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Sham tDCS: A hidden source of variability? Reflections for further blinded, controlled trials

Clara Fonteneau [a, b, c], Marine Mondino [a, b, c], Martijn Arns [d, e], Chris Baeken [f, g, h], Marom Bikson [i], Andre R. Brunoni [j, k], Matthew J. Burke [l], Tuomas Neuvonen [m], Frank Padberg [j], Alvaro Pascual-Leone [l], Emmanuel Poulet [a, b, c], Giulio Ruffini [n], Emiliano Santarnecchi [l], Anne Sauvaget [o, p], Klaus Schellhorn [d], Marie-Françoise Suaud-Chagny [a, b, c], Ulrich Palm [j], Jérome Brunelin [a, b, c, *]

[a] INSERM U1028, CNRS UMR5292, Lyon Neuroscience Research Center, Psychiatric Disorders: from Resistance to Response Team, F-69000, France
[b] University Lyon 1, Villeurbanne, F-69000, France
[c] Centre Hospitalier Le Vinatier, Lyon, F-69000, France
[d] neuroCare Group GmbH, Munich, Germany
[e] Research Institute Brainclinics, Nijmegen, the Netherlands
[f] Department of Psychiatry and Medical Psychology, Ghent University Hospital, Ghent University, Ghent, Belgium
[g] Department of Psychiatry, University Hospital UZBrussel, Brussels, Belgium
[h] Ghent Experimental Psychiatry (GHEP) Lab, Ghent, Belgium
[i] Department of Biomedical Engineering, The City College of New York, New York City, NY, USA
[j] Department of Psychiatry and Psychotherapy, University Hospital, LMU, Munich, Germany
[k] Service of Interdisciplinary Neuromodulation (SIN), Laboratory of Neuroscience (LIM27) and National Institute of Biomarkers in Neuropsychiatry (INBioN), Department and Institute of Psychiatry, University of São Paulo Medical School, São Paulo, Brazil
[l] Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
[m] Sooma Oy, Kuortaneenkatu 2, 00510, Helsinki, Finland
[n] Neuroelectrics Corporation, 210 Broadway, 02139, Cambridge, MA, USA
[o] CHU de Nantes, Psychiatric Neuromodulation Unit, Addictology and Liaison-Psychiatry Department, Nantes, France
[p] Laboratory "Movement, Interactions, Performance" (E.A. 4334), Faculty of Sport Sciences, University of Nantes, Nantes, France

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ABSTRACT

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique increasingly used to modulate neural activity in the living brain. In order to establish the neurophysiological, cognitive or clinical effects of tDCS, most studies compare the effects of active tDCS to those observed with a sham tDCS intervention. In most cases, sham tDCS consists in delivering an active stimulation for a few seconds to mimic the sensations observed with active tDCS and keep participants blind to the intervention. However, to date, sham-controlled tDCS studies yield inconsistent results, which might arise in part from sham inconsistencies. Indeed, a multiplicity of sham stimulation protocols is being used in the tDCS research field and might have different biological effects beyond the intended transient sensations. Here, we seek to enlighten the scientific community to this possible confounding factor in order to increase reproducibility of neurophysiological, cognitive and clinical tDCS studies.

Text

In light of increasing interest surrounding reproducible transcranial direct current stimulation (tDCS) studies, guidelines have emerged specifically pointing to the importance of blinding [1–3]. Blinding, or masking, is a cornerstone of randomized controlled trials and is especially challenging to be obtained for non-

* Corresponding author. Centre Hospitalier Le Vinatier, Equipe de Recherche PSYR2 - CRNL, Pôle Est - Bâtiment 416, 1er étage, BP 300 39 – 95 boulevard Pinel, 69678, Bron Cedex, France.
E-mail address: jerome.brunelin@ch-le-vinatier.fr (J. Brunelin).

