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Original Research

Evaluation of sham transcranial direct current stimulation for randomized, placebo-controlled clinical trials

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) has been investigated as therapeutic intervention in various psychiatric and neurologic disorders. As placebo responses to technical interventions may be pronounced in many clinical conditions, it is important to thoroughly develop placebo conditions which meet the requirements for application in randomized double-blind controlled trials.
Objective: The two-part experiment reported here aims at evaluating a new sham tDCS condition in healthy subjects and device operators. Sham or active tDCS is delivered after entering a number code to the device and allows blinding of the operator before and during tDCS. The sham mode has no short stimulation period.
Methods: The experimental sequence was as follows: 1) Evaluation of successful blinding by comparing placebo to active stimulation at prefrontal sites based on the rating of subjects undergoing tDCS, 2) Evaluation of successful blinding by comparing placebo to active stimulation at prefrontal sites based on the operator/observer ratings.
Results: Subjects were not able to distinguish between active and sham tDCS for prefrontal stimulation. Overall there was no relevant discomfort and tDCS was well tolerated. Operators/observers were able to identify sham stimulation based on skin reddening after active, but not after sham tDCS.
Conclusions: The tDCS sham condition investigated here may be suitable for placebo-controlled trials keeping subjects blind to treatment conditions. However, operators can easily be aware of the condition applied and they should not get involved in rating outcome measures during the course of high standard placebo-controlled trials.

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Introduction

Over the past years, transcranial direct current stimulation (tDCS) turned out to be a promising tool in treatment of various neurologic and psychiatric disorders as well as in basic cognitive and neurophysiological research [1,2]. A couple of randomized and placebo-controlled studies on tDCS treatment in affective disorders has suggested its efficacy [3]. Despite subjective impressions of DC stimulation appeared to be equal in sham and active treatment [4], blinding conditions in early studies turned out to be potentially unreliable, due to technical properties of some custom-built stimulators or an observed lack of itching skin sensations in sham treatment. Early studies used self-constructed stimulators which were manually switched off for placebo stimulation. For a better blinding, some of these devices were amended with a switch on the rear side to switch off current without patient's knowledge. Although display settings remained unchanged after stopping current flow, patients could become aware of a manipulation of the stimulator. For this reason, in some studies the stimulator was placed behind the patients. The technique of short-lasting manual or automatic current increase and decrease to simulate the itching sensation of the real stimulation in the placebo condition has frequently been used [5–13]. The method of switching off the stimulator after 30 s in the sham stimulation condition has also been used by Gandiga et al. [14] for tDCS blinding purposes and

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seemed to be effective as subjects failed to discern between active and sham stimulation. Poreisz et al. [15] reported similar results in a study on safety aspects of tDCS and experienced a low rate of correct guesses although the stimulator was switched off manually. Even if the stimulator was kept out of the patient's sight in these cases and additional covering of the display may blind the patient, the applying person is not blinded in this case and could unintentionally influence patient's reaction by expecting differences in treatment outcome and may even bias self rating. Loo et al. [16] used a programmable DC stimulator with automatical switching off and placed it behind the subjects in order to avoid reading the display. Active and sham guesses between the two groups were not different. More recent placebo-controlled trials [17,18] used a programmable DC-stimulator with ramp-in/ramp-out phases investigated here. These ramp-in phases in active and sham treatment usually last 15–30 s; early but also recent tDCS studies reported also 5 or 10 s [19–22]. Itching sensations under active tDCS were reported by participants for more than 1 min duration, especially when stimulating with 2 mA instead of 1 mA ([23]; own observation). This could be a potential differentiator for subjects and may break blinding. A recent study by O'Connell et al. on participant and investigator blinding showed that the itching sensation and skin redness could be discriminators even in tDCS-naïve persons receiving 2 mA active vs. sham tDCS [22]. Ambrus et al. [24] reported that investigators receiving tDCS were able to discern cutaneous sensations between active and sham stimulation.

However, stimulation ramp-in and ramp-out phases varied in both studies from 5 s [22] to 20 s [24]. Duration of active current before switching off was 30 s in both studies. Besides the systematic assessment of this short stimulation approach in sham tDCS [22,24], no data are available on effective blinding of tDCS without a short active stimulation period in the sham condition. Here, we therefore investigated the quality of blinding accomplished by sham tDCS in two sequential experiments without short active stimulation during sham tDCS. In the first experiment, sham tDCS was compared to active stimulation at prefrontal sites based on the rating of subjects undergoing stimulation. In the second experiment, sham tDCS was compared to active stimulation at prefrontal sites based on the operator/observer ratings.

