YALE JOURNAL OF BIOLOGY AND MEDICINE 88 (2015), pp.219-225.

ORIGINAL CONTRIBUTION

YJBM

A Feasibility Study of Bilateral Anodal Stimulation of the Prefrontal Cortex Using High-Definition Electrodes in Healthy Participants

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Transcranial direct current stimulation (tDCS†) studies often use one anode to increase cortical excitability in one hemisphere. However, mental processes may involve cortical regions in both hemispheres. This study's aim was to assess the safety and possible effects on affect and working memory of tDCS using two anodes for bifrontal stimulation. A group of healthy subjects participated in two bifrontal tDCS sessions on two different days, one for real and the other for sham stimulation. They performed a working memory task and reported their affect immediately before and after each tDCS session. Relative to sham, real bifrontal stimulation did not induce significant adverse effects, reduced decrement in vigor-activity during the study session, and did not improve working memory. These preliminary findings suggest that bifrontal anodal stimulation is feasible and safe and may reduce task-related fatigue in healthy participants. Its effects on neuropsychiatric patients deserve further study.

INTRODUCTION

Transcranial direct current stimulation (tDCS) is a non-invasive technique for brain stimulation. It modulates cortical excitability by passing a small direct current (1 ~ 2 mA) to the scalp [1,2]. Recent studies have reported that tDCS may improve mood and reduce craving for substance use in patients with addictive disorders [3-7]. Additionally, tDCS may enhance cognitive functions such as attention and working memory in healthy participants or patients with strokes, depression, or Parkinson's disease [8-12]. Therefore, tDCS is a promising strategy for enhancing brain functions in patients with neuropsychiatric conditions, including addictive disorders.

Conventional tDCS studies use two large (e.g., 35 cm^2) sponge pads as two electrodes (i.e., anode and cathode) to deliver direct current [1,2,13,14], with one "active" electrode over the cortical target and a "return" electrode on another scalp location or other body part (e.g., upper arm). Anode- or cathode-active electrodes are typically presumed to produce opposite effects on cortical excitability. At ~1 mA intensity and for a 5- to 20-minute duration, anodal stimulation increases, whereas cathodal stimulation decreases, cortical excitability as measured by transcranial magnetic stimulation

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†Abbreviations: EEG, electroencephalography; fMRI, functional magnetic resonance imaging; GLM, general linear model; HD, high-definition; POMS, Profile of Mood States; RT, reaction time; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; SD, standard deviation.

Keywords: tDCS, non-invasive brain stimulation, cognitive function, working memory, affect

Author contributions: Xu contributed to all aspects of the study, including study design, data collection and analysis, and manuscript preparation. Healy contributed to data collection. Truong, Datta, Bikson, and Potenza contributed to manuscript preparation.

Conflict of interest: Drs. Xu and Truong and Mr. Healy report no conflicts of interest. Drs. Bikson and Datta have equity in Soterix Medical Inc., a company developing tDCS-related equipment. Dr. Potenza has consulted for and advised Somaxon, Boehringer Ingelheim, Lundbeck, Ironwood, Shire, INSYS and RiverMend Health and has received research support from Mohegan Sun Casino, Ortho-McNeil, Oy-Control/Biotie, Glaxo-SmithKline, Pfizer, and Psyadon pharmaceuticals.

(TMS) motor-evoked potentials [15-17]. Assuming these neurophysiological findings generalize to other brain regions and stimulation intensities, most tDCS studies to date seek to modulate brain function by increasing the excitability of cortical regions adjacent to the anode in one hemisphere.

While this approach holds significant potential, it may not be optimal for all neuropsychiatric conditions because behaviors relevant to these conditions may involve altered functional activities in both hemispheres. For example, nicotine-dependent smokers often experience tobacco withdrawal that includes craving for smoking, negative affect, and impaired cognitive control after abstinence from smoking [18,19]. Neuroimaging studies demonstrate that cognitive control, including craving inhibition, implicates the prefrontal cortex in both hemispheres [20-23]. Furthermore, a recent tDCS study showed that anodal stimulation of either the left or the right dorsolateral prefrontal cortex reduces cue-induced craving for smoking in nicotine-dependent smokers [4]. Thus, the testing of a bifrontal anodal stimulation system is warranted. In other words, it is possible that the efficacy of tDCS for modulating brain functions may be improved by using multiple anodes (relative to using one anode) to increase the excitability of multiple cortical regions in both hemispheres simultaneously. Based on this rationale, we designed a new electrode set for performing tDCS that uses one 35 cm^2 sponge pad as a cathode and two high-definition (HD) electrodes [24] as two separate anodes. By placing the two anodes at scalp locations above the left and right dorsal lateral prefrontal cortex (i.e., AF3 and AF4, respectively, of 10/20 EEG system [25,26]) and the cathode at the occipital scalp between Oz and POz, this electrode set should provide extensive anodal stimulation to the prefrontal cortex in both hemispheres during tDCS [27]. We expect that tDCS using this innovative electrode design may increase the excitability and functional activities of the prefrontal cortex in both hemispheres simultaneously.

