Blinding is compromised for transcranial direct current stimulation at 1 mA for 20 minutes in young healthy adults

Zsolt Turi[1], Gábor Csifcsák[2], Nya Mehnwolo Boayue[2], Per Aslaksen[2], Andrea Antal[1,3], Walter Paulus[1], Josephine Groot[2,4], Guy E. Hawkins[5], Birte Forstmann[4], Alexander Opitz[6], Axel Thielscher[7,8], Matthias Mittner[2*]

[1] *Department of Clinical Neurophysiology, University Medical Center Goettingen*

[2] *Department of Psychology, University of Tromsø*

[3] *Medical Psychology, Otto-Guericke University Magdeburg*

[4] *Integrative Model-based Cognitive Neuroscience Research Unit, University of Amsterdam*

[5] *School of Psychology, University of Newcastle*

[6] *Department of Biomedical Engineering, University of Minnesota*

[7] *Department of Electrical Engineering, Technical University of Denmark*

[8] *Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Denmark*

Abstract

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method that is frequently used to study cortical excitability changes and their impact on cognitive functions in humans. While most stimulators are capable of operating in double-blind mode, the amount of discomfort experienced during tDCS may break blinding. Therefore, specifically designed sham stimulation protocols are being used. The "fade-in, short-stimulation, fade-out" (FSF) protocol has been used in hundreds of studies and is commonly believed to be indistinguishable from real stimulation applied at 1 mA for 20 minutes. We analyzed subjective reports of 192 volunteers, who either received real tDCS (n=96) or FSF tDCS (n=96). Participants reported more

*Corresponding author: matthias.mittner@uit.no

discomfort for real tDCS and correctly guessed the condition above chance-level. These findings indicate that FSF does not ensure complete blinding and that better active sham protocols are needed.

Keywords: tDCS, blinding, double-blinding, active sham tDCS, placebo

1. Introduction

Transcranial direct current stimulation (tDCS) is a safe, non-invasive brain stimulation method, which applies low-intensity (most frequently 1-2 mA) constant current between two or more electrodes placed over the scalp (Antal et al., 2017). tDCS is assumed to modulate cortical excitability depending on the polarity of the stimulation and is used to study cognitive functions in humans (Santarnecchi et al., 2015). At low intensities, tDCS induces a moderate amount of perceptual adverse effects that include cutaneous discomfort such as itching, tingling, burning or piercing sensations (Poreisz et al., 2007; Matsumoto and Ugawa, 2017; Fertonani et al., 2015).

Most tDCS studies use active sham stimulation protocols for placebo control (Davis et al., 2013). The aim of active sham stimulation is to induce cutaneous adverse effects that are indistinguishable from the real tDCS protocol without inducing the neurophysiologically relevant primary effects of the stimulation (Woods et al., 2016). The most frequently applied active sham stimulation is the so called 'fade-in, short-stimulation, fade-out' (FSF) protocol (Ambrus et al., 2012). The FSF protocol consists of three stimulation stages: It starts with a fade-in period, where the current is gradually ramped up from 0 mA to the planned intensity (e.g., 1 mA) in a relatively short (5-30s) time period. The second stage is the short stimulation period at the planned intensity, which lasts for only a very brief time period (most commonly for 30s). The final stage is the fade-out period, in which the current is gradually ramped down from the planned stimulation intensity to 0 mA over a short (5-30s) time period. The FSF protocol is an extension of the initial "FS protocol", which only consists of the initial fade-in and the short-stimulation periods (Gandiga et al., 2006). It is commonly believed that the fade-out period at the end of the active sham stimulation protocol further improves its blinding efficacy and therefore, the FS protocol is rarely applied.

The blinding efficacy of the FSF protocol depends on the intensity and duration of the real tDCS protocol to which it is being compared. While it is

commonly assumed that FSF can maintain blinding at 1 mA applied for 20 minutes (based on findings from the FS protocol from Gandiga et al., 2006), evidence suggests that blinding is compromised when tDCS is applied at 1.5 or 2 mA for 10 minutes or longer (Kessler et al., 2012; O'Connell et al., 2012; Russo et al., 2013; Wallace et al., 2016). Following these findings, FSF has been used as a control in hundreds of studies using real tDCS at 1 mA for 20 minutes.

