Received: March 11, 2014 Revised: May 21, 2014 Accepted: June 10, 2014

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12230

Reducing Transcranial Direct Current Stimulation-Induced Erythema With Skin Pretreatment: Considerations for Sham-Controlled Clinical Trials

Fabiana Guarienti, MD*†; Wolnei Caumo, MD, PhD†; Pedro Shiozawa, MD*‡; Quirino Cordeiro, MD, PhD‡; Paulo S. Boggio, PhD§; Isabela M. Benseñor, MD, PhD*; Paulo A. Lotufo, MD, PhD*; Marom Bikson, PhD¶; André R. Brunoni, MD, PhD*

Objectives: Transcranial direct current stimulation (tDCS)-induced erythema (skin reddening) has been described as an adverse effect that can harm blinding integrity in sham-controlled designs. To tackle this issue, we investigated whether the use of topical pretreatments could decrease erythema and other adverse effects associated with tDCS.

Materials and Methods: Thirty healthy volunteers were recruited, and four interventions were applied 30 min prior to tDCS in a Latin square design: placebo, ketoprofen 2%, hydroxyzine 1%, and lidocaine 5%. TDCS was applied for 30 min (2 mA, anode and cathode over F3 and F4, respectively) in two active sessions with a minimum 1-week interval. The Draize erythema scoring system scale was used to assess erythema intensity; a tDCS questionnaire was used to assess other adverse effects (e.g., tingling, itching, burning sensation, and pain).

Results: We found that ketoprofen (but not hydroxyzine or lidocaine) significantly attenuated tDCS-induced erythema regarding intensity and duration, with a medium effect compared with placebo. Erythema was overall mild, short-lived (lasting 18–24 min after tDCS ending), and more intense under the anode. Subjects with darker skin color also tended to present less intense tDCS-induced erythema. The prevalence of other adverse effects was low and did not differ between dermatological groups.

Conclusions: Ketoprofen 2% topical pretreatment might be an interesting strategy to reduce tDCS-induced erythema and might be useful for blinding improvement in further sham-controlled tDCS trials.

Keywords: Blinding integrity, erythema, ketoprofen, sham-controlled design, skin reddening, transcranial direct current stimulation

Conflict of Interest: Dr. Brunoni receives grants from FAPESP (2012/209115) and NARSAD (YI 2013). Dr. Brunoni also receives Young Investigator grants from the Brain & Behavior Research Foundation (NARSAD; YI 2013) and S.O Paulo State Research Foundation (FAPESP 2012/20911-5).

INTRODUCTION

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique widely used in neuropsychology, neurophysiology, and neuropsychiatry studies. tDCS-induced erythema (skin reddening observed after the tDCS session) is a common adverse effect that might harm study blinding, as it occurs more frequently in the active arm than the sham arm and can be immediately detected by study investigators (1–3), thereby decreasing the validity of tDCS trials (2).

For this reason, our aim was to investigate whether tDCS-induced erythema could be minimized using different dermatological treatments prior to the tDCS section. As a secondary aim, we explored whether the frequency of headache, tingling, burning sensation, sleepiness, itching, and other adverse effects could be decreased with these treatments. This study is important for further development of the technique, which has an emerging potential in the treatment of neurological and psychiatric disorders.

Address correspondence to: André Russowsky Brunoni, MD, PhD, Service of Interdisciplinary Neuromodulation, Institute of Psychiatry, Clinics Hospital, and Interdisciplinary Center for Applied Neuromodulation, University Hospital; Faculty of Medicine, University of São Paulo, São Paulo (SP), Brazil. Av. Prof Lineu Prestes 2565, third floor, CEP 05508-000. Tel.: +551130919241; Email: brunoni@usp.br

* Service of Interdisciplinary Neuromodulation & Interdisciplinary Center for Applied Neuromodulation, Department and Institute of Psychiatry, University Hospital, University of São Paulo, São Paulo, Brazil

† Laboratory of Pain and Neuromodulation, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

‡ Laboratory of Clinical Neuromodulation, Santa Casa Medical School, São Paulo, Brazil