The specific aim of this study was to assess whether tDCS, using this novel electrode design, is safe and may enhance prefrontal cortical function in healthy participants. Stimulation was applied in two sessions: one for real and the other for sham stimulation, with assessments for adverse effects, mood, and working memory obtained from participants immediately before and after each stimulation session. We assessed the tolerability and safety of the new electrode design by comparing the reported adverse effects of real and sham stimulation. We predicted that this bifrontal tDCS would be well tolerated and real stimulation would improve mood and working memory relative to sham stimulation.

MATERIALS AND METHODS

Participants

Potential participants were recruited from communities around Yale University through flyers and ads placed on Craigslist. All participants provided written informed consent approved by the Human Investigation Committee at the Yale School of Medicine. The inclusion criteria included good general physical health and ages between 18 and 60 years, inclusive. Thirty-eight participants were recruited. Among them, 31 (15 females) completed two tDCS sessions as scheduled. Their mean age was 27.2 years (standard deviation (SD) = 8.4; range: 18 to 49).

Procedure

Subsequent to baseline assessments, subjects participated in two stimulation sessions, one for real tDCS and the other for sham with a minimal interval between the two of 48 hours. The sequence of the two tDCS sessions was counterbalanced among participants. After arriving at the lab, participants completed the Profile of Mood States (POMS) [28], performed a computerized n-back task, received tDCS (either real or sham) during a resting condition, completed the tDCS Adverse Effects Questionnaire, performed the n-back task, and completed the POMS again.

tDCS

We used a 1 x 1 Low-Intensity DC Stimulator, Model 1224-B (Soterix Medical, New York, USA) to deliver stimulation. The new electrode design employed one 35 cm^2 sponge pad as a cathode and two high-definition (HD) electrodes [24] as anodes. The size of each HD electrode was 2 x 2 cm^2. For bilateral anodal stimulation, a 2 x 1 passive adaptor converted the anode line to two HD outputs. During set-up, the stimulator ensures equal current carried by the two anodes by checking the quality of scalp contact of each anode. Using multiple small HD electrodes facilitated the targeting of specific brain structures [14,27] and produced equal or less skin irritation relative to conventional sponge pads [29].

As described in a recent publication [27], high-resolution computer-based MRI-derived Finite Element modeling [27,30,31] was used to model the electric field generated by different electrode arrangements. With the arrangement of two HD electrodes placed at AF3 and AF4 of a 10/20 EEG system [25,26] and the cathode placed between Oz and POz, the modeled electric field covered the ventral and dorsal frontal and parietal cortices and the occipital cortex beneath the sponge cathode in both hemispheres [27] (Figure 1). Therefore, this electrode arrangement provided extensive anodal stimulation to the frontal and parietal cortices in both hemispheres during tDCS [27]. In the present study, this electrode placement was employed for real and sham tDCS. Real stimulation used a current of 2.0 mA for 20 min, with a current ramping up for the first 30 s to reduce skin sensations. Sham stimulation also lasted for 20 min with a current ramping up to 2.0 mA and back to 0 during the first 30 s, and then the stimulator would automatically turn off. A similar procedure has been used regularly to keep participants blind to the real and sham stimulation [4,32,33]. Therefore, this was a single-blind study.

