tDCS even if they presented response in the sertraline or placebo groups.

Finally, we used a 30 s ramp-in/15 s ramp-out in our study. As suggested by Palm et al. Palm et al. (2013), such relatively longer ramp-in phase could have attenuated itching and other skin sensations. O'Connell et al. O'Connell et al. (2012), for instance, who reported inadequate tDCS blinding, used a much shorter (5 s) ramp-in phase. Although further trials should investigate the impact of the duration of the ramp-in phase on blinding, we suggest that longer ramp-in phases are preferable for blinding purposes, especially when daily, tDCS sessions are applied. Similarly, further trials should investigate the importance of ramp-out on tDCS blinding integrity.

4.2. Improving blinding for tDCS trials

As abovementioned, the interpretation of blinding assessment by assessing patients' and raters' guessing is limited in RCTs since it is difficult to disentangle correct guessing from clinical improvement. For this reason, recent guidelines (Sackett, 2007; Schulz et al., 2010) suggest that blinding can be improved and assessed by verifying whether some trial biases were avoided such as:

(a) "contamination" (patients obtaining the treatment outside of the trial) – for tDCS, this issue is of potential concern given the simplicity and ease of use for tDCS, although at the present time tDCS is not widely available yet. If it becomes more available, researchers would need to be careful to not describing to patients the specific stimulation protocol (e.g., current dose, electrode size, electrode positioning etc.).
(b) "co-intervention" (concomitant delivery of other interventions, e.g., psychotherapy) – this can be avoided by appropriate training of raters and standardization of scales and also by adopting procedures to minimize blinding harming such as avoiding contact between participants, preventing participants to seeing the device, training tDCS appliers to adopt exactly the same procedures regardless of the intervention and so forth (Boutron et al., 2007).
(c) "biased event-reporting" (downplaying symptom reporting and assessment based on the perception of the allocation group) – this can also be avoided by using the same procedures described in (b).

Another concern of tDCS blinding is when the devices are turned off – even with the adequate training of the appliers, using automated tDCS devices could further enhance this step. Finally, as previously discussed here and reported by Palm et al. Palm et al. (2013), parallel (vs. crossover) designs should be preferred.

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Unblinding due to AEs should also be avoided. Interestingly, although we found that skin redness was more present in the active vs. sham group; this did not influence blinding, in opposite of other reports (O'Connell et al., 2012). Notably, our rate of skin redness was relatively low as previously reported (Brunoni et al., 2011; Palm et al., 2013). We conjectured that this could be due to ethnicity, since most trials were performed in Caucasian countries and Brazilians have mixed ethnicity, and redness could be differently noticed among skin colors. Nevertheless, nor whites vs. non-whites reported more skin redness (17% vs. 11%, respectively, $p = 0.47$) and neither of these groups differed on blinding assessment (correct guessing of 63% vs. 53%, respectively, $p = 0.38$) (data not shown in results). Another possibility is an attenuation of the local vasodilatation effects when daily, repeated tDCS is applied or also associated with different methodology of tDCS administration such as type of saline solution, type of electrodes and type of head bands that may all influence the degree of skin redness. Nonetheless, Loo et al. Loo et al. (2012) described higher rates of skin reddening in their 15-day tDCS trial with almost all participants of both groups presenting this AE. This discrepancy can be related that our assessment was based on the subjects' report whereas Loo et al. objectively assessed this effect.

Further, raters' relatively underperformed compared to subjects in identifying the allocation group. Also, the reason of their "hunch" was not associated with correct guessing. The factorial design can account for this finding, in which raters could have not unequivocally associated clinical improvement with tDCS effects (as sertraline was another active treatment); in addition AEs did not guide their guessing because they were overall fairly distributed between groups. Our findings also contrast with O'Connell et al. O'Connell et al. (2012) in which assessors were fairly accurate. However, in their study the assessors directly examined the stimulation site just after the session ended, whereas we interviewed participants in distinct occasions. Notwithstanding, both studies could reflect that skin redness is a short-lived effect, and we suggest that this AE can be effectively handled by introducing a short interval between tDCS session and the interview.

Another AE ("*trouble concentrating*") was associated with a *lower* likelihood of guessing. Although not formerly asked, this could mean that concentration *improvement* might be related with correct guessing. This interpretation is consistent with previous reports showing improvement of executive functioning with tDCS in depression trials (Fregni et al., 2006b; Loo and Martin, 2012) and might be, in fact, more related to symptom improvement rather than AEs.

4.3. tDCS blinding and major depression

There are specific effects associated with daily, repeated tDCS in major depression, such as treatment-emergent hypomania (Arul-Anandam et al., 2010; Baccaro et al., 2010; Galvez et al., 2011) and mania (Brunoni et al., 2011). Of note, we observed a non-statistically increased frequency of this AE in the combined treatment group and no cases in the placebo group - such cases are discussed elsewhere (Brunoni et al., 2013), as we only assessed study completers here. Considering tDCS use for depression, long-term trials are needed to disentangle whether such effect is particularly associated to tDCS.

Importantly, depressed patients might present increased sensory and warmth thresholds to electrical stimulation (Adler and Gattaz, 1993; Bar et al., 2003); these patients might also be less sensible to thermal and electrical pain (Bar et al., 2005) and, generally, have decreased pain perception compared to healthy subjects (Dickens et al., 2003). Therefore, since skin perception is key for tDCS blinding, and depressed patients seem to present decreased skin perception; tDCS blinding should be also assessed in other clinical populations.

Nonetheless, considering previous RCTs of tDCS for depression, the blinding integrity was an important concern since, as abovementioned, only 4 of 7 RCTs assessed blinding and, although they reported that blinding was adequate, in three of thee results were negative. Our study shed light in this important question by showing that tDCS vs. a pharmacological intervention presented comparable blinding integrity, and that blinding guessing beyond chance was associated to clinical improvement.

4.4. Conclusion

In a RCT for major depression with a factorial design and two active interventions (sertraline/placebo and 2 mA active/sham tDCS), blinding assessment of the pharmacological and non-pharmacological interventions was comparable. TDCS blinding was mainly associated with clinical improvement and adverse effects that possibly reflect cognitive improvement. External raters tended to be less accurate in correctly guessing the allocation group as compared to participants. To enhance blinding in tDCS trials, common procedures for other non-pharmacological trials should be followed. Particularly to skin reddening, the unblinding of this adverse effect can be managed by avoiding awareness of participants (for instance, looking at the mirror or contacting peers following stimulation) and raters – for instance, by adopting a rest period between tDCS session and the clinical interview. In addition, the use of parallel design is recommended in the context of clinical trial as to avoid more correct guessing in crossover trials.

Conflicts of Interest

None.

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