Neuroscience 265 (2014) 21–27

FRONTAL TDCS MODULATES ORBITOFRONTAL REALITY FILTERING

A. L. MANUEL, [a]* **A. W. DAVID,** [b] **M. BIKSON** [b] **AND A. SCHNIDER** [a,c]

[a] *Laboratory of Cognitive Neurorehabilitation, Department of Clinical Neurosciences, University of Geneva, Switzerland*

[b] *Neural Engineering Laboratory, Department of Biomedical Engineering, The City College of New York of the City University of New York, NY, USA*

[c] *Division of Neurorehabilitation, Department of Clinical Neurosciences, University Hospital of Geneva, Switzerland*

Abstract—Orbitofrontal reality filtering denotes a memory control mechanism necessary to keep thought and behavior in phase with reality. Its failure induces reality confusion as evident in confabulation and disorientation. In the present study, we explored the influence of orbitofrontal transcranial direct current stimulation (tDCS) on reality filtering. Twenty healthy human subjects made a reality filtering task, while receiving cathodal, anodal, or sham stimulation over the frontal pole in three sessions separated by at least 1 week. Computational models predicted that this montage can produce polarity-specific current flow across the posterior medial orbitofrontal cortex (OFC). In agreement with our hypothesis, we found that cathodal tDCS over the frontal pole specifically impaired reality filtering in comparison to anodal and sham stimulation. This study shows that reality filtering, an orbitofrontal function, can be modulated with tDCS. **© 2014 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: tDCS, confabulations, continuous recognition task, extinction, orbitofrontal cortex.

INTRODUCTION

The capacity to distinguish between thoughts relating to the present reality and thoughts that have no relation with present reality (imaginations, fantasies) is essential to keep behavior and thinking in phase with present reality. We have called this capacity orbitofrontal reality filtering, based on studies with brain lesioned patients and imaging studies (Schnider, 2008; Schnider, 2013). Patients with lesions of the posterior orbitofrontal cortex (OFC) or directly connected areas may have a confusion of reality, as evidenced by disorientation regarding time, space, and current duties, and confabulations that the patients act upon (Schnider et al., 1996; Schnider and Ptak, 1999; Schnider, 2008).

The task used in these clinical studies and subsequent imaging studies (Schnider et al., 2000b; Treyer et al., 2003, 2006) comprises several runs of a continuous recognition test constituted of the same set of pictures, but ordered differently in each run. Participants have to indicate picture recurrences only within the ongoing run, irrespective of familiarity from previous runs. Compared to healthy controls and non-confabulating amnesics, confabulating (reality-confusing) patients specifically had a steep increase of false-positive responses from run to run, indicating that they were unable to suppress the interference of memories pertaining to previously encountered, but currently irrelevant information (Schnider et al., 1996; Schnider and Ptak, 1999; Nahum et al., 2012; Bouzerda-Wahlen et al., 2013). This capacity was independent of encoding and subsequent recognition in the first run of the task. Recovery from reality confusion, as indicated by restitution of behavior in agreement with current reality, was accompanied by the ability to again handle the interference (Schnider et al., 2000a). Positron emission tomography (PET) studies using a similar paradigm with healthy subjects supported the role of the OFC, area 13, in reality filtering (Schnider et al., 2000b; Treyer et al., 2003, 2006) and in addition highlighted the involvement of subcortical structures known to constitute the brain's reward system (Treyer et al., 2003). Electrophysiological studies indicated that reality filtering is an early transient, phasic, process occurring 200–300 ms after stimulus presentation, before processes of recognition set in at 400–600 ms (Schnider et al., 2002; Wahlen et al., 2011).

