Clinical Neurophysiology 120 (2009) 80–84

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Bilateral frontal transcranial direct current stimulation: Failure to replicate classic findings in healthy subjects

Michael Koenigs [a,b], Dede Ukueberuwa [a], Paul Campion [a], Jordan Grafman [c], Eric Wassermann [a,*]

[a] Brain Stimulation Unit, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 10 Center Drive, MSC 1440, Bethesda, MD 20892-1440, USA
[b] Department of Psychiatry, University of Wisconsin – Madison, 6001 Research Park Boulevard, Madison, WI 53719, USA
[c] Cognitive Neuroscience Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 10 Center Drive, MSC 1440, Bethesda, MD 20892-1440, USA

ARTICLE INFO

Article history:
Accepted 6 October 2008
Available online 21 November 2008

Keywords:
Emotion
Cognition
Frontal lobe
Direct current
Behavior
Electrical
Non-invasive
Brain stimulation

ABSTRACT

Objective: There has been no modern effort to replicate, further characterize, or quantify the dramatic effects on affect described in controlled studies from the 1960s using bilateral frontal electrodes with an extra-cephalic reference in a mixed group composed primarily of mildly depressed individuals. We performed a comprehensive, quantitative assessment of the effects of bifrontal TDCS on emotion in 21 healthy subjects.
Methods: In a double-blind crossover study, we administered tests of emotional state, affect, emotional decision-making, arousal, and psychomotor functions during sham, anodal, and cathodal TDCS.
Results: We found no systematic effects on any measure, despite two subjects who had pronounced mood effects in the predicted direction. There were no adverse events.
Conclusions: In line with some other studies, we found no consistent effects of bifrontal TDCS on measures of emotional function of psychomotor performance.
Significance: These results demonstrate the safety of bilateral anterior frontal TDCS with an extra-cephalic reference, but raise questions about its effectiveness as a modulator of mood and emotional cognition, at least in healthy subjects.

1. Introduction

Nearly a half century ago, clinicians began exploring the application of weak electric currents to the scalp as way to modulate brain activity and, thereby, human behavior. In a pioneering study Lippold and Redfearn (1964) examined the effects of anodal (scalp positive) and cathodal (scalp negative) DC currents delivered from paired electrodes placed on the foreheads of 32 individuals drawn from the patients of an occupational therapy clinic. Subjects were fitted with battery-powered, current-controlled devices for a day and periodically assessed by clinicians, blind to the current direction, in free-form interviews. They reported that cathodal currents generally produced quietness, apathy, and withdrawal, whereas scalp-positive (anodal) currents generally elicited talkativeness, giddiness, and affects indicative of elevated mood. Further clinical studies in depressed patients (Costain et al., 1964; Ramsay and Schlagenhauf, 1966; Herjanic and Moss-Herjanic, 1967; Carney et al., 1970) have generally confirmed the beneficial effect of anodal current delivered to frontal head regions.

These and other behavioral effects are presumed to result from current-induced, polarity-specific changes in the firing rates (Purpura and McMurtry, 1964) and excitability (Nitsche and Paulus, 2000) of cortical neurons. In recent years, transcranial direct current stimulation (TDCS, as the technique is now known) has been shown to be capable of safely and reversibly altering sensory, motor, and cognitive function (Been et al., 2007), supporting the possibility that TDCS could be employed as a therapeutic intervention for neurological or psychiatric disorders (Iyer et al., 2005; Fregni and Pascual-Leone, 2007). However, recent studies demonstrating behavioral effects of frontal TDCS exclusively targeted the dorsolateral area unilaterally (Kincses et al., 2004; Fregni et al., 2005, 2006, 2007; Iyer et al., 2005; Boggio et al., 2007, 2008a,b; Fecteau et al., 2007a,b; Fregni and Pascual-Leone, 2007), leaving the effects of anterior and medial frontal stimulation unexplored in the modern era. But, given the importance of anterior medial frontal areas in affective function and the findings of Lippold and Redfearn, one might expect a bilateral anterior electrode placement to effect substantial changes in mood and decision-making.