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pharmacological interventions [4]. It consists of a set of procedures designed to keep participants (single blind procedure) and experimenters (double blind procedures) unaware of the administered intervention (active or sham) and thus avoid bias and unrelated observable effects. For subject blinding, the sham method most commonly used in tDCS studies is based on mimicking typical initial sensations of active tDCS underneath the electrode sites (e.g., tingling, itching). For experimenter blinding, allocation concealment is achieved by entering numeric codes [5] assigned to waveform arms (e.g., sham, active) or a toggle (A/B mode). In addition, some devices adjust an impedance display on the device screen that also mimics impedance changes expected in the "active" functioning of the device and detect loss of electrode contact [5].

Thus, sham procedures in non-invasive brain stimulation trials are fundamental due to the placebo response observed in non-invasive brain stimulation trials [6] and the fact that non-blinded trials overestimate the effects of subjective and objective outcomes [7]. However, the neurobiological effect of sham tDCS remains an under-addressed notion in the literature and can be subdivided into two types of effects: 1) the direct neurobiological effects, specifically the results of the type of sham used, in this case weak electrical currents; 2) the indirect neurobiological effects, that are seen across studies, e.g., general 'placebo/nocebo' or 'non-specific' effects. These would be independent of the type of sham used. With this in mind, as other interventional tools, sham tDCS has two important problematic and competing aspects.

Firstly, the blinding efficacy of current sham tDCS protocols is non-optimal and can be improved depending on blinding objectives [8–10], especially in cross-over studies. In this line, recent "active" sham protocols, based on modeling and leveraging multichannel tDCS, have been developed to mitigate the subject blinding problem [11,12]. For example, an approach could be to use multi-electrode montages, optimized to create skin sensations and effects while keeping cortical electric fields close to zero [11], using realistic head models and multichannel optimization algorithms [13]. This technique provides a way to control both objective and subjective sensation factors for double blinding in experiments and can be made even more precise when based on personalized realistic head modeling. Another possibility, put forward by recent studies [14,15], is the use of topical pretreatments to reduce erythema and minimise paraesthesia in both the active and sham group. Therefore, if successful, this would render the "active" stimulation in the sham group unnecessary and the sham group would only control for indirect neurobiological effects. More generally, while current density in the skin is always higher than in the brain, the ratio can vary by several orders of magnitude depending on the montage [16]. Moreover, blinding of the experimenters could also be improved. Indeed, skin redness after tDCS was reported to affect the blinding efficacy [17]. Therefore, regardless of the protocol used, it is critical to systematically collect data assessing the quality of the blinding. This can be as simple as asking participants what they believe they received (sham or active) and their confidence in this assessment. We recommend scientists and clinicians use the standardized questionnaire validated and published recently by Antal and colleagues (2017) [18]. The documents can be downloaded from the website: http://www.neurologie.uni-goettingen.de/downloads.html.

Secondly, sham tDCS might have biological effects beyond the intended transient sensations [19]. In most cases, sham tDCS consists in delivering a short period of active stimulation at the beginning of the stimulation session (e.g., 10 s at 0.1 mA [20], 120 s at 1 mA [21]) followed by no stimulation for a total duration equal to the duration of the active stimulation [22]. It is usually assumed that sham stimulation controls any potential effects unrelated to the direct cortical stimulation itself. Based on studies using tDCS and transcranial magnetic stimulation (TMS) over the motor cortex, sham stimulation is unlikely to produce lasting changes in cortical excitability after a single session [23]. However, several studies have investigated tDCS effects with parameters similar to those of sham parameters (i.e., short stimulation duration), with mixed findings [24–29]. Placebo-controlled studies report a differential effect of the sham stimulation, some reporting no effect of 30 s stimulation (15 s ramp-up to 2 mA, 15 s ramp-down [30]; 10 s ramp-up/down, 30 s stimulation at 1 mA [31]; 15 s ramp-up/down, 30 s stimulation at 2 mA [32]) while others finding an effect on different neurophysiological parameters (10 s ramp-up to 1 mA, 60 s ramp-down to 0.034 mA and continuous 13 min 50 s at 0.034 mA [33]; 30 s ramp-up to 2 mA, 30 s ramp-down, at the start and end of the stimulation [34]). One tDCS study investigating the neurobiological effects of parameters used in sham conditions as the primary objective reported that a single session of 15 min sham tDCS (i.e., 10 s ramp-up to 1 mA, 60 s ramp-down to 0.034 mA and continuous 13 min 50 s at 0.034 mA) had similar effects to 1 or 2 mA of 15 min stimulation [33] and different than 0 mA stimulation on an event-related EEG component (P3 amplitude). According to this study, although no behavioral effects were observed, a single session of "sham" intervention could exert neuromodulatory effects for some outcomes. Such a result could be explained by skin sensations intentionally produced in the sham arm (ramp up/down) or cortical modulation by the micro-ampere-scale current. The potential physiological effects of non-invasive micro-ampere-scale currents remain to be established, requiring effects at electric fields two orders of magnitude below those established effective in animal models [35–37]. This could be also related to the stochastic resonance model predicting that small amounts of noise injected into a system promote low-level signals leading to enhanced functions within this system [38–40]).