Reality-confusing patients continue to act according to plans that do not pertain to the present although their anticipations never come true (Schnider, 2008). These anticipations mostly correspond to previous habits: the patients are convinced that they are expected at a business meeting; that they will see their partners in a minute; that they will find their work files next door, etc. We, therefore, suspected that the basic mechanism underlying orbitofrontal reality filtering was extinction capacity, the ability to learn when anticipations are not valid anymore. Clinical studies indeed supported the hypothesis: disorientation and behaviorally spontaneous confabulation are strongly associated with a failure of extinction capacity (Nahum et al., 2009, 2012). In

*Corresponding author. Address: Service de Neurorééducation, Hôpitaux Universitaires de Genève, 26, av. de Beau-Séjour, CH-1211 Geneva 14, Switzerland. Tel: +41-22-372-3527; fax: +41-22-372-3705.

E-mail address: aurelie.manuelstocker@hcuge.ch (A. L. Manuel).

Abbreviations: ANOVA, analysis of variance; DLPFC, dorsolateral prefrontal cortex; FE, finite element; OFC, orbitofrontal cortex; SD, standard deviation; tDCS, transcranial direct current stimulation.

http://dx.doi.org/10.1016/j.neuroscience.2014.01.052
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healthy subjects, this capacity is electrophysiologically expressed by a frontal positivity at 200–300 ms, which emanates from the same brain region (medial OFC and subcortical loop) as the ability to control the interference of currently irrelevant memories (Schnider et al., 2005, 2007; Nahum et al., 2009, 2011).

In the present study, we used transcranial direct current stimulation (tDCS) – a neuromodulation technique in which low-intensity current is passed between an anode and a cathode on the scalp – to test whether stimulation of the OFC modulates performance in a reality filtering task. Animal studies demonstrated that outward (under the cathode) and inward (under the anode) current flow can, respectively, hyperpolarize or depolarize pyramidal neurons and decrease cortical excitability as measured by intrinsic excitability (Bikson et al., 2004; Reato et al., 2010; Rahman et al., 2013). Clinical studies have demonstrated that tDCS over the motor cortex modulates responses to transcranial magnetic stimulation in a polarity-specific manner, with the anode electrode typically increasing, the cathode electrode decreasing excitability (Nitsche and Paulus, 2000). For the present study, we assumed that outward current flow would reduce brain activation associated with higher cognitive function, whereas inward current flow would increase brain activation. In agreement with this assumption, tDCS has previously been used to influence memory functions. For example, working memory was improved following anodal stimulation of the left dorsolateral prefrontal cortex (DLPFC) in healthy subjects (Fregni et al., 2005; Andrews et al., 2011) and in patients with Parkinson's disease (Boggio et al., 2006) but impaired following cathodal tDCS over the posterior parietal cortex (Berryhill et al., 2010). Furthermore, memory retrieval was enhanced following left cathodal/right anodal tDCS over anterior frontal areas (Chi et al., 2010).

In this article, we present a single-blinded crossover placebo-controlled study to explore the influence of orbitofrontal tDCS on reality filtering. We used an electrode montage designed to access the medial orbitofrontal area and measured performance in a continuous recognition memory task (Schnider et al., 2010) during anodal, cathodal and sham tDCS in a within-subject design. Given that reality filtering presumably constitutes a phasic process (200–300 ms after stimulus presentation), we expected that a tonic influence like tDCS would only be able to impair this function but not improve it. This hypothesis is in agreement with a pharmacological study testing the influence of medication, which is also tonic rather than phasic, and which showed that dopaminergic stimulation by L-dopa impaired reality filtering in healthy subjects, while dopamine inhibition by risperidone failed to improve it (Schnider et al., 2010). In the assumption that outward current in the OFC exerts an inhibitory effect, we expected a specific increase of false-positive responses under the influence of cathodal tDCS over the frontal pole, similar to the error pattern of reality-confusing patients in clinically applied task versions (Schnider and Ptak, 1999).

EXPERIMENTAL PROCEDURES

Participants

Twenty healthy persons aged 24.8 ± 4.2 years (18–33 years; nine men) participated in the study. Participants provided written, informed consent and were paid to participate. No participant had a history of neurological or psychiatric illness. All procedures were approved by the Ethics Committee of the University Hospital of Geneva and performed according to the Declaration of Helsinki.