Studies have demonstrated the importance of the lower medial prefrontal cortex in mood and arousal. Bilateral lesions involving this area result in the blunting of certain emotions (Barrash et al., 2000) and changes in emotion-related decision-making (Bechara et al., 1997) while stimulation of this area with surgically implanted electrodes can alleviate severe depression (Mayberg et al., 2005). The application of direct current to lower medial

* Corresponding author. Tel.: +1 301 496 0151; fax: +1 301 480 2909.
E-mail address: wassermanne@ninds.nih.gov (E. Wassermann).

1388-2457/$34.00 Published by Elsevier Ireland Ltd. on behalf of International Federation of Clinical Neurophysiology.
doi:10.1016/j.clinph.2008.10.010

prefrontal cortex could therefore be clinically useful to modulate mood, arousal, and decision-making. In this study, we sought to determine whether TDCS applied bilaterally over anterior PFC would affect mood, arousal, and cognition in healthy subjects. We used a more comprehensive and quantitative assessment than did Lippold and Redfearn, including standardized measures of mood and arousal as well as two measures, skin conductance response to emotionally laden pictures and evaluation of moral dilemmas, that are sensitive to lesions of frontal areas involved in affective decision-making (Koenigs et al., 2007).

2. Methods

2.1. Participants

Twenty-five volunteers enrolled in the study. Participants had no history of neurological or psychiatric illness and had normal neurological examinations within one year of participating. None had previously participated in a TDCS study. Participants gave informed written consent before entering the study, which was approved by the Neuroscience Institutional Review Board at the Clinical Research Center, National Institutes of Health. Subjects whose baseline CalCAP performance (see below) was outside 2 standard deviations of the age-adjusted population mean were excluded from further participation.

2.2. TDCS

Participants underwent three sessions of TDCS (one anodal, one cathodal, and one sham). Direct current was delivered with the Phoresor II Auto Model PM850 through three 25 cm^2 sponge electrodes, moistened with tap water. The two active electrodes were placed on the forehead immediately above the orbits, centered at positions F_{p1} and F_{p2} of the 10/20 International System. The reference electrode was placed on the non-dominant arm. In their study, Lippold and Redfearn used two active electrodes approximately 1 in. in diameter (area ≈ 5 cm^2 each), placed immediately above each eyebrow, and passed maximum currents of 500 μA. This would result in a current density of approximately 50 μA/cm^2. The reference electrode was placed above the right knee. In our active stimulation conditions (both forehead electrodes anodal or cathodal) a current of 2.5 mA was delivered for 35 min, including a 5-min period of stimulation prior to testing. This combination of current and electrodes also yielded a current density of 50 μA/cm^2. For sham stimulation, the electrodes were placed at the same positions as for active stimulation (F_{p1}, F_{p2}, and arm), but the stimulator was turned on for only 30 s. Thus, participants felt the initial itching/tingling sensation associated with TDCS. This method was shown to be sufficient to keep participants blind to the stimulation condition (Gandiga et al., 2006).

2.3. Dependent measures

The outcomes of interest were changes in mood and arousal. We screened for these with three self-report measures and an objective measure of autonomic response to arousing and neutral picture stimuli. In addition, an experimenter, blind to stimulation condition, observed participants for changes in mood or arousal.

2.3.1. Mood self-report

Participants completed the Profile of Mood States (POMS; McNair et al., 1992). The POMS is a standard measure of subjective feeling state, in which participants rate a series of 65 mood descriptors (e.g., "energetic") on a scale of 1 (indicating "not at all") to 5 (indicating "extremely") to indicate how they currently feel. Each participant completed the POMS once immediately before the stimulation and once at the end of stimulation, to allow for the detection of changes in subjective feeling.