Given the enormous popularity of this sham procedure (Bikson et al., 2017), we set out to investigate its blinding efficacy using data from our recent high-powered, multi-center, pre-registered study (Boayue et al., in press). In this study, we collected data from 192 volunteers, who either received real tDCS at 1 mA for 20 minutes over the left dorsolateral prefrontal cortex (DLPFC) or FSF tDCS. The primary goal was to investigate the behavioral effects of anodal tDCS over the left DLPFC on mind-wandering but we also collected subjective reports concerning blinding efficacy and cutaneous discomfort. Here, we analyze these subjective reports in order to investigate whether FSF is an effective control procedure for tDCS applied at 1 mA over 20 minutes.

2. Material and methods

The study followed a fully pre-registered protocol (https://osf.io/bv32d/) with a sequential sampling plan for the primary research question (Boayue et al., in press). However, none of the analyses reported in the current paper were pre-registered.

2.1. Participants

The dataset contains subjective reports of 192 healthy participants (134 female, mean age: 22.2 yrs ± 3.19 yrs SD). Data was collected at three labs (N per lab=64): Amsterdam, Goettingen and Tromsø (Boayue et al., in press). The raw data and all analyses reported here are available for download at our repository (https://github.com/ihrke/2018_tdcs_blinding). Participants had no contraindication and no previous experience with tDCS as was assessed by self-reports. The study was approved by the local ethic committee and was performed according to the Declaration of Helsinki. All participants provided written informed consent before participation.

2.2. Experimenter

The experimenters were responsible for the recruitment and data collection in each center (Amsterdam, Göttingen, Tromsø). As part of the training, all experimenters were instructed about safety, ethical considerations of transcranial electrical stimulation and about the principles of good scientific practice. Before the start of the pilot measurement, the experimenters received a series of written, video and in-person training about the correct application of tDCS. The training ensured that the quality of electrode preparation was appropriate, including finding the target location, cleaning the skin, preparing the skin-electrode interface and applying the conductive medium. The experimenters followed a fully pre-registered protocol, standardized across labs. In each lab, the experimenters collected at least two pilot measurements before the data collection of the real experiment. Data from the pilot measurements were not included in the data analysis. During the pilot experiments, the experimenters were supervised by a researcher with history of prior experience in tDCS. The real data collection started when the experimenter met the requirement of performing tDCS independently.

The experimenter in Amsterdam was a native Dutch speaker (author J.G.), whereas the experimenter in Goettingen was a native German, male medical student (6-7th semester). Three experimenters collected the data in Tromsø, (including author N.M.B.). Two were native Norwegian speakers (one female, one male), whereas N.M.B. is fluent Norwegian speaker at C1 level (according to the Common European Framework of Reference for Languages). Instructions were fully computerized and translated into the local languages by competent, native speakers.

2.3. Electrode preparation and stimulation protocols

The fully pre-registered protocol detailing electrode preparation and stimulation application steps is available at the following location (https://osf.io/qdk3x/) and summarized below.

First, the electrode locations were determined using an EEG cap adjusted for head size. Then, alcohol on de-makeup pads was used to clean the skin surface where electrodes were positioned. A small amount of Ten20 conductive electrode paste (Weaver and Company, USA) was homogeneously distributed over the previously cleaned skin areas and on the surfaces of the rubber electrodes. Medium pressure was applied to enable good electrode-skin contact. The anode electrode (4×4 cm) was placed over the F3 location (according to the international 10/20 EEG system), whereas the cathode

(7×5 cm) over the right supraorbital region. The electrodes were held in place by the conductive electrode paste and two loops of cohesive elastic fixation bandage (MaiMed GmbH, Germany). The pressure of the elastice bandage was adjusted individually to avoid too much pressure on the head while maintaining proper fixation. Impedance levels were required to be $\leq$ 10kΩ.

The stimulation was administered using a neuroConn DC-stimulator (neuroConn GmbH, Germany). The real tDCS protocol lasted for 20 minutes of continuous stimulation at 1 mA, whereas the FSF protocol for 15s at 1 mA. In addition, we utilized 30s-long fade-in/out periods at the beginning and at the end of both tDCS protocols. The details of the real and the FSF protocols are summarized in Figure 1 A and B. The stimulator was operating in study mode: The active sham and the real stimulation protocols were assigned to pseudo-codes B and C, respectively.

