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SHORT COMMUNICATION

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

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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 min. We analysed subjective reports of 192 volunteers, who either 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

active sham tDCS, blinding, double-blinding, placebo, transcranial direct current stimulation

Abbreviations: DC, direct current; DLPFC, dorso-lateral prefrontal cortex; EEG, electroencephalogram; FS, fade-in, short-stimulation; FSF, fade-in, short-stimulation, fade-out; HDI, highest-density interval; SART, Sustained Attention to Response Task; tDCS, transcranial direct current stimulation.

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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 (Fertonani, Ferrari, & Miniussi, 2015; Matsumoto & Ugawa, 2017; Poreisz, Boros, Antal, & Paulus, 2007).

Most tDCS studies use active sham stimulation protocols for placebo control (Davis, Gold, Pascual-Leone, & Bracewell, 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 (5–30 s) 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 30 s). 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 (5–30 s) 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, Hummel, & Cohen, 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 min (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 min or longer (Kessler, Turkeltaub, Benson, & Hamilton, 2012; O'Connell et al., 2012; Russo, Wallace, Fitzgerald, & Cooper, 2013; Wallace, Cooper, Paulmann, Fitzgerald, & Russo, 2016). Following these findings, FSF has been used as a control in hundreds of studies using real tDCS at 1 mA for 20 min.

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-centre, pre-registered study (Boayue et al., 2019). In this study, we collected data from 192 volunteers, who either received real tDCS (20 min) or FSF tDCS (40 s) at 1 mA over the left dorsolateral prefrontal cortex (DLPFC). The primary goal was to investigate the behavioural 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 analyse these subjective reports in order to investigate whether FSF is an effective control procedure for tDCS applied at 1 mA over 20 min.

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., 2019). 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 ± 3.19 years *SD*) collected at three labs (*N* per lab = 64): Amsterdam, Göttingen, and Tromsø (Boayue et al., 2019). 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 committee 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 centre (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 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. N.M.B., the author, 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 ≤10 kΩ.

The stimulation was administered using a neuroConn DC-stimulator (neuroConn GmbH, Germany). The real tDCS protocol lasted for 20 min of continuous stimulation at 1 mA, whereas the FSF protocol lasted for 15 s at 1 mA. In addition, we utilized 30 s-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 1a,b. The stimulator was operating in study mode: The active sham and the