2.3.2. Forced-choice arousal

Participants completed a forced-choice description of their arousal level. During each session, the participants chose "increase," "decrease," or "no change" to indicate what they felt was the overall effect of each stimulation condition.

2.3.3. Autonomic arousal

We collected skin conductance responses (SCRs) to emotional pictures. Participants viewed 10 arousing and 10 neutral pictures per session. We selected pictures from the International Affective Picture System (IAPS; Lang et al., 2001). The IAPS is a standardized and well-characterized collection of visual images that are supplied with normative ratings of valence and arousal from 1 to 9. Arousing pictures included images of mutilated human bodies and erotic scenes, while neutral pictures depicted common objects, such as tableware or books. The mean arousal level, determined from the published IAPS ratings, was 7.07 for the arousing pictures and 2.41 for the neutral pictures ($t = 83.0$; $p < .001$). Pictures were displayed on a laptop computer in a darkened room.

Skin conductance was recorded from electrodes placed on the thenar and hypothenar eminences of the non-dominant hand, using the Coulbourn Isolated Skin Conductance Coupler. Evoked SCRs were defined as the maximal SCR deflection originating during the period from 1 to 4 s after picture onset with minimum amplitude of 0.05 mS.

Immediately following the collection of SCR data, the participants viewed the same series of pictures a second time, and rated their subjective experience of each picture (i.e., "How emotionally arousing did you find the picture?") on a scale of 1 (indicating "not at all") to 7 (indicating "extremely").

2.3.4. Moral judgment

We screened for effects of bifrontal TDCS on a moral judgment test that is sensitive to ventrolateral prefrontal cortex (vmPFC) damage (Koenigs et al., 2007). In this test, participants made judgments on a series of "high conflict" moral dilemmas. Each scenario featured the choice to sacrifice one or more people to preserve the well-being of a greater number of others. For example:

> *Enemy soldiers have taken over your village. They have orders to kill all remaining civilians. You and some of your townspeople have sought refuge in the cellar of a large house. Outside you hear the voices of soldiers who have come to search the house for valuables. Your baby begins to cry loudly. You cover his mouth to block the sound. If you remove your hand from his mouth his crying will summon the attention of the soldiers who will kill you, your child, and the others hiding out in the cellar. To save yourself and the others you must smother your child to death.*
> *Would you smother your child in order to save yourself and the other townspeople?*

Participants responded by pushing a numbered button (1–7) to indicate the degree to which they endorsed the proposed action (with "1" indicating the participant definitely would not perform the proposed action and "7" indicating that the participant definitely would perform the proposed action). Endorsement of the proposed action is presumed to reflect more coldly rational, or "utilitarian", reasoning. We constructed three sets of scenarios (seven scenarios per set). Participants responded to a different set of seven scenarios in each stimulation condition. We conducted a pilot study with 11 participants to ensure that the each of the three sets of scenarios were matched for mean response rating ($F = .001$; $p > .99$). Each of the three scenario sets was counterbalanced with each of the three stimulation conditions across subjects.

2.3.5. Psychomotor speed and accuracy

As a check for safety and generalized effects on alertness, we tested basic psychomotor function with the California Computerized Assessment Package (CalCAP; Miller, 1990). Participants completed two subtests of the CalCAP: "Choice Reaction Time-Digits" and "Sequential Reaction Time 1". In the Choice Reaction Time (CRT) test, participants viewed a series of single digit numbers, presented one at a time on a computer monitor. Participants were instructed to push the spacebar whenever they saw the digit "7" appear in the series. In the Sequential Reaction Time (SRT) test, participants again viewed a series of single digit numbers, presented one at a time on a computer monitor. Participants were instructed to push the spacebar whenever they saw two of the same numbers in sequence (e.g., a "3" followed by another "3"). Participants completed these tests once before beginning the TDCS (pre-TDCS) and once at the end of testing (post-TDCS). The difference in reaction time (RT) between pre-TDCS and post-TDCS for each subtest was calculated for each subject in each stimulation condition. In addition to monitoring performance of individual participants before and after each treatment, we performed group analyses of the data.