Methods and materials

Subjects

Sixteen healthy subjects (25–33 years) participated in this study. The test persons of the second experiment had already completed the first experiment. Subjects with a history of psychiatric or neurological disorders or taking any medication including herbal drugs were excluded from the experiment. All subjects were right-handed, as assessed by the Edinburgh–Handedness Test, and naïve to tDCS. All subjects gave their written informed consent and were compensated for participation. The information sheet comprised the explanation of frequent adverse effects such as itching and tingling skin sensation, skin reddening, and headache. There was no information on differences between active and sham condition. The experiments were approved by the Ethics Committee of the University of Munich and conducted in accordance to the Declaration of Helsinki.

DC stimulation

For DC stimulation, a neuroConn *eldith* DC-stimulator PLUS with study mode was used (neuroConn GmbH, Ilmenau, Germany). This device is a microprocessor-controlled, battery-driven constant current source, complying with the Medical Device Directive of the European Union (CE-certified). Application time, current range and frequencies are programmable, settings can be saved. Active or sham stimulation mode is chosen by manual entering of different number codes. These codes, delivered in the stimulator manual and distributed by the principle investigator, activate either sham or active stimulation. The sham tDCS mode starts with a variable ramp-in and ramp-out phase, followed by an impedance control mode with small measuring pulses of 100–200 μA amplitude every 400–550 ms for the same period as in the active condition, and ends with another ramp-in and ramp-out phase (see Supplemental Fig. 1). During sham mode the display imitates the settings of the active mode by simulating typical parameters of current strength, voltage and impedance. In case electrode contacts loosen, impedance increases and stimulation is automatically terminated in both modes. Even in this case, the operator does not notice any difference between active and sham devices, however the operator is informed by a display message that the stimulation was terminated due to impedance exceed. DC was applied through a pair of tap-water soaked sponge electrodes with a surface area of 35 cm^2 (7×5 cm), fixed by rubber bands on the head. In this study different durations of DC stimulation (10, 20 min) were used.

Experiment 1

Ten test persons (5 females, 5 males; mean age 28.9 ± 2.7; age range 25–33; naïve to tDCS) had to distinguish if they received active or sham stimulation. Subjects received active and sham stimulation in randomized order, being unaware of having only one or both conditions. Random sequence was obtained from a computerized random generator. Stimulation was applied by an operator (member of the study group) blinded to the condition. During stimulation, test persons were sitting in a reclining chair in a separate room with only the operator present who was instructed not to communicate on any detail of the stimulation. Before and after stimulation, test persons were separated from each other to avoid communication about tDCS. 2 mA tDCS was applied over 20 min with a ramp-in and ramp-out phase of each 15 s, with at least 48 h interval between the two stimulations; the anode was placed over the left dorsolateral prefrontal cortex (DLPFC), cathode over the right supraorbital region. The duration of 20 min stimulation was chosen to imitate the situation of study interventions as many interventional studies of the past years used a 20 min protocol. Subjects had to evaluate their sensations during both stimulations on a 5-item scale ranging from not at all unpleasant over lightly, moderate, fairly to highly unpleasant. After the second stimulation they were asked if they had perceived a difference between the stimulations and which condition they had received. Furthermore they had to fill in a 5-item scaled questionnaire comprising the topics pain, tingling, itching sensation, burning sensation, fatigue, nervousness, difficulties in concentration, changes in visual perception, headache and unpleasant sensation. The second questionnaire was answered during and after stimulation, in the questionnaire answered after stimulation, the item "unpleasant sensation" was replaced by "nausea".

