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

Turi, Zsolt; Csifcsák, Gábor; Boayue, Nya Mehnwolo; Aslaksen, Per; Antal, Andrea; Paulus, Walter; Groot, Josephine; Hawkins, Guy E; Forstmann, Birte; Opitz, Alexander

Total number of authors:
12

Published in:
European Journal of Neuroscience

Link to article, DOI:
[10.1111/ejn.14403](https://doi.org/10.1111/ejn.14403)

Publication date:
2019

Document Version
Peer reviewed version

[Link back to DTU Orbit](#)

Citation (APA):

Turi, Z., Csifcsák, G., Boayue, N. M., Aslaksen, P., Antal, A., Paulus, W., Groot, J., Hawkins, G. E., Forstmann, B., Opitz, A., Thielscher, A., & Mittner, M. (2019). Blinding is compromised for transcranial direct current stimulation at 1 mA for 20 minutes in young healthy adults. *European Journal of Neuroscience*, 50(8), 3261-3268. <https://doi.org/10.1111/ejn.14403>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

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

Zsolt Turi¹, Gábor Csifcsák², Nya Mehnwolo Boayue², Per Aslaksen²,
Andrea Antal^{1,3}, Walter Paulus¹, Josephine Groot^{2,4}, Guy E. Hawkins⁵,
Birte Forstmann⁴, Alexander Opitz⁶, 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*

Running title: Compromised blinding at 1 mA 20 min frontal tDCS

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

*Corresponding author: matthias.mittner@uit.no

received real tDCS (n=96) or FSF tDCS (n=96). Participants reported more 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 (20 minutes) or FSF tDCS (40s) at 1 mA over the left dorsolateral prefrontal cortex (DLPFC). The primary goal was to investigate the behavioral effects of real tDCS over the left DLPFC (anode electrode) 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 $\pm$ 3.19 yrs SD) collected at three labs (N per lab=64): Amsterdam, Göttingen and Tromsø ([Boayue et al., in press](#)). The raw data and all reported analyses are available for download at our repository (https://github.com/ihrke/2018_tdcS_blinding). Participants had no contraindication and no previous experience with tDCS, which was assessed by self-reports. The study was approved by the local ethics committees at all three universities (Amsterdam, Göttingen, Tromsø) 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 an experienced tDCS researcher. The real data collection started when the experimenter met the requirement of performing tDCS independently.

The experimenter in Amsterdam was a female native Dutch speaker and a research master student in neuroscience in her last year (author J.G.), whereas the experimenter in Göttingen was a native German, male medical student (6-7th semester, 4th year). Three experimenters collected the data in Tromsø. Author N.M.B. is a male Ph.D. student in neuroscience and a fluent Norwegian speaker at C1 level (according to the Common European Framework of Reference for Languages). The two other experimenters were native Norwegian speakers (one female, one male), both clinical psychology students (7-8th semester, 4th year). 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. **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 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 elastic bandage was adjusted individually to avoid too much pressure on the head while maintaining proper fixation. Impedance levels were required to be $\leq 10\text{k}\Omega$.

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 would have consisted of 30s fade-in/out periods and a 40s-long short-stimulation period for our settings. This is because the duration of the active sham protocol for neuroConn DC-stimulators is restricted to be the duration of the active stimulation protocol (1200 s) divided by 30, resulting in 40s for our setup. However, due to the nature of the present pre-registered replication study (Boayue et al., in press), the active sham protocol was desired to be 15 s (instead of the 40 s short-stimulation period provided by the neuroConn DC-stimulators) 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 30 s after the start of the stimulation (until that time the displays were identical) to avoid accidental unblinding of the experimenter. For all participants, a second, post-stimulation impedance measurement was performed to retrospectively detect and document potential increases of impedance-levels above the safety limits which would have triggered the built-in safety switch and turned off the stimulator. **The second impedance measurement was performed at the end of the stimulation.** This measurement confirmed that all impedance values were below the safety limit also at the end of the stimulation.

Participants performed a cognitive task (Sustained Attention to Response Task; SART) while receiving the stimulation (Boayue et al., in press). **The SART is a Go-NoGo task that is frequently employed in mind-wandering**

studies. The total duration of the SART was 40 minutes and the task consisted of two 20-minute-long blocks with a short break in between. TDCS was applied only in the first 20 minutes. During the break (after the end of the stimulation), the experimenters performed the second impedance measurement.