§ Laboratory of Cognitive and Social Neurosciences, Mackenzie Presbyterian University, São Paulo, Brazil

¶ Department of Biomedical Engineering, City College of New York, City University of New York, New York, NY, USA

METHODS

Subjects

We recruited 30 healthy adult participants. The local and national ethics committees approved the study, and all participants provided written informed consent. We did not include participants presenting any active dermatosis, skin allergy, skin marks, recent exposure to intense sunlight or artificial tanning, or topical or systemic skin treatment in the region where the electrodes were placed. In addition, we did not include subjects with previous or present history of neuropsychiatric disorders, as we performed two active tDCS sessions over the frontal area.

Design

All participants received two active 30-min tDCS sessions, with a minimum 1-week interval to avoid carry-over effects. We performed a Latin square randomization, in which each electrode (anode and cathode) was randomized to receive two out of four skin creams.

Procedures

The study was conducted in rooms with controlled temperature and humidity (temperature 20°C ± 2°C, relative humidity 50% ± 5% relative humidity) so as to ensure standardization of the dermatologic evaluation.

The following procedures were adopted:

1. First, the skin was examined so as to ensure that no erythema or irritation was present.
2. Thirty minutes prior to the tDCS session, we gently cleaned the skin electrode sites using alcohol gel to remove lotion, cream, dirt, sebum, and the like from the skin of participants. We did not scrub the skin.
3. After that, the cream was applied in the corresponding region. This step lasted 20 min.
4. The skin was gently cleaned again in the same manner as previously described so as to remove the cream and therefore avoid inducing iontophoresis of the substance during direct current stimulation.
5. After 10 min, the tDCS session was started.

The anode and the cathode were respectively placed over the left and right dorsolateral prefrontal areas (F3 and F4 areas, respectively), as in prior depression trials (4,5). The electric current was 2 mA, and the electrode size was 25 cm^2. The electrodes were inserted in sponges of similar size, which were soaked with NaCl 0.45% (72 mmol/L NaCl). This concentration was chosen according to prior research reporting that subjects (6) perceive concentrations in the range of 15 to 140 mM as more comfortable. We used a ramp-in of 30 sec and ramp-out of 15 sec. We used a battery-powered constant-current device.

All creams were white, odorless, and of similar consistency. The skin creams contained: 1) vehicle only (placebo), composed of cutin, emollients, water, and transcutol; 2) ketoprofen 2%, a nonsteroidal anti-inflammatory agent; 3) hydroxyzine 1%, an antihistamine; and 4) lidocaine 5%, an anesthetic agent.

Assessments

Clinical and demographic data were collected from each participant. We used the Fitzpatrick chromatic scale that assesses skin color and pigmentation after sun exposure, ranging from I to VI. This variable was further dichotomized as binary by combining participants in types II and III (low-pigment skin) and doing the same for types IV and V (high-pigment skin). No participant had skin type I or VI.

Adverse effects were assessed using a specific questionnaire (7). When the subject reported an adverse effect, we asked him/her to grade its severity (mild, moderate, severe, very severe) and relationship with tDCS, using a Likert scale (from "no relation" to "complete relationship"). An adverse effect was considered to be present if the participant described it as being at least remotely associated with tDCS.

For the assessment of our main outcome (erythema), we used the Draize scoring system scale, which grades erythema from 0 (no erythema) to 4 (severe erythema). Secondary outcomes were the presence/absence of adverse tDCS effects and erythema. Data were collected immediately before tDCS started, 10 min after tDCS onset (except for erythema), immediately after tDCS ended, and thereafter at every 6 min, until the variable was no longer observable or after 5 observations (30 min).

Statistical Analysis

Statistical analysis was performed using SPSS (IBM Statistics) version 20 (IBM, Armonk, NY, USA). Analyses were considered significant at a two-sided $p \leq 0.05$. Baseline data were described using means and frequencies.