The data was collected in a double-blind fashion. Although neuroConn DC-stimulators can run in double-blind stimulation mode, the built-in active sham protocol consists of 30s fade-in/out periods and a 40s-long short-stimulation period. However, due to the nature of the present pre-registered replication study (Boayue et al., in press), the active sham protocol was confined to 15s which is why double-blind mode could not be used. Since the display window of the stimulator between protocols was slightly different, it was covered 30s after the start (until that time the displays were identical) of the stimulation to avoid accidental unblinding of the experimenter.

Participants performed a cognitive task (Sustained Attention to Response Task; SART) while receiving the stimulation (Boayue et al., in press). The total duration of the SART was 40 minutes, and tDCS was applied in the first 20 minutes. In the informed consent, participants were informed about the intensity and the duration of the real stimulation condition. Participants were also informed that they would either receive real or placebo stimulation. The details of the placebo stimulation (i.e., duration and intensity) were not specified, only that it would feel identical to the real stimulation condition but would purportedly apply no current.

2.4. Assessing stimulation discomfort and blinding efficacy

A 7-point Likert-scale was used to assess the amount of discomfort and the blinding efficacy of the FSF protocol. The questionnaires were completed at the end of the experiment by the participants. To investigate the amount of discomfort, participants were required to answer the question *"Please rate*

the magnitude to which the placement and/or effect of either electrode was disturbing during the task (e.g., feeling that the electrodes were dislocated, wet or cold feeling in the skin under the electrodes, tingling or itching in the skin under the electrodes, etc.)!". Available response categories ranged from "not at all" (1) to "very strong" (7). To study the blinding efficacy, participants were asked to answer the question *"Please tell us if you think you were receiving real or fake (placebo) stimulation today!"* with response categories between "definitely sham" (1) and "definitely real" (7).

2.5. Analysis method

We used Bayesian estimation of ordinal probit regression models (Bürkner and Vuorre, 2018) designed specifically for analysing ordinal data (Liddell and Kruschke, 2018). We report our results in terms of posterior mean parameters along with the 95% highest-density interval (HDI) calculated from the posterior distribution. This measure quantifies the interval in which the true parameter is located with 95% probability given the applied model. We conclude that a parameter is different from zero if the 95% interval excludes zero. For more details, see Supplemental Analyses.

3. Results

Our results are summarized graphically in Figure 1 C and 1 D. Regarding the blinding efficacy, excluding subjects who were undecided, there were 2.6 as many subjects in the real stimulation group who guessed that they received real stimulation (52 with scores > 4 vs. 20 with scores < 4). In contrast, this figure was only 1.19 for the sham group (38 with scores > 4 vs. 32 with scores < 4). We submitted these responses for guessing stimulation condition to an ordinal regression model using lab (Amsterdam, Goettingen, Tromsø) and actual stimulation condition (anodal, sham) as predictors. We found that the effect of real stimulation was reliable ($b = 0.35$, HDI=$[0.06, 0.65]$). This effect was robust against different choices of the analysis method (see Supplemental Analysis). While including lab as a factor was preferred by model-selection criteria, there was no clear effect for generally higher or lower scores across labs ($b_{\mathrm{GOE}} = 0.33$ $[-0.03, 0.69]$, $b_{\mathrm{TRM}} = -0.10$ $[-0.45, 0.28]$).

The findings for the discomfort question were similar. In general, all subjects reported relatively low discomfort ($M = 2.5$, SD=1.56). In a parallel model to that for the blinding question, real stimulation had a positive effect ($b = 0.34$ $[0.04, 0.63]$) though that effect was slightly less robust to