Experiment 2

While 6 volunteers (3 females, 3 males; mean age 27.4 ± 2,83; range 26–30, naïve to tDCS before experiment 1) received DC stimulation, 5 observers (3 females, 2 males; mean age 27.1 ± 3.40; range 26–31; members of the study group) had to guess whether active or sham stimulation was applied. One test person after another was seated in a reclining chair with the operator behind them and the observers were grouped together in front of them in

a distance of 2 m. All participants were instructed to be silent during the test procedures. Observers did not know the questionnaire in advance and they were prevented from communicating during the breaks between the consecutive stimulations. They were unaware if test persons having only one or both conditions, however each volunteer received active and sham 2 mA tDCS in random order over 10 min with at least 2 h interval between both conditions. Random sequence was obtained from a computerized random generator. tDCS was applied by an experienced member of the study group not involved in the trial. As adverse effects already can be seen after a few minutes of stimulation, a shorter stimulation period was chosen, as compared to the first experiment, to avoid stronger neuromodulating effects. Observers had to fill in a questionnaire evaluating subject's reaction, changes in facial expression, pain, skin redness, sweating under the electrode area, sound or vibrations. The latter were defined as tremor of skin muscles by a sudden discharge or current pulse.

Data analysis and statistics

SPSS 13.0 was used for all statistical analyses. In experiment 1 and 2, paired *t*-tests were performed, in experiment 1 additionally Fisher's exact test for the variables "correct guesses" and "all guesses".

Results

Results of experiment 1

In the first questionnaire, 70% of the test persons rated sham stimulation not at all disagreeable, 20% reported it as slightly and 10% as moderately unpleasant. During active stimulation, 50% reported tDCS as not at all unpleasant, 30% slightly and 20% moderately unpleasant. In the second questionnaire, subjects frequently reported tingling (70% vs. 50%) and burning (60% vs. 59%) during active resp. sham stimulation (Table 1). After stimulation, fatigue was frequent in both groups (40% after active, 30% after sham stimulation) (Table 1). Active stimulation resulted in significantly more itching sensations, nervousness and headache than sham stimulation ($P < 0.05$, paired *t*-test). Pain and burning sensations were more intense during active tDCS than after stimulation ($P < 0.05$). Also tingling, burning sensations, and nervousness were significantly more pronounced ($P < 0.05$) during tDCS than after stimulation (Table 2).

Fifty percent of subjects were unable to differentiate between both stimulation conditions (no correct guess in 10 of 20 guesses), 20% (4/20) guessed one condition correctly and 30% (6/20) guessed both conditions correctly. Fisher's exact test showed no significance between active and sham stimulation for correct guesses ($P = 0.92$) and all guesses (2-tailed, $P = 0.65$).

Results of experiment 2

Overall, observed reactions did not significantly differ between sham and active stimulation except for skin redness, which was significantly more frequent after active stimulation compared to sham tDCS ($t = 3.495$; $P = 0.038$). Changes in facial expression and pain were trendwise more frequent in sham stimulation than in active stimulation ($t = -1.975$; $P = 0.058$ resp. t 1.989; $P = 0.056$). Sweating, sound or vibration did not occur in any of the conditions. *T*-test subanalyses with regard to order showed significant differences between "any reaction in subjects" during the second stimulation ($t = 2.168$; $P = 0.048$) for the sham mode, "change in facial expression" during first and second stimulation for the sham mode ($t = -2.606$; $P = 0.021$ resp. t 2.449; $P = 0.028$), and "pain" during first stimulation for the sham mode ($t = -2.323$; $P = 0.036$) (Table 3).

Observers were able to identify 47/60 (78%) stimulations correctly (22/30 or 73% after first stimulation; 25/30 or 83% after second stimulation). The difference in discrimination between the first and second stimulation was not significant ($t = 1.00$; $P = 0.36$; SD = 0.55).

Discussion

In this study, a novel sham tDCS condition was tested for its application in placebo-controlled double-blind trials as such trials are needed for approval of any therapeutic application of tDCS in

Table 1
Adverse effects of active and sham tDCS during and after stimulation.

	Incidence[a] and intensity[b]	During stimulation		After stimulation	
		Active	Sham	Active	Sham
Pain	Incidence	2	2	0	1
	Intensity	1.0 ± 0	2.0 ± 1.4	0	1.0 ± 0
Tingling	Incidence	7	5	2	1
	Intensity	2.0 ± 1.6	2.0 ± 0.7	2.0 ± 1.4	1.0 ± 0
Itching sensation	Incidence	3	1	2	1
	Intensity	1.7 ± 1.6	2.0 ± 0	1.0 ± 0	1.0 ± 0
Burning sensation	Incidence	6	5	1	1
	Intensity	1.6 ± 0.8	1.8 ± 0.8	1.0 ± 0	1.0 ± 0
Fatigue	Incidence	4	3	4	3
	Intensity	1.5 ± 0.6	2.0 ± 0	1.5 ± 0.6	1.3 ± 0.6
Nervousness	Incidence	0	2	0	0
	Intensity	0	1.5 ± 0.7	0	0
Difficulties in concentration	Incidence	0	0	0	0
	Intensity	0	0	0	0
Changes in visual perception	Incidence	0	0	0	0
	Intensity	0	0	0	0
Headache	Incidence	1	0	0	0
	Intensity	1.0 ± 0	0	0	0
Unpleasant sensation	Incidence	2	2		
	Intensity	1.5 ± 0.7	1.5 ± 0.7		
Nausea	Incidence			0	0
	Intensity			0	0