For the main outcome, we performed a repeated-measures linear mixed-model analysis (*mixed* function in SPSS) using fixed effects, 100 interactions, and the restricted maximum likelihood method. The dependent variable was Draize score, and the independent variables were the main and interaction effects of time, group (type of cream), electrode (anode and cathode), and Fitzpatrick scale. When a significant interaction between time and other variables was observed, we performed pairwise comparisons at each time point (for the group variable, we compared the active creams vs. placebo). Cohen's *d* and eta-squared (η^2) were used to estimate the effect size of between-group differences; values of 0.2, 0.5 and 0.8 (Cohen's *d*) and 0.01, 0.06 and 0.14 (η^2) respectively represent small, medium and large effect sizes (8).

We also performed subgroup analyses using the same model as described above, however only using one independent variable at a time. The variables assessed were gender, skin pigmentation, and electrode (anode vs. cathode). These analyses allowed us to verify potential different erythema intensity according to each variable.

The secondary outcomes were explored using χ^2-tests at each time point to compare the frequency of adverse effects and erythema. Finally, we carried out survival analyses and Cox proportional hazards for assessment of erythema duration according to the variables group and type of electrode.

RESULTS

Most participants were women ($N = 25$), with a mean age of 24.6 (SD 4.8) years. The predominant skin color was white, and 70% of participants presented a Fitzpatrick skin type of II or III (Table 1).

Erythema

Erythema, as evaluated per Draize scores, was generally mild, with a peak intensity immediately after the ending of tDCS (mean =

Table 1. Clinical and Demographic Characteristics of the Sample.

Sample	Data
Subjects, *N*	30
Age, mean (SD)	24.6 (4.8)
Gender, *N* (%)	
Male	5 (16.7)
Female	25 (83.3)
Fitzpatrick type, *N* (%)*	
Type I	0 (00.00)
Type II	4 (13.33)
Type III	17 (56.67)
Type IV	8 (26.67)
Type V	1 (3.33)
Type VI	0 (00.00)
Smoking habits, *N* (%)	
No smoker	22 (73.33)
Former smoker	1 (3.33)
Socially smoker	5 (16.67)
Smoker	2 (6.67)
Ethnicity, *N* (%)	
Caucasian	25 (83.33)
Black	1 (3.33)
Asian	3 (10.00)
Brown	1 (3.33)

*Type I: white, very fair, red, or blond hair, blue eyes, freckles, always burns, never tans; type II: white, fair skin, red or blond hair, blue, hazel or green eyes, usually burns, tans with difficulty; type III: cream white, fair with any eye or hair color, sometimes mild burn, gradually tans; type IV: brown, typical Mediterranean Caucasian skin, rarely burns, tans with ease; type V: dark brown, Middle Eastern skin type, very rarely burns, tans easily; type VI: black, never burns, tans very easily.

1.1, SD = 0.75), and progressively decreasing over time, according to observations performed 6, 12, 18, 24, and 30 min after tDCS ending (mean = 0.67, SD = 0.64; mean = 0.33, SD = 0.5; mean = 0.15, SD = 0.36; mean = 0.08, SD = 0.28; and mean = 0.02, SD = 0.16, respectively).

The mixed-model analysis revealed main effects for time ($F_{7,928}$ = 143.44, $p < 0.01$), time × group ($F_{21,822} = 1.6$, $p = 0.042$), and time × electrode ($F_{7,928} = 2.39$, $p = 0.02$). No other interactions were significant ($p > 0.24$). In the *post hoc* pairwise comparisons, we found significant effects only for ketoprofen 2% vs. placebo, immediately after the ending of tDCS (Cohen's $d = 0.31$, $\eta^2 = 0.023$, $p = 0.05$) and 6 and 12 min after that ($d = 0.55$, $\eta^2 = 0.07$, $p < 0.01$ and $d = 0.33$, $\eta^2 = 0.026$; $p = 0.02$, respectively). In all these comparisons, the use of ketoprofen 2% attenuated the tDCS-induced erythema as compared with placebo (Fig. 1).