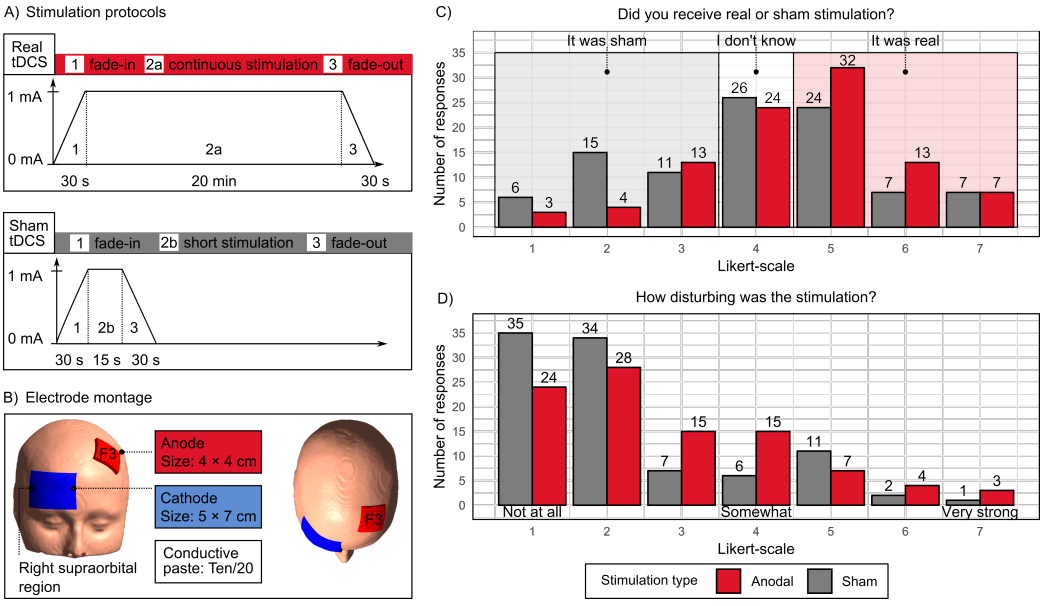

Figure 1: (A) The stimulation parameters for the real and FSF tDCS protocols. (B) The electrode montage. (C) Responses to the blinding question were generally more correct in the real-stimulation condition (red) when compared to sham (grey). (D) Participants receiving real stimulation reported greater discomfort.

model-specification than the effect on the blinding question (see Supplemental Analyses).

4. Discussion

TDCS applied at 1 mA for 20 minutes is one of the most frequently used protocols in the literature and it is commonly assumed to be effectively blinded by the FSF protocol (Gandiga et al., 2006). Our data, collected from a brain stimulation study with the highest sample size investigating this issue to date, challenge this assumption: We found that our subjects could, to a degree, distinguish between active and sham conditions. It is important to note that this effect was present despite the fact that 1) none of the participants had any prior experience with tDCS and 2) every participant took part in only one condition so that they did not have a reference frame to which to compare their experience. It is likely that the actual distinguishability can be much stronger in many studies using repeated measures (O'Connell et al., 2012; Greinacher et al., 2018) and/or participants with prior exposure to tDCS (Ambrus et al., 2012). This effect may be even more pronounced in the clinical context: Whereas healthy participants most frequenty subject to single-session tDCS, patients usually receive multi-session tDCS over a duration of several weeks (Loo et al., 2018). Furthermore, we found compromised blinding despite the fact the our participants received no detailed information about the active sham protocol (O'Connell et al., 2012). We expect that informing the participants about the details of the active sham protocol in the informed consent forms (which may be recquired in certain clinical context or requested by the local ethic committees) can further facilite the correct identification of the different stimulation conditions.

The assumption that 1 mA tDCS for 20 minutes can be effectively blinded by the FSF protocol is based on a single study including 24 healthy volunteers and 23 chronic stroke patients with a mean age between 46.3 and 62.3 years (Gandiga et al., 2006). Recent evidence indicates that the tDCS-induced discomfort may depend on age: It is lower in older than in younger participants (Wallace et al., 2016). This difference in the sensitivity may be part of the reason why our younger volunteers (mean age: 22.2 years) could better distinguish between real and active sham stimulation protocols than older participants (Gandiga et al., 2006), and also explain why the blinding was compromised among younger adults. Given that a large number of tDCS

studies recruits young adults, our finding is an important contribution to the field.