Experimental design

Each subject participated in three sessions differing by stimulation: frontal anodal stimulation, cathodal inhibition, or sham. The order of sessions was pseudorandomized between participants to reach a quasi equilibrium between all six session-order possibilities. Sessions were separated by at least one week to avoid carry-over effects of tDCS and the memory task. Questionnaires on potential side effects and task difficulty were administered at the end of each session.

Continuous recognition task

A short version of the same experimental procedure as used in a previous study was applied (Schnider et al., 2010). The task consisted of 12 sequences of a continuous recognition task, separated only by a red slide. For each picture, participants had to indicate by button press whether the picture had already appeared within the ongoing sequence (''yes, seen within this sequence''; right button press with the right middle finger) or not (''no, not seen within this sequence yet''; left button press with the right index finger). Each sequence was composed of the same 18 meaningless geometric designs, among which nine were randomly selected to be repeated once during the sequence, yielding a total of 27 trials in each sequence. Subjects were thus expected to say 18 times ''no'' (first appearance of a picture) and nine times ''yes'' (repetition) per sequence. As the pictures rapidly become familiar, the difficulty of the task lies in the necessity to sense whether an item looks familiar due to its previous appearance within the ongoing sequence (the ''current reality'') rather than a previous sequence.

Each trial started with the presentation of a black fixation cross for 500 ms. The inter-stimulus interval was 2000 ms. In total, the task included 324 stimuli (plus 11 red slides to indicate the switch between sequences) and lasted 14 min. At the beginning of the first session, a practice task lasting 5 min and consisting of four sequences, but with other images (108 stimuli and three red slides) was administered.

Behavioral data acquisition and analysis

The variables of interest for the continuous recognition test were the number of errors and the response time for items presented for the first time within a sequence (false positives as our measure of impaired reality

filtering) and for repeated items (false negatives as the measure of impaired item recognition) within the sequence. To assess how performance was influenced by habituation to the task, we analyzed accuracy and response time as a function of sequence (sequence 2–12) and session order (session 1–3).

The first sequence of each session was excluded from the main analysis because there is no interference from previous presentation; all items are new in the first sequence. However, this first sequence was analyzed across stimulation conditions to assess whether participants experienced the items as similarly new at the beginning of each session.

Statistical analyses were performed with Statistica 7.0 (StatSoft). The effects of stimulation on errors and response times were assessed with a one-way (three stimulation conditions) repeated measures analysis of variance (ANOVA) and post hoc comparisons were performed using the Fisher LSD test. Effect sizes (partial eta squared) are reported for significant results.

Questionnaires

To seize possible differences in participants' awareness between stimulation conditions, we applied a questionnaire by Brunoni et al. (2011). Following each tDCS session, participants evaluated the intensity of perceptual sensation items with a 4-point rating scale (1 = absent, 4 = severe) and indicated whether the sensation was related to the stimulation or not with a 5-point rating scale (1 = none, 5 = definite). The questionnaire included the following possible tDCS side-effects: headache, neck pain, scalp pain, tingling, itching, burning sensation, skin redness, sleepiness, trouble concentrating, acute mood change and others. In addition, participants filled out a questionnaire assessing task difficulty on a 5-point scale (1 = not difficult, 5 = very difficult) after each session. To test for differences between stimulation conditions, data were analyzed with Friedman's Chi-square test.

Transcranial direct current stimulation

Direct electrical current was delivered by a battery-driven NeuroConn DC brain stimulator (NeuroConn, Ilmenau, Germany) using a pair of rubber electrodes enclosed in saline-soaked sponges. To stimulate the OFC, the active electrode (to which the terms anodal and cathodal refer) was placed horizontally over FpZ (between Fp1 and Fp2 and over the glabella) according to the 10–20 EEG system. The return electrode was placed over the vertex, Cz of the 10–20 EEG system. The rationale for choosing Cz as the reference electrode is that studies have shown that increasing the distance between the two electrodes results in increased brain current density due to a decrease of current shunt across scalp (Miranda et al., 2006; Bikson et al., 2010). We did not choose a more posterior electrode as in previous studies (e.g. occipital cortex, Karim et al. (2010) and Bellaïche et al. (2013)), because of potential phosphene induction which could have interfered with stimulus processing in our experiment (Antal et al., 2003a, b). We used electrodes of two different sizes: 35 cm^2 for the active electrode, and 100 cm^2 for the return electrode. This setup has been suggested to decrease brain current density and functional efficacy under the reference electrode (Nitsche et al., 2007, 2008).