[a] Incidence: number of participants reporting the adverse effect.
[b] Intensity: mean intensity and SD on a 5-item-scale.

Table 2
Adverse effects of active and sham tDCS: results of paired *t*-tests of the analyses active tDCS vs. sham tDCS, during active tDCS vs. after active tDCS and during sham vs. after sham tDCS.

		Active tDCS vs. sham tDCS	During active tDCS vs. after active tDCS	During sham tDCS vs. after sham tDCS
Pain	Incidence	n.s.	$P < 0.05^{*}$	n.s.
	Intensity	n.s.	n.s.	n.s.
Tingling	Incidence	n.s.	n.s.	$P < 0.05^{*}$
	Intensity	n.s.	$P < 0.10^{\dagger}$	$P < 0.10^{\dagger}$
Itching sensation	Incidence	$P < 0.05^{*}$	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.
Burning sensation	Incidence	n.s.	$P < 0.05^{*}$	$P < 0.05^{*}$
	Intensity	n.s.	$P < 0.05^{*}$	$P < 0.05^{*}$
Fatigue	Incidence	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.
Nervousness	Incidence	$P < 0.05^{*}$	n.s.	$P < 0.05^{*}$
	Intensity	n.s.	n.s.	n.s.
Difficulties in concentration	Incidence	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.
Changes in visual perception	Incidence	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.
Headache	Incidence	$P < 0.05^{*}$	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.

* Column 3: significantly higher with active tDCS, columns 4 and 5: significantly higher during tDCS stimulation.
† Trendwise higher during tDCS.

Table 3
Observed reactions during active versus sham stimulation: total and with regard to order (paired *T*-test).

	Stimulation mode		*P* (2-tailed) (both stimulations)	*P* (first stimulation)	*P* (second stimulation)
	Active (mean ± SD)	Sham (mean ± SD)			
Any reaction in subjects	1.3 ± 0.7	1.5 ± 1.1	0.293	0.140	0.048*
Change in facial expression	1.2 ± 0.5	1.5 ± 1.1	0.058	0.021*	0.028*
Pain	1.2 ± 0.5	1.4 ± 0.9	0.056	0.036*	0.055
Skin redness	3.2 ± 1.1	2.1 ± 1.2	0.002*	0.038*	0.001*
Sweating	Not observed				
Sound/vibration	Not observed				

*Significance < 0.05.

neurological or psychiatric disorders. The stimulator used allows blinding of both patients and operator, as the sham condition is delivered by an automatic function programmed in advance by a person without direct involvement in the study process, e.g., the principal investigator. This new function renders manipulation of the stimulator for switching off current unnecessary as active or sham mode is activated at the beginning of the stimulation by entering a number code. Another feature differing from recently used stimulation protocols is the fade-out of current after ramp-in without a short-stimulation period. Although a short (e.g., 30 s) period of active stimulation does not appear to have a neuromodulating effect beyond stimulation [1], unpleasant skin sensation seems to outlast the short period stimulation, could be correlated with the subject's arousal [24] and may interfere with the subject's assumptions on the condition received.

In our study, slight differences in the perception of active vs. sham stimulation modes in subjects undergoing tDCS occurred, however, subjects were not able to reliably identify the stimulation mode. In contrast, experienced operators may be able to guess whether active or sham tDCS is applied even when the control of the device is masked by a cover. Experience in tDCS seems to lead to a higher discrimination rate between active and sham stimulation as Ambrus et al. [25] and O'Connell et al. [22] showed in healthy volunteers.