Finally, Kaplan–Meier analysis revealed that the median duration of observable erythema was 24 min. This median was shorter for the ketoprofen 2% group (18 min), although the difference was not statistically significant ($p = 0.55$).

Other Adverse Effects

Headache, tingling, burning sensation, sleepiness, and itching were more frequent during the first 10 min after tDCS (during stimulation) and immediately after tDCS ended. There were no statistical differences among groups in the frequency of any adverse effect (Fig. 2).

Subgroup Analysis

tDCS-induced erythema in the skin site where the anode was placed was significantly more intense than in the cathode site

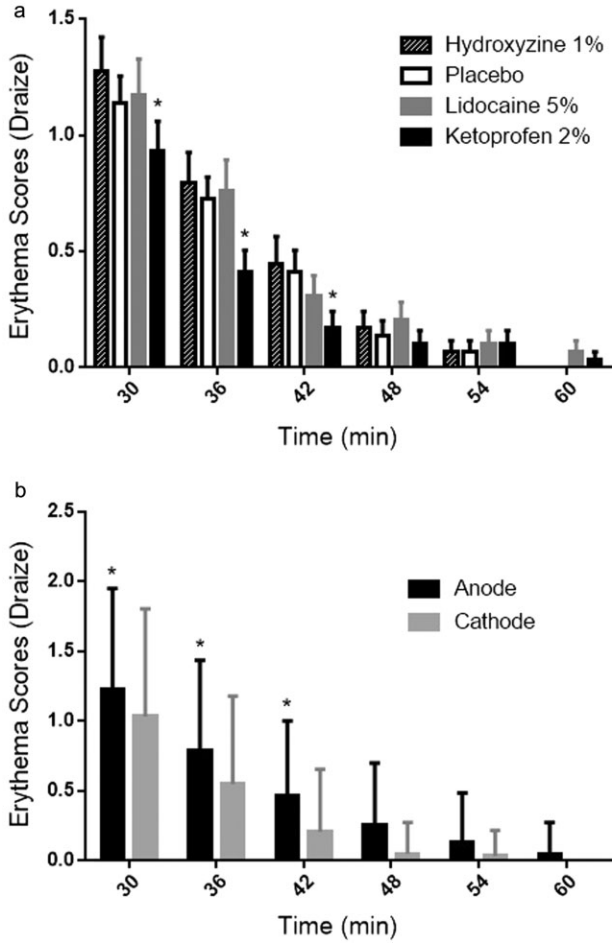

Figure 1. Bars showing erythema intensity (Draize scores) over time (min) and standard deviation (SD). The erythema was evaluated every 6 min after the end of tDCS stimulation (time 30). a. Comparison of erythema intensity according to the skin cream type. b. Comparison of erythema under the anode and the cathode. *$p \leq 0.05$ vs. placebo.

immediately after the ending of tDCS ($d = 0.25$, $\eta^2 = 0.015$, $p = 0.01$), and 6, 12, and 18 min later (respectively: $d = 0.38$, $\eta^2 = 0.034$; $d = 0.53$, $\eta^2 = 0.065$; $d = 0.95$, $\eta^2 = 0.184$;, $p < 0.01$ for all observations) (Fig. 1). Also, the median observable erythema duration was significantly shorter during cathodal stimulation than anodal (18 vs. 24 min, hazard ratio = 1.25, $p = 0.01$).

In addition, we found no significant differences in erythema intensity in males vs. females ($F_{6,811} = 1.11$, $p = 0.35$). However, we observed a trend ($F_{6,811} = 1.83$, $p = 0.09$) for higher erythema intensity in volunteers with lighter skin. *Post hoc t*-tests further revealed that participants with lighter skin presented greater skin reddening immediately after the ending of tDCS ($d = 0.41$, $\eta^2 = 0.04$, $p = 0.04$) and 6 min after ($d = 0.45$, $\eta^2 = 0.048$, $p = 0.02$). No significant differences were observed at other time points.