In the informed consent form, participants were informed about the intensity and the duration of the real stimulation condition. Participants were also informed that they would receive either 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. No further information about the stimulation protocol was provided to the participants. It is possible that providing this information might have biased the intensity of the reported adverse effects (Ambrus et al., 2012) and consequently the blinding efficacy of the FSF protocol. However, in order to be able to give informed consent, participants had to be informed about the dose of the real tDCS protocol and that a sham protocol would be used.

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. Participants received no further instructions about filling out the questionnaires. 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), “somewhat” (4), 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), “I don’t know” (4) and “definitely real” (7). The used questionnaires are available in all three languages in our repository (English template: <https://osf.io/r3vba/>, Dutch: <https://osf.io/mhvyw/>, Norwegian: <https://osf.io/4ygda/>, German: <https://osf.io/n3hfa/>).

2.5. Analysis method

We used Bayesian estimation of ordinal probit regression models (Bürkner and Vuorre, 2018) designed specifically for analyzing 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. Even though we believe that our reported Bayesian analyses are superior for the analysis of ordinal-scale data (Liddell and Kruschke, 2018) we also report standard frequentist analyses that do not take the ordinal scale into account. The results of these analyses are reported in our Supplemental Materials and are in line with those from our primary analysis.

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, Göttingen, Tromsø) and actual stimulation condition (real, sham) as predictors. We found that the effect of real stimulation (coded as anodal) was reliable ($b = 0.35$, HDI=[0.06, 0.65]), indicating that subjects could more accurately guess that they were receiving real stimulation when they actually did. 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 ($b_{\text{GOE}} = 0.33$ [-0.03, 0.69], $b_{\text{TRM}} = -0.10$ [-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]), indicating that subjects receiving real stimulation reported more discomfort than those receiving sham stimulation. However, that effect was slightly less robust to 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 frequently 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 that 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 required in certain clinical context or requested by the local ethics committees) can further facilitate 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 frequently 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 identify 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 shorter 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 thought the stimulation was on (yes or no) and how confident they were in their answers (11-point Likert-scale). This approach resulted in very detailed information about the time-course of the subjectively perceived cutaneous sensations associated with different tDCS protocols. However, we speculate that repeatedly asking participants to evaluate their scalp sensations would inevitably bias the participants toward focusing more on skin-sensations. Therefore, the results of this study may have overestimated the degree to which subjects are able to distinguish sham from real stimulation in most common study setups that do not feature repeated evaluations. In our study, participants performed a cognitive task while receiving the stimulation and they were only asked about blinding retrospectively (as, indeed, subjects in Greinacher et al., 2018, also were). This assessment method is the most common way in studies aiming to measure the possible cognitive effects of tDCS. We therefore believe that our results provide a more accurate estimate of the actual blinding efficacy of the FSF protocol in most studies.

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](#)).

One possible limitation of the study is that one of the questions was assessing both the level of cutaneous discomfort as well as electrode dislocation and other non-stimulation sensations caused by the electrodes. By combining Ten20 conductive paste with elastic, self-adhesive, textile bandage we are confident that the electrodes adhered well to the head without major electrode dislocation. This was confirmed subjectively by our experimenters who stated that the electrodes were demanding to remove even at the end of the experiment. In addition, there is no reason to believe that any such non-stimulation effects should differ between the real and the sham stimulation protocols, especially given our strict double-blind protocol which ensured that electrode preparations were identical between the two groups. We therefore argue that any differences between sham and real stimulation is due to the cutaneous sensations caused by the real stimulation rather than differences in electrode preparation.

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, 2018), 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 vasodilation-induced redness underneath the electrodes (Durand et al., 2002; O'Connell et al., 2012; Ezquerro et al., 2017) both of which have previously been identified as potential factors which can break blinding (O'Connell et al., 2012; Palm et al., 2013; Guarienti et al., 2015).