However, the absence of a short active stimulation period during sham tDCS seems to have no impact on the differentiation of both conditions: In experiment 1, correct discriminations were on a lower level compared to the haphazard hit ratio which supports findings of Fregni et al. [10], Gandiga et al. [14] and Wassermann et al. [26]. Discomfortable side effects occurred in both sham and active condition with incidences of up to 70%, although intensities were low with maximum in itching skin sensations during active stimulation and in tiredness after sham stimulation. The latter could be explained by a lack of mental activation over 20 min and has already been described as "nocebo-like effect" [27]. Incidence of itching skin sensation, headache, and nervousness were significantly larger during active stimulation compared to sham stimulation. Intensity of side effects did not differ between both conditions. Gandiga et al. reported similar frequency of itching skin sensations during active stimulation, but burning sensations doubled in our study compared to Gandiga et al. [14] and Poreisz et al. [15]. This could be explained with a lower current strength (1 mA) and partially shorter stimulation period (9–15 min resp. 20 min) and the use of saline soaked sponges in the studies by Poreisz et al. and Gandiga et al. compared to our protocol in this experiment (2 mA over 20 min). Increased discomfort had also been reported by Dundas et al. with their investigation of elevated current strength [23]. McFadden et al. [28] proposed the use of topical anesthetics for the reduction of itching sensations, additionally hampering the differentiation between active and sham stimulation.

In experiment 2, overall 78% of the observers were able to identify the active stimulation condition, whereas observers were not able to discriminate between conditions in the study of Gandiga et al. [14]. However, our results could be biased by the experience of the observers who nearly all were members of the tDCS study group. Although observers in our study rated changes in facial expression and pain more intensive by trend during sham stimulation, only discrimination of skin redness was significant. This differentiator between active and sham stimulation has already been reported by Iyer et al. [4], Loo et al. [16] as well as in the recent trials by O'Connell [22] and Ambrus [24]. Observers' correct guesses increased from 73% in the first stimulation to 83% in the second stimulation, but this difference was not significant. Thus, tDCS operators should not be involved in clinical ratings and should have little contact to subjects undergoing tDCS in placebo-controlled trials. Moreover, the rater should not be able to see the skin under the electrodes after stimulation, because skin reddening allows observers to discern reliably between sham and real stimulation.

The present study has several limitations, which should be discussed. First, the small sample size could have prevented rejecting the null hypothesis. A larger number of participants, e.g., 20–30, would have been necessary to achieve reliable statistical power. This is particularly relevant for the results of experiment 1, where descriptive differences did not reach the level of significance. Second, the reports on itching sensations during active stimulation might have been diminished if the ramp-in and ramp-out phases were longer, e.g., 20–30 s. However, in their recent study, O'Connell et al. [22] used a short ramp-in and ramp-out phase of even only 5 s without reduction in perception comfort, as compared to 15 s ramp-in and -out in most recent studies. Third, the test persons could have influenced the observers' rating in the second experiment by unintended gesture or non-verbal communication. Although they were naïve to tDCS before the study, they could have made experience in discerning between active and sham condition in the first experiment. This could have led to a false-positive result on differentiation between both conditions of tDCS. The latter might also be due to the rating done by experienced members of the study group as observers might differently evaluate mild symptoms according to their guess of given treatment and understate mild adverse events [29]. This might be a relevant limitation in clinical trials because testing for blinding after intervention can be influenced by the assumption that the patient received the active treatment, by over or underestimating adverse effects or by additional care of the clinicians when the expected improvement of symptoms is missing [29]. Forth, in experiment 1, the comparability of the questionnaire on adverse effects during and post-stimulation is hampered by changing "unpleasant sensation" to "nausea". This was done to systematically assess nausea that rarely occurred after active stimulation in our previous investigations. However, in this sample there was no incidence of nausea and it is not mentioned in the respective literature so far.

In the past years several studies have addressed the problems of blinding in controlled trials investigating non-invasive brain stimulation as therapeutic intervention (for a review see Brunoni & Fregni [30]). However, successful blinding still is not assessed regularly [22]. Although recommendations for clinical trial design have been given in these two publications, clinicians and investigators could face problems with the conductance of time- and personnel-intensive study protocols in order to assure sufficient blinding. Thus, the suggestions of Brunoni & Fregni [30], Ambrus et al. [24], and O'Connell et al. [22] could be augmented with some details:

Cross-over design

Apart from carry-over effects that could be induced by long term neuroplasticity changes and which could blur active and sham effects, participants might be able to correctly guess the stimulation conditions due to different adverse effects. Both skin redness and itching sensation are more frequent and intense in the active condition when using 2 mA [22] and the intensity of itching/burning sensations increases after 4th or 5th stimulation when conducting an active stimulation series (own observation). These effects are not seen in sham stimulation. An adequate interval between both conditions could exclude carry-over effects that were mentioned by Brunoni & Fregni [30] and eventually could fade patients' memory on skin sensations. However, the ability of participants to differentiate active and sham stimulation by skin sensations seemed to be limited in this study.