DISCUSSION

Main Findings

In the present study evaluating tDCS-induced erythema, our main findings were the following: 1) the erythema was more intense over the anode (vs. the cathode) site; 2) a trend was observed for subjects with lighter skin presenting more skin reddening com-

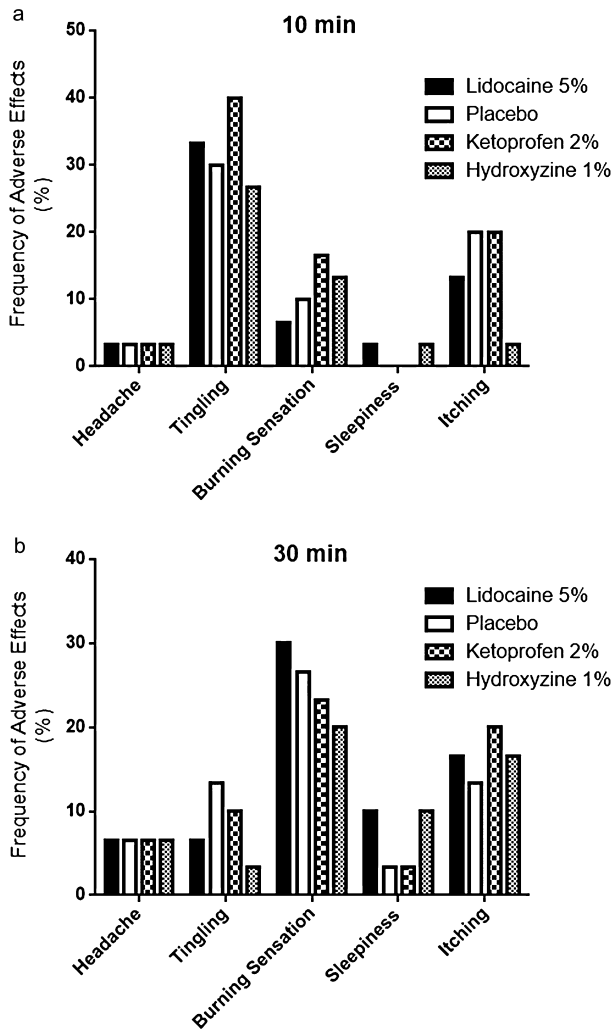

Figure 2. Frequency of adverse effects (headache, tingling, burning sensation, sleepiness, and itching) after 10 min (a) and 30 min (b) of transcranial direct current stimulation onset. Some adverse effects (neck pain, local pain, concentration difficulty, and mood change) are not displayed because they were reported by <0.1% of the sample.

pared with those with darker skin; and 3) topical pretreatment with ketoprofen 2%, but not hydroxyzine 1% or lidocaine 5%, significantly attenuated tDCS-induced erythema.

The latter finding—with a medium effect size compared with placebo—indicates that ketoprofen 2% can be applied in studies in which skin reddening might be an important concern—for example, protocols stimulating the more visible forehead area or using higher current densities. Conversely, this intervention increases procedural time and might not outweigh the benefits of reducing tDCS-induced erythema according to the study design. Another important issue is whether the applied substances might penetrate into the skull, the brain, or the bloodstream via iontophoresis. For this reason, the substances were removed after a 20-min application.

The difference in skin reddening between the anode and cathode sites was initially small immediately after tDCS ending, although it increased within 6–18 min of tDCS ending; this was associated with both a faster decrease in cathode-induced erythema and a slower decrease in anode-induced erythema. In this context, the expression "make-or-break excitation" is used to describe how cathodal stimulation elicits immediate vasodilatation, whereas anodal stimulation interferes with it (9). Although it is unknown why vasodilatation under the anode is delayed compared with the cathode, possible mechanisms include different directions of pH change (according to current polarity), with accumulation of protons under the anode impeding the occurrence of vasodilatation during stimulation. In our study, we only measured erythema after electric stimulation, which might explain the more prolonged and intense erythema under the anode.