2.4. Blinding procedure

Each stimulation session involved two experimenters. One operated the stimulator and the other conducted the testing. The stimulator operator was aware of the stimulation condition, but had no other involvement in the study procedures. The other experimenter, who conducted all testing with the participant, was not present for the onset of stimulation and remained blind to the stimulation condition.

3. Results

3.1. Participants

Of the 25 individuals initially enrolled in the study, one was excluded because her initial CalCAP score was >2 standard deviations below the published population mean. Two subjects could not schedule all of the testing sessions and one withdrew after one session. The remaining 21 participants (12 men and 9 women; mean age 25.6, SD 5.8) were entered in the analysis of the group data.

3.2. Observational

The blinded experimenter did not perceive any striking or systematic changes in mood, arousal, or verbal output during any of the stimulation conditions. The only notable effect of the stimulation was that at the onset of stimulation, subjects routinely reported feeling a tingling or itching sensation under the electrodes.

3.3. Self-report: POMS

The 65 mood items were grouped into six factors (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment) in accordance with the POMS manual (McNair et al., 1992). To test the effect of stimulation condition on the self-reported change score (post-stimulation minus pre-stimulation) for the six factors of mood items (Table 1), we conducted a repeated-measures ANOVA. There was no significant interaction between stimulation condition and mood factor ($F = .33$; $p = .97$).

3.4. Self-report: forced choice arousal

During each session, the participant performed a forced-choice description of change in arousal since stimulation onset (Table 1). For each stimulation condition, "no change" was selected by a majority of participants. The proportion of participants selecting "increase," "decrease," and "no change" in arousal was nearly identical for each condition (Yates' $\chi^2 = .12$; $p > .99$). Thus, neither anodal nor cathodal stimulation had any different effect on self-reported arousal than did sham stimulation.

3.5. SCRs and subjective responses to IAPS pictures

We conducted a repeated-measures ANOVA to determine whether stimulation condition (anodal, cathodal, or sham) had any effect on SCRs to neutral or arousing pictures (Table 1). There was no significant main effect of stimulation condition ($F = 1.61$; $p = .21$) on SCRs, nor was there a significant interaction between stimulation condition and picture type ($F = .56$; $p = .57$). We also determined the effect of stimulation condition on the subjective ratings of emotional arousal for each picture type (Table 1). Again there was no main effect of stimulation condition ($F = .26$; $p = .77$) and no significant interaction ($F = .57$; $p = .57$).

3.6. Moral judgment

There was no significant effect of stimulation condition on the responses (level of endorsement of the proposed action) in the moral judgment test ($F = .61$; $p = .55$; Table 1).

Table 1
Test data.

Test	Stimulation condition		
	Anodal	Cathodal	Sham
POMS			
Tension-anxiety	−0.14 (0.09)	−0.17 (0.12)	−0.22 (0.17)
Depression-dejection	−0.01 (0.08)	−0.07 (0.09)	−0.08 (0.09)
Anger-hostility	−0.05 (0.07)	−0.02 (0.06)	−0.04 (0.09)
Vigor-activity	−0.27 (0.19)	−0.22 (0.21)	−0.31 (0.20)
Fatigue-inertia	−0.06 (0.17)	−0.06 (0.18)	−0.07 (0.17)
Confusion-bewilderment	0.05 (0.19)	0.02 (0.11)	−0.07 (0.10)
Forced choice arousal			
Increased	5	4	4
Decreased	2	2	1
No change	14	15	16
SCRs (IAPS)			
Neutral pictures	0.015 (0.032)	0.021 (0.045)	0.037 (0.014)
Arousing pictures	0.026 (0.035)	0.049 (0.089)	0.042 (0.056)
Subjective ratings (IAPS)			
Neutral pictures	1.60 (0.39)	1.84 (0.75)	1.77 (0.75)
Arousing pictures	4.80 (1.19)	4.74 (1.06)	4.80 (1.09)
Moral judgment			
Endorsement	3.77 (1.28)	3.95 (1.46)	4.07 (1.25)
CalCAP			
CRT	8.9 (20.7)	5.9 (64.4)	23.7 (29.2)
SRT	13.4 (54.6)	9.5 (50.9)	11.6 (58.5)