Measures

The POMS consists of 65 five-point mood-related items [28]. They were used to calculate scores for six sub-

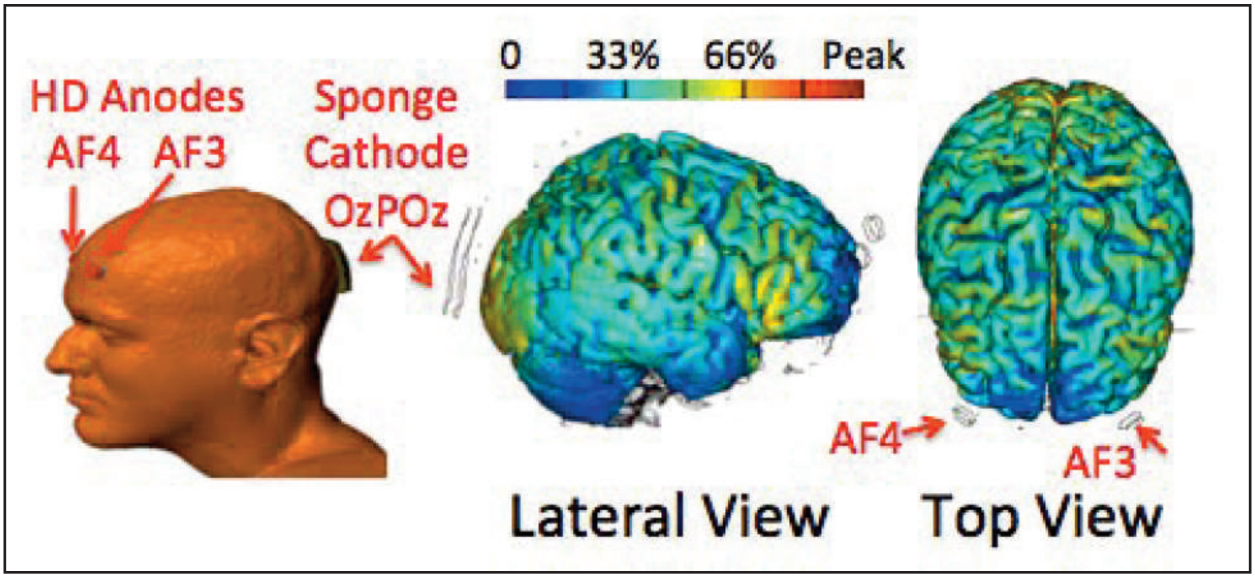

Figure 1. Electrode placements and modeled electric fields. The diagram of the head shows electrode locations (anodes: AF3 and AF4; cathode: between Oz and POz). Colors on the brain show electric fields generated by this electrode set. The color bar indicates the percentage of maximum strength of the electric current in the brain induced by the specified tDCS in an arbitrary unit. Abbreviations: HD: high-definition.

scales relating to tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. For all subscales, except for vigor-activity, a higher score indicated a more negative mood state. This study calculated a score for total mood disturbance by adding the scores of all subscales except the vigor-activity subscale items. A tDCS Adverse Effect Questionnaire was used to assess tDCS adverse effects, including headache, neck pain, scalp pain, scalp irritation, tingling, skin redness, sleepiness, trouble concentrating, and acute mood change [34,35].

The n-back task consisted of 1- and 2-back conditions and used individual digits from 0 to 9 presented on the screen as stimuli. It used a block design with a 5 s instruction screen between blocks. During each task block, each digit was presented for 500 ms and the interstimulus interval (ISI) was 1000 ms. During the 1- and 2-back conditions, targets were repetitions of the digits presented one and two trials before, respectively. A total of 40 digits were presented in each block, and 20 percent of these digits were targets. Participants were instructed to press a button on a Mac laptop keyboard as soon as possible when they detected a target. The 1-back condition imposed little working-memory load, while the 2-back condition required both effortful attention and considerable working-memory. Parameters measuring task performance included reaction time (RT) and frequencies of omission errors and commission errors. Omission errors involved missed responses to targets, with the frequency equaling the number of missed responses divided by the total number of targets in the task. Commission errors involved incorrect responses to non-target trials, with the frequency equaling the number of incorrect responses divided by the number of total non-target trials in the task.

Data Analysis

Frequencies of tDCS-related adverse effects between the real and sham sessions were compared using SPSS Chi-square tests. The scores on POMS and RTs and error rates on the n-back task were analyzed separately using the SPSS general linear model (GLM) for repeated measures. These scores and performance parameters were dependent variables, and test sessions (real versus sham) and blocks (pre- versus post-tDCS) were within-subject variables. Statistical analyses were performed to assess whether dependent variables showed significant differences in change after real versus sham tDCS and/or interaction effects with respect to blocks and sessions. The statistical significance threshold was set at $p < 0.05$.