A direct current of 1 mA with a fade-in and fade-out of 8 s was delivered for 18 min for the anodal and cathodal stimulation conditions. The first task started 4 min after the onset of the stimulation to ensure that tDCS had reached maximum effect when the experiment started (Nitsche and Paulus, 2000).

For the sham condition, the electrodes were placed as for active stimulation, but the current was turned off after 30 s. The participants thus felt the sensation of electrical stimulation under the electrodes. This procedure was shown to reliably blind participants (Gandiga et al., 2006). Current densities for the three sessions were maintained below the safety limit of 0.052 mA/cm^2 (Nitsche et al., 2003; Iyer et al., 2005). The impedance was controlled by the device and kept low ($< 10\ \Omega$) for all stimulation sessions.

Modeling of tDCS stimulation

Electrical fields induced by tDCS were modeled to assess the areas of underlying brain modulation (Fig. 1). The main objective of the model was to predict whether significant current reached our region of interest for this study, i.e., the posterior medial OFC. A finite-element model was generated using previously described and validated protocols (Bikson et al., 2012; Truong et al., 2012, 2013; Turkeltaub et al., 2012; Edwards et al., 2013; Antal et al., 2014). The model was based on a high-resolution magnetic resonance imaging of an adult male at 1-mm × 1-mm × 1-mm resolution, and segmented according to the following isotropic conductivity values: skin, fat, skull, cerebrospinal fluid, gray matter, white matter, or air (Soterix Medical, New York, NY, USA). The finite-element (FE) mesh produced by the segmentation procedure (ScanIP, Exeter, UK) was further calculated for the computation of electric fields (COMSOL Multiphysics, Burlington, MA, USA). Within the FE model, isotropic conductivities were assigned for each tissue and electrode and boundary settings applied. The sponges were assigned a conductivity of 1.4 and the electrodes 5.99e7 S/m. The electric field values were scaled for 1 mA of inward current.

The tDCS current-flow for our electrode montage predicted that stimulating with an active electrode over the frontopolar cortex induced wide-spread frontal modulation (Fig. 1). Importantly, it confirmed that this montage achieved a significant current flow in the posterior medial OFC, i.e., our region of interest.

RESULTS

Continuous recognition task

Overall performance was not influenced by the type of stimulation: the total percentage of errors (mean ± standard deviation (SD): anodal, 19 ± 7%;