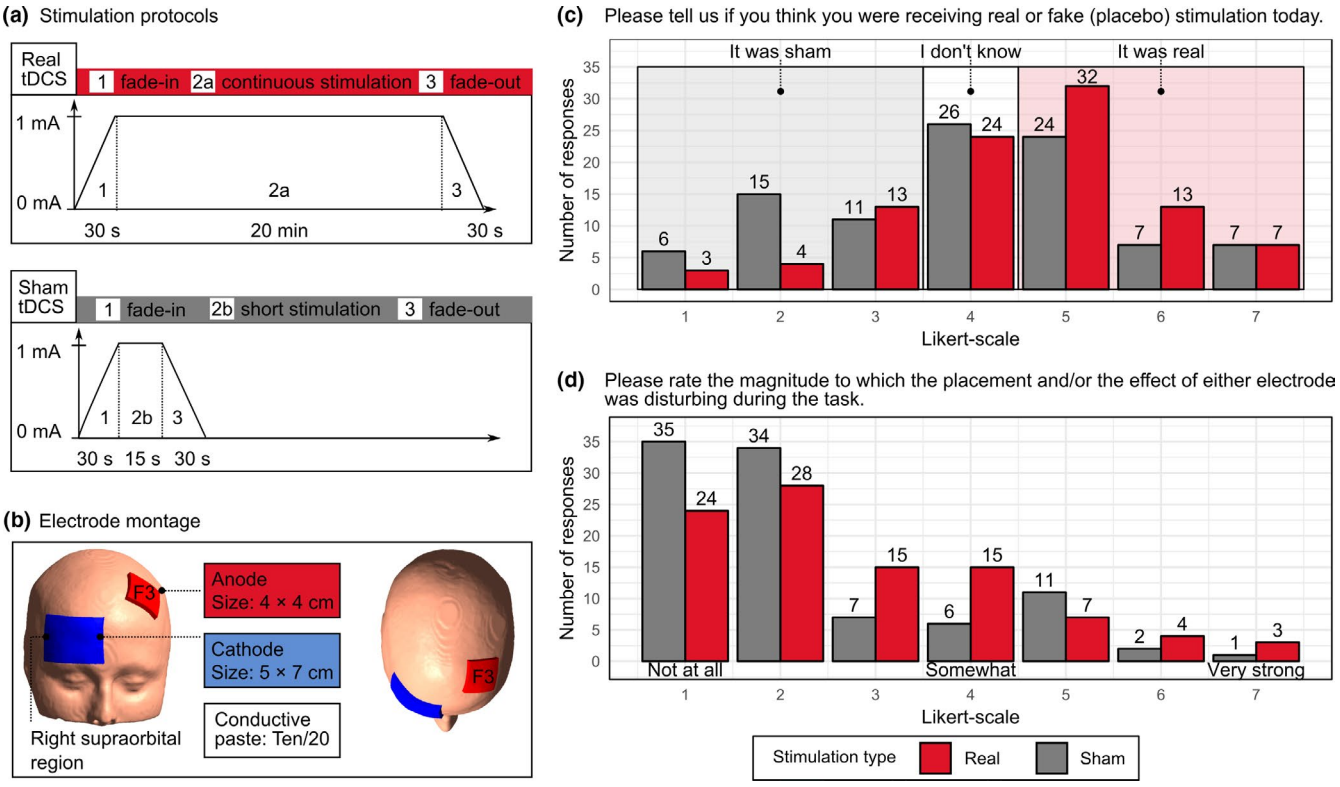

FIGURE 1 (a) The stimulation parameters for the real and FSF tDCS protocols. (b) The electrode montage. (c) Subjective responses to the blinding question were generally more correct in the real stimulation condition (red) when compared to sham (grey). (d) In addition, participants receiving real stimulation reported greater discomfort. [Colour figure can be viewed at wileyonlinelibrary.com]

real stimulation protocols were assigned to pseudo-codes b and c respectively.

The data were 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 30-s fade-in/out periods and a 40-s 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 (1,200 s) divided by 30, resulting in 40 s for our setup. However, due to the nature of the present pre-registered replication study (Boayue et al., 2019), 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. As 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., 2019). The SART is a Go-NoGo task that is frequently employed in mind-wandering studies. The total duration of the SART was 40 min and the task consisted of two 20-min-long blocks with a short break in between. TDCS was applied only in the first 20 min. 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 & Vuorre, 2018) designed specifically for analysing ordinal data (Liddell & 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 & 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 Supporting Information and are in line with those from our primary analysis.

3 | RESULTS

Our results are summarized graphically in Figure 1 c,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 Supporting Information). 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 ($b_{GOE} = 0.33$ [−0.03, 0.69], $b_{TRM} = -0.10$ [−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 Supporting Information).

4 | DISCUSSION

TDCS applied at 1 mA for 20 min 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 (a) none of the participants had any prior experience with tDCS and (b) 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 (Greinacher, Buhôt, Möller, & Learmonth, 2018; O'Connell et al., 2012) 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 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 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 min 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 30-s fade-in/out periods and 20-s 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: 15 vs. 20 s). One important difference is the duration of the real tDCS: Whereas in our study it was 20 min, Greinacher et al. (2018) used 10 min. Blinding efficacy of FSF protocols seems to be better for real tDCS protocols with shorter stimulation durations (e.g., 10 min). This may explain why our participants (receiving 20 min 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 30 s 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 towards 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, Antunes, & Thielscher, 2015; Woods et al., 2016). Application of conductive paste has several advantages over saline solution that include 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, Thickbroom, & Mastaglia, 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 modelling 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 (Greinacher et al., 2018; O'Connell et al., 2012).

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 disclocation. 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 are 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 min (Greinacher et al., 2018; Kessler et al., 2012; O'Connell et al., 2012; Russo et al., 2013; Wallace et al., 2016), 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, Vasylenko, & Fagerlund, 2014) and cognitive domains (Turi, Mittner, Paulus, & Antal, 2017; Turi et al., 2018), there seems to be an urgent need to test alternative active sham protocols (Boonstra, Nikolin, Meisener, Martin, & Loo, 2016; Palm et al., 2013) or develop better active sham protocols to effectively maintain blinding. One possibility may be considering to utilize topical anaesthetic cream to reduce cutaneous sensations (Guarienti et al., 2015; Guleyupoglu, Febles, Minhas, Hahn, & Bikson, 2014; McFadden, Borckardt, George, & Beam, 2011) and vasodilation-induced redness underneath the electrodes (Durand, Fromy, Bouyé, Saumet, & Abraham, 2002; Ezquerro et al., 2017; O'Connell et al., 2012) both of which have previously been identified as potential factors which can break blinding (Guarienti et al., 2015; O'Connell et al., 2012; Palm et al., 2013).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA ACCESSIBILITY

The raw data and all reported analyses are available for download at our repository (https://github.com/ihrke/2018_tdcs_blinding).Materials used for this study are available at our repository (https://osf.io/bv32d/)..

AUTHOR CONTRIBUTIONS

ZT: technical advice on tDCS, collected data, and wrote the paper; GC: designed the study, collected data, and commented on the paper; NB: designed the study, and drafted the paper; PA: technical advice, and commented on the paper; AA: technical advice on tDCS, collected data, and commented on the paper; WP: technical advice on tDCS, commented on the paper; JG: collected data, and commented on the paper; GH: technical advice on data analysis, and commented on the paper; BF: designed the study, and commented on the paper; AO: technical advice on computational modelling, and commented on the paper; AT: technical advice on computational modelling, commented on the paper; MM: designed the study, coordinated the activity, analysed the data, and drafted the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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