As with other therapeutic tools, the possible effects of sham tDCS itself could be enhanced when repeated sessions are delivered. Indeed, repeated-sessions of tDCS is a promising therapeutic intervention to decrease symptoms and improve cognition in neuropsychiatry. Some of the variability in study outcomes [22] might arise from sham inconsistencies. Indeed, since the first sham-controlled clinical study, numerous sham parameters have been described. For example, recent studies investigating the clinical impact of tDCS in patients with major depression were assessed from a systematic literature search using the following terms: ("tDCS" AND ("depression" OR "MDD") AND ("2018" OR "2017"). From the 106 eligible studies identified in September 2018, we focused on the 4 randomized controlled trials (RCT) [41–44]. Interestingly, sham parameters of these studies differ (current was turned off automatically after 30 s of 2 mA stimulation [41]; 30 s of 0.5 mA stimulation [42]; ramp-up 30 s/ramp-down 15 s, 30 s of 2 mA stimulation [43]; constant current of 0.034 mA + 2 ramps throughout sham intervention up to 1 and 0.5 mA (10 s ramp-up, 60 s ramp-down) [44]). Aside from this example from recent studies of tDCS in major depressive disorder, the use of different sham parameters in clinical studies reveals significant variations of the injected electric charge from 15 [42] to 109 [33] mC. Another point to consider in these clinical studies is the potential impact of repeated low-intensity sham stimulations, which could produce behavioral changes in the control condition that confound detection of therapeutic responses to the active arm. Thus, sham methodology could be an important parameter among others (session duration, total number of session, number of sessions a day, duration between two sessions, current intensity, site of stimulation) in the design of tDCS clinical studies, not only for blinding, but also to investigate potential specific neuromodulatory effects linked to the sham stimulation itself.

Several sham protocols for tDCS have been reported in the literature (Fig. 1). Based on a recent review [3], 84% of 173 studies report using similar approaches as reported in an early study by Gandiga et al. [45]. However, the original protocol (i.e., 10 s ramp-up followed by 30 s of active stimulation at 1 mA before manually turning off the stimulator, Fig. 1A) has been modified, adjusting (1) the intensity and duration of active current being delivered (from "no current" to 2 min at 1 mA), (2) the duration of ramp-in and ramp-out phases (e.g., 5–30 s), and (3) the number of ramps done throughout the stimulation. Indeed, a newer sham protocol proposed 2 periods of active stimulation, including ramps up/down with 10–30 s of stimulation in between, over the first and last seconds of the stimulation [46] (Fig. 1B).

In order to help practitioners deliver adequate and reproducible sham treatment interventions, several commercial stimulators include a 'double blind study mode', which delivers a built-in-sham mode. However, sham-placebo modes vary across stimulator brands, which could be a confounding factor when comparing studies and in multicenter studies using various devices across centers (Table 1). In addition, it should be noted that these sham parameters can also be adapted upon request to the companies.

Thus, we urge scientists and clinicians to be aware of the sham parameters they used and accurately report them in scientific literature, including when not using the preprogrammed built-in 'double blind study mode'. This is particularly critical for studies that use devices not designed for tDCS (e.g., iontophoresis devices such as the Intelec Advanced Therapy System, Chattanooga, USA).