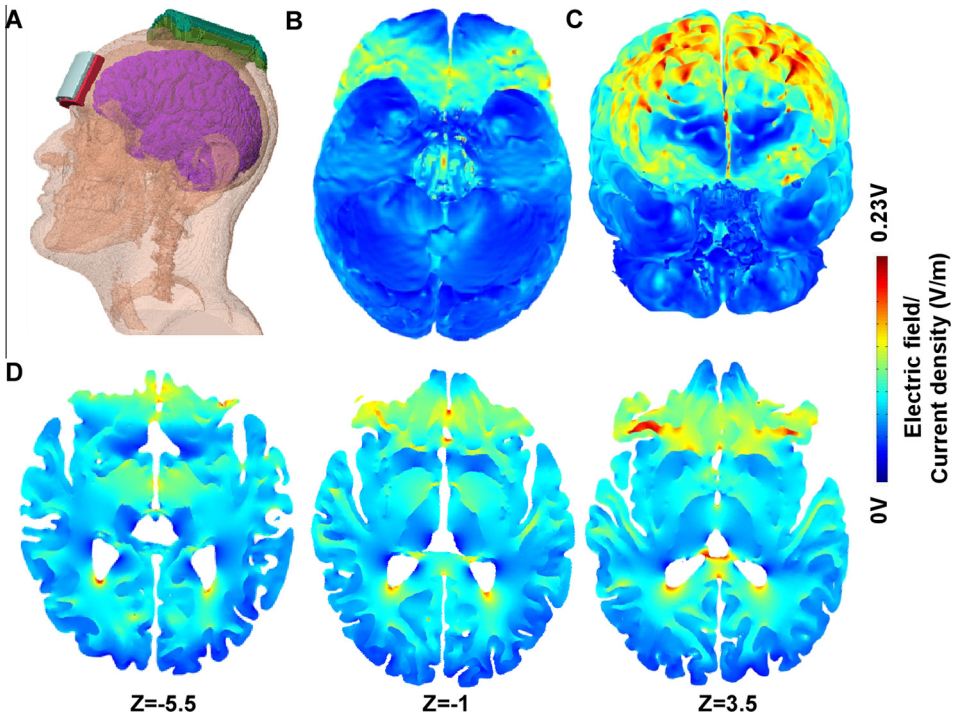

Fig. 1. Modeling of tDCS-induced electrical fields. (A) Electrode montage. Placement of the electrode pads on OFC and vertex. The predicted magnitude of induced electrical field following cathodal OFC and anodal vertex stimulation is shown for the bottom view (B), front view (C) and (D) axial slices with red areas indicating the areas of maximal current density. The model serves to confirm the expected effect of this montage on the medial OFC. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

cathodal, 20 ± 7%; sham, 19 ± 5%; $F_{(2,38)} = 1.88$, $p = 0.16$) and mean response time (anodal, 653 ± 207 ms; cathodal, 634 ± 194 ms; sham, 671 ± 186 ms; $F_{(2,38)} = 1.71$, $p = 0.19$) did not differ between stimulation conditions.

However, stimulation had a specific influence on the number of false positives (errors in response to new items: anodal (11 ± 8%, min: 0.5%, max: 37.8%), cathodal (14 ± 9%, min: 1.5%, max: 37.6%) and sham (11 ± 8%, min: 1%, max: 33.9%) differed significantly (Fig. 2, $F_{(2,38)} = 3.31$, $p = 0.047$; $\eta_p^2 = 0.15$). Post-hoc Fisher's test revealed a significant difference between cathodal and anodal stimulation ($p = 0.02$), and between cathodal and sham ($p = 0.04$) stimulation; anodal and sham stimulation did not differ. Conversely, the rate of errors on repeated items (i.e., false negatives) did not vary as a function of stimulation condition ($F_{(2,38)} = 1.03$, $p = 0.37$): anodal (37 ± 0%, min: 10.1%, max: 91.9%), cathodal (33 ± 22%, min: 8.08%, max: 88.8%) and sham (34 ± 18%, min: 10.3%, max: 82.8%).

Response times for new (mean ± SD: anodal, 637 ± 213 ms; cathodal, 617 ± 200 ms; sham, 646 ± 188 ms; $F_{(2,38)} = 0.97$, $p = 0.39$) stimuli were not significantly influenced by the stimulation. There was a trend for shorter response times for repeated items under cathodal stimulation (anodal, 755 ± 215 ms; cathodal, 723 ± 197 ms; sham, 766 ± 206 ms; $F_{(2,38)} = 3.19$, $p = 0.052$).