Skin redness

As skin redness turned out to be stronger after active stimulation, this discrimination could be masked e.g., by the application of acetylsalicylic acid [31] or by applying skin crème right after taking off the electrodes, which handicaps a differentiation due to the white over coating and could diminish skin irritations. However, after taking off the electrodes, the operator gets aware of the skin redness and may discriminate between active and sham stimulation. For this reason, the contact between operator and patient should be minimized as possible. For immediate ratings or neurophysiological examinations, patients could wear a headdress, as proposed by O'Connell et al. [22]. As patients and volunteers still have the possibility to break the blinding by a look into the mirror, covering the stimulated areas seems to be reasonable.

Patients' expectations

Ambrus et al. [24] reported that participants are required to sign an information sheet on itching sensations, headache, and skin irritations before their trials. They discussed the nocebo-like effects of a comprehensive information of the participants which has to be taken into account when estimating ratio of adverse effects. Furthermore they report that subjects' level of arousal could have influenced cognitive task performance. However, both the increased attention to adverse effects after the advice at the beginning and a high arousal level could interfere with the perception of tDCS-induced sensations and lead to an overestimation of itching sensation during active tDCS. Additionally patients' beliefs of receiving either active or sham tDCS could lead to a hypersensivity for adverse effects during sham stimulation or to a hyposensivity for adverse effects during active stimulation. For a correlation of the rate of adverse effects and the arousal of the test person, arousal could be assessed before and during tDCS with questionnaires containing visual analog scales for nervousness, anxiety, fatigue, tiredness, etc.

Testing for blinding

While Ferguson et al. [32] emphasize the necessity of reporting a minimum of information on allocation, blinding methods and test for blinding, a subsequent discussion on that topic shows different opinions on the necessity of testing for blinding in clinical trials. Altman et al. [33] state that a marked outcome or adverse events could influence patients' guesses when testing for blinding is done after completion of the trial and they suggest this testing to be done before beginning the allocated intervention. The possible break of blinding by a successful treatment is also emphasized by Senn [34] and Sackett [35]. As skin redness or adverse events like skin burns are likely to break blinding, testing for blinding should be executed before beginning the stimulation series. This is in contrast to recent preclinical and clinical studies.

Unintended interference in psychiatric patients

With the growing application of tDCS in patients with delusional or hallucinatory disorders, operators will be confronted with the frequent fear of current application to the brain. However, the verbal contact between operator and patient on the stimulation procedures should be minimized to avoid unintended influence of the participant by gesture or verbal communication during the stimulation period, and patients' guesses should not be influenced by a manipulation of the stimulator. For the latter, a programmable stimulator is useful, however not mandatory. Leaving the room is not appropriate for a quick intervention in case of adverse events and for maintaining contact when stimulating psychiatric patients. As operators and patients could be unblinded after taking off the electrodes, reddened areas should also be covered after each stimulation, even if clinical rating is done by an independent investigator at the end of a stimulation series.

Conclusion

Although sham and active DC stimulation have been frequently used in tDCS trials, the problem of efficient double blinding has not been fully addressed yet. As mentioned, experienced participants are able to differ between active and sham stimulation, when switching off the stimulator after a few seconds of DC. In our trial, the sham device delivers sham or active stimulation when entering a number code to assure blinding of the operator between the stimulation process. Though operators may be blinded by entering a number code, they might be able to differentiate between real and sham stimulation by skin redness after active stimulation. This well-known problem of tDCS application could be improved by covering the stimulation area after taking off the electrodes and immediate separation between operator and participant. Additionally, clinical rating should be performed by an independent investigator. Taking into account these limitations, the sham DC stimulation protocol used in this study helps to ensure an efficient blinding of operators and participants until taking off the electrodes and could be used for double-blind, placebo-controlled clinical trials.

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Supplementary data

Supplementary data related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.brs.2013.01.005.

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