With this in mind, we have detailed in Supplementary Material 1 the sham-controlled studies using bifrontal (F3/F4/FP1/FP2) and fronto-temporal montages (F3FP1/T3P3) based on recent major reviews [22,47,48] and divided them depending on their sham parameters described (device "turned off", short stimulation) and looked the impact on their primary outcome. We report that out of 103 studies, only 14 studies do not report a short active stimulation (only ramps), 51 studies report using ramp-down before turning off the device and 44 studies report shutting off the device after the active stimulation. Of those 103 studies, 46 were excluded from further investigation due to missing information concerning the sham parameters used. With the remaining 57 studies, we were able to investigate if the total charge in the sham arm had an effect (Yes or No) on the primary outcome (Supplementary Material 2). From this analysis, the total charge delivered doesn't seem different when comparing studies showing no effect of active tDCS compared to sham tDCS (n = 6; 94 mC (± 115)), compared those showing an effect (n = 51; 73 mC (± 69)). This should be taken with caution, as very few negative studies (n = 6) could be analyzed. Thus, to date, no recommendation can be made regarding a specific sham protocol and none seem to be more rigorous than another. Further studies are needed to assess the direct and indirect effects of sham protocols.

Choosing the optimal control condition is another important issue to consider. The field has mainly focused on "active sham" control conditions mimicking stimulation sensations as realistically as possible. This approach has partly been chosen because "placebo" control conditions have been strongly criticized in TMS and drug research [49–53] and because "active sham" control conditions could improve the blinding effect. Remarkably, systematic assessment of blinding has been more often reported in brain stimulation trials compared to drug trials [54]. Moreover, control groups or waiting lists, used in psychotherapy and mindfulness