For "POMS", the mean change in self-reported mood score (post-stimulation minus pre-stimulation) is reported for each of the six factors of mood items (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, confusion-bewilderment). For "Forced Choice Arousal", the numbers of participants reporting "increased," "decreased," or "no change" in arousal for each stimulation condition are reported. For "SCRs (IAPS)", mean SCRs to each picture type (neutral and arousing) are reported, with standard errors in parentheses. For "Subjective Ratings (IAPS)", mean subjective arousal ratings to each picture type are reported, with standard errors in parentheses. For "Moral Judgment", mean levels of endorsement of the proposed action are reported, with standard errors in parentheses. For "CalCAP", mean RT differences (post-stimulation minus pre-stimulation) for each subtest (CRT and SRT) are reported in ms, with standard errors in parentheses. There was no significant effect of stimulation condition on any of the measures.

3.7. CalCAP

We determined the effect of stimulation condition on psychomotor speed, as measured with the two CalCAP subtests (Table 1). The dependent variable of interest was the difference in RT between the pre-TDCS administration and the post-TDCS administration. In the group analysis, there was no significant main effect of stimulation condition ($F = .57$; $p = .57$), nor was there a significant interaction between stimulation condition and CalCAP subtest ($F = .32$; $p = .73$). Furthermore, no subject showed $a > 1$ SD change in performance for both tests in any single TDCS session.

3.8. Spontaneous subjective reports

The one subject who withdrew reported several hours of dysphoria after leaving the clinical center following his first session, which was cathodal TDCS. Notably, his POMS scores increased by. 27 for depression-dejection, by. 43 for fatigue-inertia, and decreased by. 20 for vigor-activity. Since he received only cathodal TDCS, it is not certain whether the effect was specifically related to TDCS. Another participant did report polarity-specific changes in mood following TDCS. Upon arriving for his second session, the individual remarked that for an hour or two after the first session (the previous day), he felt "high" and found himself spontaneously smiling, which was unusual for him. The individual described himself as normally anxious, but he reported feeling unusually "care-free" and "worry-free" following his first session of TDCS. His POMS scores decreased by. 93 for vigor-activity, by. 27 for depression-dejection, and by. 25 for anger-hostility. Following his second and third sessions, the individual stated spontaneously that neither session had the same anxiolytic effect that the first session had. On breaking the blind, we found that he had received anodal TDCS in the first session, followed by cathodal and sham.

4. Discussion

In this study, we detected no systematic subjective or objective effects of bifrontal TDCS on mood or several measures of arousal and emotional cognition in healthy adults. This finding stands in contrast to Lippold and Redfearn's pioneering study (1964), where clinically observable changes in affect occurred during bilateral frontal TDCS. Indeed the absence of any consistent findings in our 21 subjects is noteworthy given the fact that Lippold and Redfearn reported acute and striking behavioral changes in a majority of their 32 subjects.

Two of our subjects reported pronounced subjective changes, but overall our results are consistent with a previous attempt to replicate the Lippold and Redfearn findings in six subjects (Sheffield and Mowbray, 1968), which also reported no significant effects of anodal or cathodal bifrontal TDCS on mood, alertness, or psychophysiological indices.

There are several methodological differences that may contribute to the discrepant results. Probably, the most important is the duration of stimulation. In our study, participants underwent 35 min of stimulation per session, but Lippold and Redfearn applied variable durations of current, in many cases 1–5 h per session. Although recent studies of TDCS demonstrated measurable physiological effects within a few minutes of current onset (Nitsche and Paulus, 2000), it is possible that mood and arousal effects from anterior bifrontal TDCS may only emerge after many minutes or even hours of stimulation.