In a recent pre-registered study it was shown that the blinding efficacy of the FSF protocol is compromised even for the most frequenty used 1 mA and 10 minute-long real tDCS protocol, when a repeated-measure study design is used (Greinacher et al., 2018). In this study, tDCS was applied over the left primary motor cortex (anode) and over the right supraorbital region (cathode). The FSF protocol consisted of 30s fade-in/out periods and 20s short stimulation period (Greinacher et al., 2018). FSF protocols in this stimulation parameter range were previously assumed to be effective for maintaining blinding (Ambrus et al., 2012). Contrary to the expectations, participants were able to correctly idenfity active sham and real tDCS protocols based on the differences in the time course of the subjectively perceived cutaneous discomfort (Greinacher et al., 2018). The stimulation parameters used in this study were similar to the ones reported here: Both used 1 mA tDCS, comparable electrode montage and a FSF protocol (with identical fade-in/out periods and similar short stimulation periods: 15s vs 20s). One important difference is the duration of the real tDCS: Whereas in our study it was 20 minutes, Greinacher et al. (2018) used 10 minutes. Blinding efficacy of FSF protocols seems to be better for real tDCS protocols with shorther stimulation durations (e.g., 10 minutes). This may explain why our participants (receiving 20 minutes tDCS) were able to correctly identify stimulation conditions, even after a single stimulation session. Another important difference between the two studies is the way blinding efficacy was assessed. In Greinacher et al. (2018), participants were asked every 30s whether they think the stimulation is on (yes or no) and how confident they are in their answers (11-point Likert-scale). Altough this study provided detailed information about the actual time-course of the subjectively perceived cutaneous-sensations associated with different tDCS protocols, one may argue that this procedure inevitably biased the participants toward focusing more on skin-sensations. In our study, participants performed a cognitive task while receiving the stimulation and they were only asked about blinding retrospectively. The assessment method used by our study is the most common way in studies aiming to measure the possible cognitive effects of tDCS and the blinding efficacy of the sham/control stimulation relative to the real tDCS protocol.

In the present study, we used Ten20 conductive paste instead of saline solution or conductive gel. The use of gel and conductive paste has become

increasingly popular over recent years (Saturnino et al., 2015; Woods et al., 2016). Application of conductive paste has several advantages over saline solution that includes better control of the spread of the conductive medium over the skin and better adherence to the curved surface of the skull. This allows more stable positioning compared to the saline-saturated sponge and rubber bandage method. Moreover, it can be safely combined with functional magnetic resonance imaging and there is no need for rehydration over the time-course of longer stimulation sessions. We do not believe that the choice of conductive medium has an impact on blinding efficacy for the following reasons. While there is some evidence that cutaneous sensations even in the most commonly used saline solution at various concentration levels (15, 140 and 220 mM) may be perceived differently by participants (Dundas et al., 2007), the low sample size (N=14) does not permit to draw strong conclusions. We are unaware of any studies explicitly assessing the level of discomfort and the efficacy of blinding using different conductive media. However, a computational modeling study compared peak electric fields in the skin of the most commonly used conductive media, including "Spectra 360" gel, "Signa Gel" and "Ten20" (Saturnino et al., 2015). This study found highest peak electric field in the skin for the lower gel conductivities but it is unclear how these differences in peak electric field magnitudes are translated into subjectively-experienced cutaneous discomfort. Furthermore, other studies that have demonstrated ineffective blinding for FSF employed saline solution (O'Connell et al., 2012; Greinacher et al., 2018).

Given the accumulating evidence about ineffective blinding of the FSF protocol for real tDCS between 1 and 2 mA over 10 and 30 minutes (O'Connell et al., 2012; Kessler et al., 2012; Russo et al., 2013; Wallace et al., 2016; Greinacher et al., 2018), we conclude that our findings are not limited to the exact stimulation parameters used in this study, but instead demonstrate a general pattern about ineffective blinding for the most commonly used stimulation protocols. Given that tDCS is a potent placebo-inducing procedure both in the clinical (Aslaksen et al., 2014) and cognitive domains (Turi et al., 2017, in press), there seems to be an urgent need to test alternative active sham protocols (Palm et al., 2013; Boonstra et al., 2016) or develop better active sham protocols to effectively maintain blinding. One possibility may be to consider to utilize topical anaesthetic cream to reduce cutaneous sensations (McFadden et al., 2011; Guleyupoglu et al., 2014; Guarienti et al., 2015) and vasodilatation-induced redness underneath the electrodes (Durand et al., 2002; O'Connell et al., 2012; Ezquerro et al., 2017) both of which have previ-

ously been identified as potential factors which can break blinding (O'Connell et al., 2012; Palm et al., 2013; Guarienti et al., 2015).

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