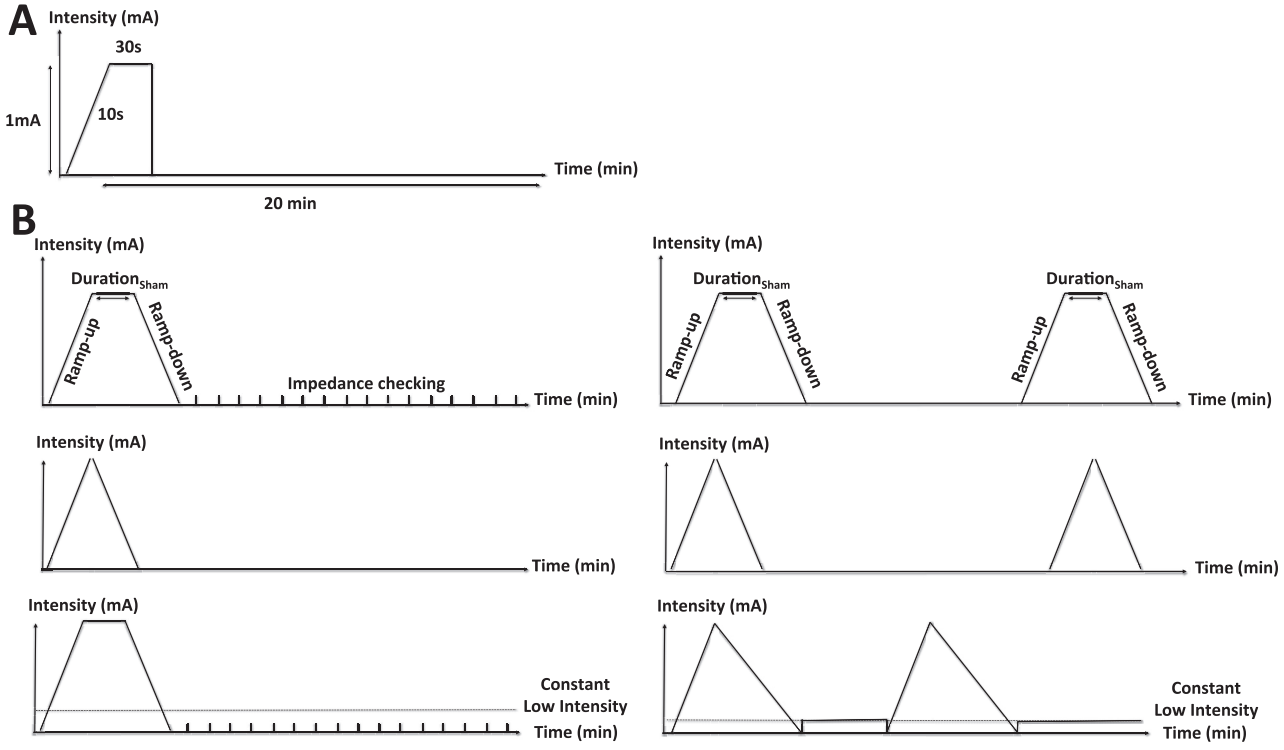

Fig. 1. Illustration of different sham protocols used in tDCS studies – A) Original Gandiga sham protocol: 10s ramp-up, 30s stimulation, turn off the stimulator. **B) Adapted tDCS protocols:** The stimulation period is the same for both active and sham interventions. Depending on studies, sham tDCS consists in either 1 or 2 ramps per session (beginning, middle or/and end) with different duration of ramps (5, 8, 10, 15, 30 s). Different durations of active stimulation are delivered at the beginning and/or end of the stimulation period ($Duration_{Sham}$ = 5, 8, 10, 15, 20, 30, 40, 60, 120 s). The period of active stimulation reaches the same or reduced peak intensity compared to the intensity delivered in the active intervention. Lastly, some studies report a constant low intensity stimulation (0.016 or 0.034 mA) [33,44].

Table 1
Main parameters of the different built-in-sham modes from commonly used commercial stimulators, as described in their manuals. Constant intensity for each stimulator was reported for the current available devices. It should be kept in mind that analogue electronic of the current source could have a 'noise' of equal or below 0.010 mA. Y=Yes; N=No.

	neuroConn*(Ilmenau, Germany)*	Soterix Medical Inc *(New York, USA)*	Neuroelectrics Starstim *(Barcelona, Spain)*	Sooma*(Helsinki, Finland)*
$Duration_{Sham}$ (s)	$Duration_{Active}$(s)/30	Programmable	Programmable	None
Peak intensity (mA)	Same as in active condition	Programmable	Same as in active condition	Same as in active condition
Constant intensity (mA)	±0.010	0.012 to 0.024	<0.010	0.3
Number of ramp up/down periods	1 (beginning)	Programmable	1 or 2 (2nd optionally at the end)	1 (beginning)
Ramp up/Ramp down duration	Same as active	Programmable	Programmable	0.1 mA/s
Impedance check	Brief pulses of 110 μA over 15 ms every 550 ms	Emulated	Fake impedance	Continuous current 0.3 mA
Single/Double blind mode	Y/Y	Y/Y	Y/Y	Y/Y
Example Active stimulation of 20 min at 1 mA, 30s ramps	30 s ramp up, 1 mA stimulation during 40 s, 30 s ramp down = 1 min 40s stimulation = 70 mC + impedance check (3.48 mC)	(30 s ramp up to 1 mA, 30 s ramp down)$_{beginning + end}$ = 2 min stimulation = 60 mC	(30 s ramp up to 1 mA, 30 s ramp down)$_{beginning + end\ optional}$ = 1 or 2 min stimulation = 30 or 60 mC	10 s ramp up to 1 mA, 7 s ramp down to 0.3 mA for 20 min, 3 s ramp-down at the end = 20 min stimulation = 370 mC

research for example, do not allow true double-blind trials [55,56]. A final complicating factor is the growing body of research suggesting that control conditions themselves may be capable of meaningfully modulating relevant brain regions/networks [57]. Realistic and elaborate sham tDCS protocols could invoke strong therapeutic expectations and thus induce particularly large placebo effects. This relates to the notions of 'differential placebo effects', the concept that different types of placebos (e.g. inert pill versus sham device) may yield different magnitudes of placebo response [58–60]. This is a topic that has been studied for decades, but becomes paramount as sophisticated medical technologies require elaborate placebo controls to maintain blinding integrity.