RESULTS

Participants did not report any clinically significant adverse effects after either real or sham stimulation, and no participant quit the study due to adverse effects. Relative to sham stimulation, real stimulation was more likely to be associated with tingling (Pearson Chi-Square Value = 4.4; df = 1; $p = 0.036$, Cramer's V = 0.28) (Table 1). No other between-condition measures of adverse effects differed at $p < 0.05$.

RTs on the n-back task showed a main effect of block. RTs reduced significantly post- relative to pre-tDCS at both 1-back ($F(1, 30) = 9.4$; $p = 0.005$, Partial Eta Squared = 0.24) and 2-back conditions ($F(1, 30) = 8.7$; $p = 0.006$, Partial Eta Squared = 0.23). RTs did not differ according to session (For 1-back: $F(1, 30) = 1.3$; $p = 0.27$, Partial Eta Squared = 0.04; For 2-back: $F(1, 30) = 0.3$; $p = 0.56$, Partial Eta Squared = 0.01), and no significant interactions between block and session were observed (For 1-back:

Table 1. tDCS adverse effects (%*) in real and sham stimulation sessions.

	Headache	Neck Pain	Scalp Pain	Scalp Irritation	Tingling	Skin Redness	Sleepiness	Trouble Concentrating	Mood Changes
Real	23.3	3.3	16.7	26.7	60.0	10.0	16.7	6.7	33.3
Sham	27.6	6.9	17.2	13.8	34.5	10.3	31.0	3.4	17.2

*percent of total participants in real or sham study session reporting any adverse effect

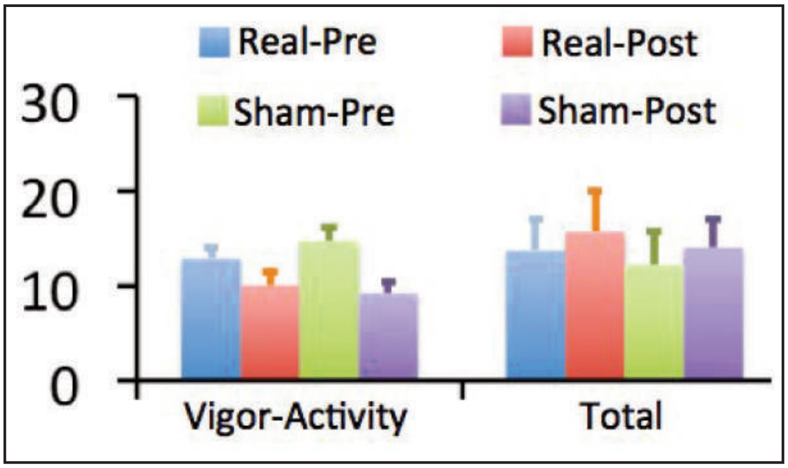

Figure 2. Scores on the Profile of Mood State (POMS). Bar graphs show scores on the vigor-activity subscale and total scale of negative affect of POMS before and after tDCS during real and sham stimulation sessions. Error bars indicate standard errors of the mean. The vigor-activity subscale included items relating to how lively, active, energetic, cheerful, alert, full of pep, carefree, and vigorous individuals feel. The total score included all items except the vigor-activity subscale items.

$F(1, 30) = 0.4$; $p = 0.51$, Partial Eta Squared = 0.02; For 2-back: $F(1, 30) = 1.1$; $p = 0.30$, Partial Eta Squared = 0.04). Both omission and commission error frequencies did not show significant effects at either load condition.

Figure 2 shows POMS scores. Participants showed a significant block effect on scores of vigor-activity subscale; i.e., reduced at the end relative to at the beginning of both tDCS sessions ($F(1, 30) = 38.8$; $p < 0.001$, Partial Eta Squared = 0.56). The scores on this subscale showed a significant session x block two-way interaction effect. Specifically, there was a greater reduction in vigor-activity during the sham relative to real session ($F(1, 30) = 4.7$; $p = .038$, Partial Eta Squared = 0.14). This subscale includes items relating to how lively, active, energetic, cheerful, alert, full of pep, carefree, and vigorous individuals rate themselves. A greater score on this subscale generally indicates that one feels more energetic, less fatigued, and in a better mood. Total mood-disturbance scores showed a significant block effect, with scores increased at the end relative to at the beginning of both tDCS sessions ($F(1, 30) = 21.0$; $p < 0.001$, Partial Eta Squared = 0.41). However, the scores did not show significant main effects of session or interaction effects between block and session ($F(1, 30) = 0.8$; $p = 0.38$, Partial Eta Squared = 0.03).