References

- Ambrus, G. G., Al-Moyed, H., Chaieb, L., Sarp, L., Antal, A., Paulus, W., 2012. The fade-in–short stimulation–fade out approach to sham tDCS—reliable at 1 ma for naive and experienced subjects, but not investigators. *Brain Stimulation* 5 (4), 499–504.
- Antal, A., Alekseichuk, I., Bikson, M., Brockmüller, J., Brunoni, A., Chen, R., Cohen, L., Dowthwaite, G., Ellrich, J., Flöel, A., et al., 2017. Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. *Clinical Neurophysiology* 128 (9), 1774–1809.
- Aslaksen, P. M., Vasylenko, O., Fagerlund, A. J., 2014. The effect of transcranial direct current stimulation on experimentally induced heat pain. *Experimental Brain Research* 232 (6), 1865–1873.
- Bikson, M., Brunoni, A. R., Charvet, L. E., Clark, V., Cohen, L. G., Deng, Z.-D., Dmochowski, J., Edwards, D., Frohlich, F., Kappenman, E., et al., 2017. Rigor and reproducibility in research with transcranial electrical stimulation: An nimh-sponsored workshop. *Brain Stimulation*.
- Boayue, N. M., Csifcsák, G., Aslaksen, P., Turi, Z., Antal, A., Groot, J. M., Hawkins, G., Forstmann, B., Thielscher, A., Opitz, A., Thielscher, A.,

- Mittner, M., in press. Increasing propensity to mind-wander by transcranial direct current stimulation? a registered report. *European Journal of Neuroscience*.
- Boonstra, T. W., Nikolin, S., Meisener, A.-C., Martin, D. M., Loo, C. K., 2016. Change in mean frequency of resting-state electroencephalography after transcranial direct current stimulation. *Frontiers in Human Neuroscience* 10, 270.
- Bürkner, P. C., Vuorre, M., Sep 2018. Ordinal regression models in psychology: A tutorial.
URL psyarxiv.com/x8swp
- Davis, N. J., Gold, E., Pascual-Leone, A., Bracewell, R. M., 2013. Challenges of proper placebo control for non-invasive brain stimulation in clinical and experimental applications. *European Journal of Neuroscience* 38 (7), 2973–2977.
- Dundas, J., Thickbroom, G., Mastaglia, F., 2007. Perception of comfort during transcranial dc stimulation: effect of nacl solution concentration applied to sponge electrodes. *Clinical Neurophysiology* 118 (5), 1166–1170.
- Durand, S., Fromy, B., Bouyé, P., Saumet, J., Abraham, P., 2002. Vasodilatation in response to repeated anodal current application in the human skin relies on aspirin-sensitive mechanisms. *The Journal of Physiology* 540 (1), 261–269.
- Ezquerro, F., Moffa, A. H., Bikson, M., Khadka, N., Aparicio, L. V., de Sampaio-Junior, B., Fregni, F., Bensenor, I. M., Lotufo, P. A., Pereira, A. C., et al., 2017. The influence of skin redness on blinding in transcranial direct current stimulation studies: a crossover trial. *Neuromodulation* 20 (3), 248–255.
- Fertonani, A., Ferrari, C., Miniussi, C., 2015. What do you feel if i apply transcranial electric stimulation? safety, sensations and secondary induced effects. *Clinical Neurophysiology* 126 (11), 2181–2188.
- Gandiga, P. C., Hummel, F. C., Cohen, L. G., 2006. Transcranial dc stimulation (tdcs): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology* 117 (4), 845–850.

- Greinacher, R., Buhôt, L., Möller, L., Learmonth, G., 2018. The time course of ineffective sham blinding during 1ma tdc. bioRxiv.
URL <https://www.biorxiv.org/content/early/2018/11/05/462424>
- Guarienti, F., Caumo, W., Shiozawa, P., Cordeiro, Q., Boggio, P. S., Benseñor, I. M., Lotufo, P. A., Bikson, M., Brunoni, A. R., 2015. Reducing transcranial direct current stimulation-induced erythema with skin pre-treatment: considerations for sham-controlled clinical trials. *Neuromodulation* 18 (4), 261–265.
- Guleyupoglu, B., Febles, N., Minhas, P., Hahn, C., Bikson, M., 2014. Reduced discomfort during high-definition transcutaneous stimulation using 6% benzocaine. *Frontiers in Neuroengineering* 7, 28.
- Kessler, S. K., Turkeltaub, P. E., Benson, J. G., Hamilton, R. H., 2012. Differences in the experience of active and sham transcranial direct current stimulation. *Brain Stimulation* 5 (2), 155–162.
- Liddell, T. M., Kruschke, J. K., 2018. Analyzing ordinal data with metric models: What could possibly go wrong? *Journal of Experimental Social Psychology* 79, 328–348.
- Loo, C. K., Husain, M. M., McDonald, W. M., Aaronson, S., O'Reardon, J. P., Alonzo, A., Weickert, C. S., Martin, D. M., McClintock, S. M., Mohan, A., et al., 2018. International randomized-controlled trial of transcranial direct current stimulation in depression. *Brain stimulation* 11 (1), 125–133.
- Matsumoto, H., Ugawa, Y., 2017. Adverse events of tdc and tacs: a review. *Clinical Neurophysiology Practice* 2, 19–25.
- McFadden, J. L., Borckardt, J. J., George, M. S., Beam, W., 2011. Reducing procedural pain and discomfort associated with transcranial direct current stimulation. *Brain Stimulation* 4 (1), 38–42.
- O'Connell, N. E., Cossar, J., Marston, L., Wand, B. M., Bunce, D., Moseley, G. L., De Souza, L. H., 2012. Rethinking clinical trials of transcranial direct current stimulation: participant and assessor blinding is inadequate at intensities of 2ma. *PloS One* 7 (10), e47514.