Another potentially important difference between the studies is the participant group characteristics. Whereas Lippold and Redfearn (1964) studied a group comprised mainly of individuals who had experienced "mild depression" and/or more severe psychiatric symptoms, we and Sheffield and Mowbray studied only screened, healthy adults. While some studies of unilateral repetitive transcranial magnetic stimulation of the frontal cortex in healthy subjects (George et al., 1996; Pascual-Leone et al., 1996) produced hemisphere-specific mood changes, a study of anodal TDCS, delivered to the left and right dorsolateral prefrontal cortex (Fregni et al., 2008) found effects on tobacco craving, but none on mood. TDCS like antidepressant medications may have greater effects on the mood of depressed or emotionally labile individuals than on typical healthy subjects. Interestingly, the participant in our sample who reported a dramatic polarity-specific mood change had experienced significant anxiety in the past, although he had never received a formal diagnosis or treatment. It should be noted, however, that Lippold and Redfearn formed their hypothesis based on their experience with a number of healthy subjects.

A third difference between our study and the Lippold and Redfearn study is the size of the electrodes. We used an electrode area of 50 cm^2, whereas Lippold and Redfearn used two 1-in. diameter electrodes (total area $\approx 10\ cm^2$). However, we passed a current of 2.5 mA, while the earlier study used currents up to 0.5 mA, so in both studies, the current density was approximately 50 $\mu A/cm^2$. It is possible, if not likely, that the difference in electrode size, alone, was responsible for the difference in outcome.

This is one of relatively few contemporary studies (Ferrucci et al., 2008) to place the reference electrode off the head. While this placement makes sense as a way of removing the confounding influence of an active reference on the head, concerns have been raised regarding the safety of passing currents through the base of the brain, especially since Lippold and Redfearn reported one subject who developed nausea, muteness, respiratory difficulty, and impaired fine motor control after accidentally receiving anodal current at 3 mA (Dr. Lynn Bindman, personal communication to EMW). It is reassuring that we encountered no untoward brain effects other than the case of dysphoria described above. In particular, there were no acute changes in psychomotor speed, a sensitive indicator of cognitive impairment.

While we were unsuccessful in our goal of modulating emotional processing in the human frontal lobe with DC polarization and more fully characterizing the mood and arousal effects reported in earlier work, this study indicates that moderate doses and durations of DC current delivered to both frontal lobes with the reference electrode off the head are well tolerated. We also observed interesting mood effects in two subjects, suggesting that continued refinement of the technique may yield more reliable effects in the future.

Acknowledgments

This work was supported by the Intramural Research Program, NINDS, NIH. The authors wish to thank Ms. Devee Schoenberg for editing the manuscript.

References

Barrash J, Tranel D, Anderson SW. Acquired personality disturbances associated with bilateral damage to the ventromedial prefrontal region. Dev Neuropsychol 2000;18(3):355–81.

Bechara A, Damasio H, Tranel D, Damasio AR. Deciding advantageously before knowing the advantageous strategy. Science 1997;275(5304):1293–5.

Been G, Ngo TT, Miller SM, Fitzgerald PB. The use of tDCS and CVS as methods of non-invasive brain stimulation. Brain Res Rev 2007;56(2):346–61.

Boggio PS, Nunes A, Rigonatti SP, Nitsche MA, Pascual-Leone A, Fregni F. Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. Restor Neurol Neurosci 2007;25(2):123–9.

Boggio PS, Rigonatti SP, Ribeiro RB, Myczkowski ML, Nitsche MA, Pascual-Leone A, et al. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int J Neuropsychopharmacol 2008a;11(2):249–54.