In subgroup analyses, a trend for subjects with lighter skin presenting higher erythema intensities was observed. This might be related to the constitutive properties of the skin—for instance, low-pigment skin burns easily in sunlight (10) and presents lower pain resistance and greater subcutaneous vasodilatation after capsaicin provocation (11). In our study, subjects with lighter skin might have experienced higher tDCS-induced skin vasodilatation and thus more erythema. Another explanation relates to the ease of observation of the phenomenon: It might be easier to observe skin reddening in subjects with fair skin given the visual contrast between the reddish erythema color and the lighter skin color.

Interestingly, we did not observe any influence of pretreatment with lidocaine or hydroxyzine on adverse effects such as itching, burning, local pain, or tingling. This is in apparent contrast with McFadden et al. (12), who reported reduced pain and discomfort associated with tDCS when using local anesthetics. However, the authors employed higher current densities than we (0.125 vs. 0.08 A/m^2) and measured pain every minute for 6 min whereas our first adverse effect measurement was after 10 min of tDCS onset. Their measures also focused on pain and discomfort symptoms, whereas we assessed the presence of tDCS-related adverse effects and not their severity—therefore, such adverse effects could have been attenuated by the skin treatments, but nonetheless presented and reported by the participants.

Methodological Aspects

In our study we used alcohol gel for skin cleansing, which could have induced skin irritation and erythema. Nevertheless, we enrolled only subjects without any skin condition, and we also checked whether erythema and irritation occurred after alcohol use. In fact, Löffler et al. (13) observed that alcohol-induced skin irritation occurs in the context of previously irritated skin, in some cases being a confounding effect of the sensation of alcohol applied to skin that was already damaged. Finally, the use of alcohol swabs has already been described in a methodological paper as a form of skin preparation before high-definition tDCS (14).

Also, we used two 30-min sessions of tDCS at 2 mA. Although most studies apply 20-min sessions, recent clinical trials have applied several sessions of 30 min (15) or even 40 min (16). In addition, in our study we used a session charge of 0.005 C, or 60 times the minimum threshold for inducing lesions, according to an animal study (17). Therefore, electric currents were applied in an adequate range regarding safety.

In the present study, we used a 72-mmoL/L NaCl solution, in accordance with recent tDCS literature reviews suggesting that the NaCl concentration should range between 15 mM and 140 mM (18–20); according to the study of Dundas et al. (6), solutions in these concentrations are more likely to be perceived as comfortable.

The erythema was evaluated by direct clinical observation. Nonetheless, the scoring system of Draize is one widely used validated method of visual evaluation of erythema (21). Further, all subjects were assessed by the same examiner (FG), who remained blinded to

the intervention group throughout the trial. Second, we performed bifrontal tDCS sessions, thus using a protocol commonly employed in major depression studies (4).

Finally, further studies are needed to assess the influence of other factors in tDCS-induced erythema, such as the molarity of the NaCl solution, the time period of the stimulation session, and the use of other experimental procedures for cream application.

CONCLUSION

Ketoprofen topical pretreatment reduces tDCS-induced erythema. Further sham-controlled tDCS trials can adopt this intervention, particularly when blinding is a sensitive issue. We also observed that tDCS-induced erythema is milder, shorter-lived, and more intense under the anode and in subjects with lighter skin color. These findings are of methodological value in developing and standardizing further tDCS clinical trials.

Acknowledgments

This work was supported by the National Council for Scientific and Technological Development (CNPq; 455157/2013-8).

Authorship Statement

Drs. Brunoni and Guarienti designed and conducted the study, including patient recruitment, data collection, and data analysis. Drs. Guarienti and Brunoni prepared the manuscript draft with important intellectual input from Drs. Shiozawa, Caumo, Bikson, Benseñor, Lotufo, Boggio, and Cordeiro. All authors approved the final version of the manuscript. All authors had complete access to the study data.