- Palm, U., Reisinger, E., Keeser, D., Kuo, M.-F., Pogarell, O., Leicht, G., Mulert, C., Nitsche, M. A., Padberg, F., 2013. Evaluation of sham transcranial direct current stimulation for randomized, placebo-controlled clinical trials. *Brain Stimulation* 6 (4), 690–695.
- Poreisz, C., Boros, K., Antal, A., Paulus, W., 2007. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Research Bulletin* 72 (4-6), 208–214.
- Russo, R., Wallace, D., Fitzgerald, P. B., Cooper, N. R., 2013. Perception of comfort during active and sham transcranial direct current stimulation: a double blind study. *Brain Stimulation* 6 (6), 946–951.
- Santaracchi, E., Brem, A.-K., Levenbaum, E., Thompson, T., Kadosh, R. C., Pascual-Leone, A., 2015. Enhancing cognition using transcranial electrical stimulation. *Current Opinion in Behavioral Sciences* 4, 171–178.
- Saturnino, G. B., Antunes, A., Thielscher, A., 2015. On the importance of electrode parameters for shaping electric field patterns generated by tdc. *Neuroimage* 120, 25–35.
- Turi, Z., Bjørkedal, E., Gunkel, L., Antal, A., Paulus, W., Mittner, M., 2018. Evidence for cognitive placebo and nocebo effects in healthy individuals. *Scientific Reports* 8 (1), 17443.
- Turi, Z., Mittner, M., Paulus, W., Antal, A., 2017. Placebo intervention enhances reward learning in healthy individuals. *Scientific Reports* 7, 41028.
- Wallace, D., Cooper, N. R., Paulmann, S., Fitzgerald, P. B., Russo, R., 2016. Perceived comfort and blinding efficacy in randomised sham-controlled transcranial direct current stimulation (tdcs) trials at 2 ma in young and older healthy adults. *PloS One* 11 (2), e0149703.
- Woods, A. J., Antal, A., Bikson, M., Boggio, P. S., Brunoni, A. R., Celnik, P., Cohen, L. G., Fregni, F., Herrmann, C. S., Kappenman, E. S., et al., 2016. A technical guide to tdc, and related non-invasive brain stimulation tools. *Clinical Neurophysiology* 127 (2), 1031–1048.

Acknowledgements

The writing of this paper was supported by the Research Program, University Medical Center, University of Goettingen awarded to ZT. AT received support from Lundbeckfonden (R118-A11308) and Novo Nordisk Fonden by a synergy grant on Biophysically adjusted state-informed cortex stimulation (BASICS; NNF14OC0011413).

Conflict of Interest statement

The authors declare no conflict of interest.

Author Contributions

TZ: technical advice tdc, collected data, wrote paper; NB: designed study, collected data, commented on paper; GC: designed study, drafted paper; PA: technical advice; commented on paper; AA: technical advice tdc, collected data, commented on paper; WP: technical advice tdc, commented on paper; JG: collected data, commented on paper; GH: technical advice data analysis, commented on paper; BF: designed study, commented on paper; AO: technical advice comp modeling, commented on paper; AT: technical advice comp modeling, commented on paper; MM: designed study, coordinated activity, analysed data, drafted paper;

List of abbreviations

tDCS transcranial direct-current stimulation

FSF fade-in, short-stimulation, fade-out

FS fade-in, short-stimulation

DLPFC dorso-lateral prefrontal cortex

EEG electroencephalogram

DC direct-current

SART Sustained Attention to Response Task

HDI Highest-density interval

Figure Captions

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

A) Stimulation protocols

B) Electrode montage

C) Please tell us if you think you were receiving real or fake (placebo) stimulation today.

D) Please rate the magnitude to which the placement and/or the effect of either electrode was disturbing during the task.