Boggio PS, Sultani N, Fecteau S, Merabet L, Mecca T, Pascual-Leone A, et al. Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: a double-blind, sham-controlled study. Drug Alcohol Depend 2008b;92(1–3):55–60.

Carney MW, Cashman MD, Sheffield BF. Polarization in depression. Br J Psychiatry 1970;117(539):474–5.

Costain R, Redfearn JW, Lippold OC. A controlled trial of the therapeutic effect of polarization of the brain in depressive illness. Br J Psychiatry 1964;110:786–99.

Fecteau S, Knoch D, Fregni F, Sultani N, Boggio P, Pascual-Leone A. Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. J Neurosci 2007a;27(46):12500–5.

Fecteau S, Pascual-Leone A, Zald DH, Liguori P, Theoret H, Boggio PS, et al. Activation of prefrontal cortex by transcranial direct current stimulation reduces appetite for risk during ambiguous decision making. J Neurosci 2007b;27(23):6212–8.

Ferrucci R, Mameli F, Guidi I, Mrakic-Sposta S, Vergari M, Marceglia S, et al. Transcranial direct current stimulation improves recognition memory in Alzheimer disease. Neurology 2008;71:493–8.

Fregni F, Pascual-Leone A. Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. Nat Clin Pract Neurol 2007;3(7):383–93.

Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 2005;166(1):23–30.

Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A. Treatment of major depression with transcranial direct current stimulation. Bipolar Disord 2006;8(2):203–4.

Fregni F, Orsati F, Pedrosa W, Fecteau S, Tome FA, Nitsche MA, et al. Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. Appetite 2007.

Fregni F, Liguori P, Fecteau S, Nitsche MA, Pascual-Leone A, Boggio PS. Cortical stimulation of the prefrontal cortex with transcranial direct current stimulation reduces cue-provoked smoking craving: a randomized, sham-controlled study. J Clin Psychiatry 2008;69(1):32–40.

Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol 2006;117(4):845–50.

George MS, Wassermann EM, Williams WA, Steppel J, Pascual-Leone A, Basser P, et al. Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation (rTMS) of the prefrontal cortex. J Neuropsychiatry Clin Neurosci 1996;8:172–80.

Herjanic M, Moss-Herjanic B. Clinical report on a new therapeutic technique: polarization. Can Psychiatr Assoc J 1967;12(4):423–4.

Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology 2005;64(5):872–5.

Kincses TZ, Antal A, Nitsche MA, Bartfai O, Paulus W. Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. Neuropsychologia 2004;42(1):113–7.

Koenigs M, Young L, Adolphs R, Tranel D, Cushman F, Hauser M, et al. Damage to the prefrontal cortex increases utilitarian moral judgements. Nature 2007;446(7138):908–11.

Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): Instruction manual and affective ratings, The Center for Research in Psychophysiology, University of Florida; 2001.

Lippold OC, Redfearn JW. Mental changes resulting from the passage of small direct currents through the human brain. Br J Psychiatry 1964;110:768–72.

Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. Neuron 2005;45(5):651–60.

McNair DM, Lorr M, Droppleman LF. Edits manual for the Profile of Mood States (revised edition). San Diego (CA): Educational and Industrial Testing Service; 1992.

Miller EN. California Computerized Assessment Battery (CalCAP) Manual. Neurology. Los Angeles: Software; 1990.

Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527(Pt 3):633–9.

Pascual-Leone A, Catalá MD, Pascual-Leone A. Lateralized effect of rapid-rate transcranial magnetic stimulation of the prefrontal cortex on mood. Neurology 1996;46:499–502.

Purpura DP, McMurtry JG. Intacellular activities and evoked potential changes during polarization of motor cortex. J Neurophysiol 1964;18(1):166–85.

Ramsay JC, Schlagenhauf G. Treatment of depression with low voltage direct current. South Med J 1966;59(8):932–4.

Sheffield LJ, Mowbray RM. The effects of polarization on normal subjects. Br J Psychiatry 1968;114(507):225–32.