Thus, several promising research avenues can be put forward with regard to decreasing the influence of sham tDCS, with the main aim of keeping the balance between maintaining participant blinding and limiting the development of sham into an 'active control' condition. One the one hand, with the perspective of using tDCS in clinical settings, the use of an "active control", i.e. stimulating a region considered inactive with regard to the main question, as with TMS [61], could be recommended in some cases, however, with the risk of including an active control with unknown neurophysiological effects. Alternatively, the use of "active controls" based on realistic head modeling with multi-electrode montages exploiting scalp shunting mechanisms can be explored as discussed above [11]. On the other hand, sham tDCS conditions could also be reduced to a minimum of active components, even going as far as no active components, when using protocols with topical pretreatments [14,15]. Furthermore, new protocols could be developed in order to detect the dissociation between direct and indirect neurobiological effects, as done in other research fields (e.g. neurofeedback, [62]).

In summary, the use of different sham stimulations can be a confounding factor in reconciling results across clinical, cognitive, and neurophysiological studies of tDCS. Indeed, when functional neuroimaging, at different spatial and temporal levels (biological, functional and structural) is used to gain new useful information for inferring the mechanisms of action of tDCS (e.g., Refs. [63,64]) conclusions are drawn based on comparison between active and sham interventions. Questions that should be further explored include whether certain modalities of sham tDCS have a neurobiological effect, and if so, which ones. In addition, the cumulative clinical effects of low-intensity, repeated sham tDCS should be further investigated, as a recent controlled trial suggested that it could have meaningful antidepressant effects [44]. Ultimately, more research is necessary to ascertain the direct neurobiological effects of sham tDCS protocols and evaluate their reliability [[65], but see Ref. [66]]. It should be underscored that simply "turning off" the tDCS device could harm blinding, therefore overestimating the signal of active stimulation. In addition, accurately reporting sham interventions is crucial to help increase reproducibility in the tDCS research field (sham should be reported with the same rigor as any stimulation dose; [67]). Future meta-analyses could also include investigating pre-post effect sizes of all sham conditions across studies (e.g., larger effect size for 'ramp-up-ramp-down' vs 'constant low intensity' shams?), as done in a recent meta-analysis looking specifically at the effects of sham tDCS on corticospinal excitability [68]. Nevertheless, in parallel to a reliable sham arm, other aspects should be considered in order to have reproducible tDCS studies, such as better training of practitioners and reporting of the electrode preparation (e.g., saline quantity, reuse, cleaning method,...) and placement [2]. Our hope is that a better understanding of these neurobiological processes can decrease the noise in controlled trials, ultimately clarifying tDCS efficacy.

Conflicts of interest

M.A. is a minority shareholder in neuroCare Group (Munich, Germany) and received research funding from neuroCare Group, Germany and equipment support from Deymed, neuroConn, Brainsway and Magventure. M.B. is a shareholder in Soterix Medical Inc. The City University of New York has patents on brain stimulation with M.B. as inventor. A.R.B. is recipient of a CAPES/Alexander von Humboldt fellowship award for experienced researchers and is a consultant from Neuroconn GmbH. The Laboratory of Neuroscience receives financial support from the Beneficent Association Alzira Denise Hertzog da Silva and the CAPES/INCT program "National Institute of Biomarkers in Psychiatry" (INBioN), Brazil. T.N. is a shareholder at Sooma Oy. F.P. received research support from neuroConn GmbH, Ilmenau, Germany, and Brainsway Inc., Tel Aviv, Israel, as well as speaker's honorarium from Mag&More GmbH, Munich, Germany, and neuroCare Group. G.R. is a shareholder and works for Neuroelectrics Corporation, Spain. K.S. is a shareholder and works for neuroCare Group GmbH. E.S. is supported by the BROAD Institute at Harvard-MIT (Boston, MA, USA) via 2016P000351, by the Defense Advanced Research Projects Agency (DARPA), USA via HR001117S0030, by the Beth Israel Deaconess Medical Center (BIDMC), USA via the Chief Academic Officer (CAO) grant 2017. E.S. received research support by Cognito Therapeutics, a spin-off of MIT, USA. U.P. received paid speakership from neuroCare Group, Germany and has a private practice with neuroCare Group, Munich, Germany. J.B. is supported by the Fondation Pierre Deniker, France. C.F., M.M., C.B., M.J.B., E.P., A.S., M.F.S.C. report no disclosures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2018.12.977.

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