How to Cite This Article:

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 Pretreatment: Considerations for Sham-Controlled Clinical Trials. Neuromodulation 2015; 18: 261–265

REFERENCES

1. Brunoni AR, Schestatsky P, Lotufo PA, Bensenor IM, Fregni F. Comparison of blinding effectiveness between sham tDCS and placebo sertraline in a 6-week major depression randomized clinical trial. *Clin Neurophysiol* 2014;125:298–305.
2. O'Connell NE, Cossar J, Marston L et al. Rethinking clinical trials of transcranial direct current stimulation: participant and assessor blinding is inadequate at intensities of 2 mA. *PLoS ONE* 2012;7:e47514.
3. Palm U, Reisinger E, Keeser D et al. Evaluation of sham transcranial direct current stimulation for randomized, placebo-controlled clinical trials. *Brain Stimul* 2013;6:690–695.
4. Brunoni AR, Ferrucci R, Fregni F, Boggio PS, Priori A. Transcranial direct current stimulation for the treatment of major depressive disorder: a summary of preclinical, clinical and translational findings. *Prog Neuropsychopharmacol Biol Psychiatry* 2012;39:9–16.
5. Ferrucci R, Bortolomasi M, Brunoni AR et al. Comparative benefits of transcranial direct current stimulation (tDCS) treatment in patients with mild/moderate vs. severe depression. *Clin Neuropsychiatry* 2009;6:246–251.
6. Dundas JE, Thickbroom GW, Mastaglia FL. Perception of comfort during transcranial DC stimulation: effect of NaCl solution concentration applied to sponge electrodes. *Clin Neurophysiol* 2007;118:1166–1170.
7. Brunoni AR, Amadera J, Berbel B et al. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int J Neuropsychopharmacol* 2011;14:1133–1145.
8. Cohen J. *Statistical power analysis for the behavioral sciences*. New Jersey: Lawrence Erlbaum Associates, 1988.
9. Tartas M, Bouye P, Koitka A et al. Cathodal current-induced vasodilation to single application and the amplified response to repeated application in humans rely on aspirin-sensitive mechanisms. *J Appl Physiol* 2005;99:1538–1544.
10. Brenner M, Hearing VJ. The protective role of melanin against UV damage in human skin. *Photochem Photobiol* 2008;84:539–549.
11. Wang H, Papoiu AD, Coghill RC et al. Ethnic differences in pain, itch and thermal detection in response to topical capsaicin: African Americans display a notably limited hyperalgesia and neurogenic inflammation. *Br J Dermatol* 2010;162: 1023–1029.
12. McFadden JL, Borckardt JJ, George MS, Beam W. Reducing procedural pain and discomfort associated with transcranial direct current stimulation. *Brain Stimul* 2011;4:38–42.
13. Loffler H, Kampf G, Schmermund D, Maibach HI. How irritant is alcohol? *Br J Dermatol* 2007;157:74–81.
14. Villamar MF, Volz MS, Bikson M et al. Technique and considerations in the use of 4×1 ring high-definition transcranial direct current stimulation (HD-tDCS). *J Vis Exp* 2013;77:e50309.
15. Plow EB, Obretenova SN, Halko MA et al. Combining visual rehabilitative training and noninvasive brain stimulation to enhance visual function in patients with hemianopia: a comparative case study. *PM & R* 2011;3:825–835.
16. Bolognini N, Vallar G, Casati C et al. Neurophysiological and behavioral effects of tDCS combined with constraint-induced movement therapy in poststroke patients. *Neurorehabil Neural Repair* 2011;25:819–829.
17. Liebetanz D, Koch R, Mayenfels S et al. Safety limits of cathodal transcranial direct current stimulation in rats. *Clin Neurophysiol* 2009;120:1161–1167.
18. Nitsche MA, Cohen LG, Wassermann EM et al. Transcranial direct current stimulation: state of the art 2008. *Brain Stimul* 2008;1:206–223.
19. Brunoni AR, Nitsche MA, Bolognini N et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul* 2012;5:175–195.
20. DaSilva AF, Volz MS, Bikson M, Fregni F. Electrode positioning and montage in transcranial direct current stimulation. *J Vis Exp* 2011;pii: 2744.
21. Kumar MG, Lin S. Transdermal iontophoresis: impact on skin integrity as evaluated by various methods. *Crit Rev Ther Drug Carrier Syst* 2008;25:381–401.