Participants' individual performance was consistent across conditions: total error rate under anodal and

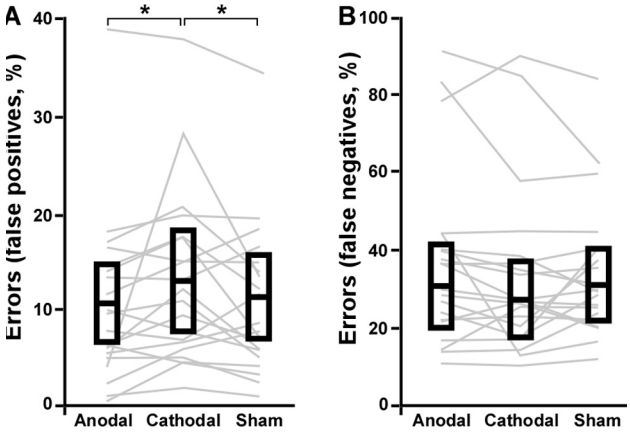

Fig. 2. Behavioral results. Error rates under the influence of anodal, cathodal or sham stimulation in response to (A) items presented for the first time in the sequence (false positives) and (B) items repeated within the sequence (false negatives). Boxes indicate the means ± SD and * indicate significant differences. Individual values are shown in the background in gray.

cathodal stimulation highly correlated with total errors under sham stimulation respectively ($r = 0.86$ and 0.86, $p < 0.001$) and between the two active stimulation conditions ($r = 0.93$, $p < 0.001$). These results indicate that inter-individual differences were more important overall than the performance modulations induced by stimulation, an observation concurring with a previous study (Schnider et al., 2010).

Repeated measures ANOVAs with factors Sequence (sequence 2–12) and Type of stimulation (anodal,

cathodal, sham) showed that performance (total error rate and response time) was constant across sessions. There was no interaction between Type of stimulation and Sequence ($F_{(20,380)} < 0.92$, $p > 0.57$) and no main effect of Type of stimulation ($F_{(2,38)} < 1.75$, $p > 0.34$) neither for error rate nor response time. Error rates did not significantly vary as a function of sequences ($F_{(10,190)} = 1.41$, $p = 0.17$). However, there was a main effect of Sequence for response times with RTs getting shorter during the course of the experiment ($F_{(10,190)} = 3.06$, $p = 0.01$; $\eta_p^2 = 0.63$). On average response time decreased by 5% (anodal, 4%; cathodal, 9%; sham, 2%), indicating that subjects got used to task difficulty across sequences without notable fatigue.

One-way repeated measures ANOVAs with factor Session (first, second, last session; irrespective of stimulation type) showed that session did not influence the total error rate ($F_{(2,38)} = 0.15$, $p = 0.85$). However, response time decreased by 9% as a function of session ($F_{(2,38)} = 7.39$, $p < 0.01$; $\eta_p^2 = 0.28$), indicating a general habituation to the task across sessions.

Performance in the first sequence, which did not require reality filtering, was stable across the three sessions (error rate: $F_{(2,38)} = 0.15$, $p = 0.86$; response time: $F_{(2,38)} = 0.76$, $p = 0.47$), indicating that subjects experienced the items as similarly new at the beginning of each session.

Questionnaires

All participants tolerated tDCS well and reported only minor side effects like headache, tingling, itching, burning sensation, skin redness, sleepiness, trouble concentrating whose intensity did not differ between stimulation conditions (Friedman's Chi-square test, all p-values $\geqslant 0.11$). There was no significant difference in perceived difficulty (anodal, 3.95 ± 0.76; cathodal, 3.90 ± 0.45; sham, 3.60 ± 0.82; Friedman's Chi-square test, all p-values $\geqslant 0.22$), indicating that participants were efficiently blinded to the stimulation conditions.

DISCUSSION

This study shows polarity-specific effects of tDCS on an orbitofrontal function: orbitofrontal reality filtering. As predicted, cathodal stimulation over the frontal pole, assumed to inhibit the OFC, led to an increase in false positives in the continuous recognition task, while anodal stimulation did not modulate performance in comparison to sham stimulation. Recognition of true repetitions was not significantly influenced by stimulation, although response times to repeated pictures tended to be faster under cathodal stimulation. Cathodal tDCS over the frontal pole thus mimicked the error pattern – an increase of false-positive responses – of reality-confusing patients having lesions of the OFC or directly connected structures (Schnider et al., 1996; Schnider and Ptak, 1999; Nahum et al., 2012).

The study complements a rich literature on tDCS' influence on memory functions. Recent studies showed that working memory could be improved by anodal (Fregni et al., 2005; Andrews et al., 2011) or impaired by cathodal stimulation of the DLPFC (Elmer et al., 2009). Boggio et al. (2009) demonstrated that recognition memory was subject to modulation as well: anodal tDCS of the anterior temporal cortex throughout the encoding and retrieval phases effectively decreased the rate of false positives in a recognition memory task, while keeping the rate of veridical memories unchanged. The present study demonstrates that tDCS also modulates orbitofrontal reality filtering.

In healthy subjects, controlling whether a thought refers to reality or not, takes place between 200 and 300 ms and consists in a transient interference with the activation of memory traces (Schnider, 2003, 2013). In the case of a currently irrelevant memory, a phasic signal characterized by a positive frontal potential originating from the OFC is emitted (Schnider et al., 2002; Wahlen et al., 2011). This phasic signal indicates that an upcoming memory (thought) does not pertain to the present reality. We hypothesize that with cathodal stimulation, this phasic "reality check" signal is attenuated so that more memories of previous stimulus occurrences induce the feeling of pertaining to the current task segment, that is, "current reality", as operationally defined in our task.

Given the phasic character of reality filtering, we did not expect a facilitating effect of tDCS, which exerts a prolonged effect, on reality filtering. In any case, the result, albeit expected, is a disappointment from a clinical perspective. Reality confusion based on deficient reality filtering is a pervasive disorder and an immense challenge to a rehabilitation team; patients may enact false ideas at any time and put themselves into danger (Schnider et al., 1996; Schnider, 2008; Nahum et al., 2010). While dopamine-antagonists (neuroleptics) may help occasional patients to remain in contact with reality (Pihan et al., 2004), no reliably effective treatment is known. The present study confirms that tDCS, too, is very unlikely to be helpful in such situations.

A critical question for our study is whether the chosen electrode setup for tDCS actually reached and modulated activity in the OFC. The question is all the more pertinent as the effects of tDCS on higher cognitive function are still poorly understood and have indeed rarely been studied (Bikson et al., 2013). The head model calculated for our electrode montage strongly supports the contention: tDCS over the frontal pole is apparently capable of modulating activity in the OFC. We predicted outward current flow using this specific montage which is a reasonable substrate to assume inhibitory effects (Bikson et al., 2013). In addition to the calculated model, the fact that cathodal stimulation over the frontal pole induced an error pattern similar to orbitofrontal lesions strongly supports the idea that the setup chosen for this study indeed inhibited the posterior OFC. The result of the present study is, therefore, entirely compatible with previous lesion and imaging studies (Schnider, 2008, 2013), which revealed the key role of the OFC in reality filtering.

Our model also predicts intense current flow in DLPFC. It is, therefore, possible that tDCS may also have influenced frontal executive functions that we did

not test in this study. On the basis of the present data alone, one cannot completely exclude that failure of such functions contributed to the deficit in orbitofrontal reality filtering observed in the present study. However, in clinical studies, deficient reality filtering was regularly independent of executive dysfunction (working memory, inhibitory control, susceptibility to interference, mental fluency, etc.) (Schnider et al., 1996, 2000a; Schnider and Ptak, 1999; Nahum et al., 2009, 2012). Also, there is no case on the record with reality confusion due to impaired reality filtering with exclusive, even extended, lesion of the DLPFC (Schnider, 2008).

CONCLUSION

Although additional work is needed to fully understand the effect of tDCS on higher cognitive functions, this study shows that the process of reality filtering, an orbitofrontal function, can be influenced in a polarity-specific way through tDCS applied over the frontal pole.

Acknowledgments—We thank Dr. Adrian Guggisberg for helpful comments on the manuscript. This work was supported by the Swiss National Science Foundation, Grant No. 320030-132447 to A.S., The Wallace H Coulter Foundation, The United States Department of Defence, and The National Institutes of Health.

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(Accepted 27 January 2014)
(Available online 4 February 2014)