DISCUSSION

To our best knowledge, this is the first study to assess the feasibility of bilateral anodal stimulation of the prefrontal cortex using HD electrodes. The main findings were that: 1) real stimulation was tolerable and did not generate significant adverse effects; and 2) real stimulation relative to sham stimulation attenuated decreases in score on a vigor-activity subscale in participants during the study session. However, it did not improve performance on the n-back working-memory task.

Bifrontal Stimulation

For enhancing cognitive function including working memory, tDCS studies usually place the anode above the prefrontal cortex in one hemisphere and the cathode at the contralateral supra-orbital area or extracranial body part to avoid the potential negative effect of cathodal stimulation on brain regions [36-39]. More recently, several studies placed the cathode above the prefrontal cortex opposite to the anodal stimulation and named this electrode arrangement as bifrontal stimulation [40-42]. Because cathodal stimulation decreases while anodal stimulation increases cortical excitability [15-17], the bifrontal stimulation used in the current study is different from the bifrontal stimulation employed in these prior studies.

As mentioned in the introduction, there are at least three lines of evidence that indicate that the bilateral anodal stimulation of the prefrontal cortex might be more effective than unilateral stimulation in enhancing cognitive function and/or ameliorating psychiatric symptoms. The first is that many cognitive functions such as working memory and top-down control often involve the prefrontal cortex bilaterally, albeit in some cases to varying degrees. Functional magnetic resonance imaging (fMRI) studies regularly show task-related activity in the prefrontal cortex in both hemispheres while healthy participants perform cognitive tasks [43-45]. The second is that many psychiatric conditions show complex features that may involve brain regions in both hemispheres. For example, fMRI studies show that tobacco craving after overnight smoking abstinence is associated with increased activity in the left lateral prefrontal cortex [22,46], while impaired cognitive control is associated with increased activity in the right lateral prefrontal cortex [23,47]. The third is that anodal stimulation of either the left or the right prefrontal cortex enhances similar cognitive functions such as working memory and top-down attention control [4,36,48], suggesting that increasing excitability of the prefrontal cortex in both hemispheres simultaneously may enhance certain brain functions.

Tolerability

Participants in the current study did not report significant adverse effects induced by tDCS. A common adverse effect, and the only one to show a between-condition difference, was skin tingling. Two recent tDCS studies also used HD electrodes and found no significant adverse effects [13,49]. Therefore, the new electrode arrangement used in the current study appears safe and tolerable to participants.

Affect

The effects of "traditional" forms of tDCS on affect/emotion in healthy participants and patients have been assessed previously. Among healthy participants, tDCS reduced stress and negative affect induced by unpleasant pictures [42,50-53] and attenuated decrements in vigilance during a sustained attention task [54]. Among patients, tDCS improved symptoms in patients with depression [10,40,41], reduced intensity of distress related to tinnitus [55], and alleviated chronic neuropathic pain [56], although not all studies have reported significant effects of tDCS on affect and emotion [50,57,58]. The current study showed a promising effect of attenuating decrements in vigor-activity after real relative to sham stimulation. This finding is in line with the finding of attenuated decrements in performance on a vigilance task in healthy participants after unilateral anodal stimulation [54] and supports our prediction that bilateral anodal stimulation might reduce task-related fatigue as indexed by scores on the vigor-activity subscale. This finding warrants additional investigation in patients that might be particularly sensitive to stress-related fatigue, including individuals with addictions.

Working Memory

Multiple studies have assessed the effects of anodal stimulation of the prefrontal cortex on working memory. Findings from these studies are not fully consistent. Several studies report improved performance on working-memory tasks after real relative to sham stimulation [9,38,39,59], whereas several studies do not find significant effects of real stimulation [37,57,60]. Furthermore, among those reporting improved performance, some studies report increased accuracy [8,32,61] while others report reduced RTs [59,62]. The reasons for the different findings from different studies are not clear and may involve differences in working-memory tasks, working-memory capacities of participants, electrode arrangements, and stimulation parameters used in different studies [36,37,63,64]. The present study did not find significant improvement on task performance after real relative to sham stimulation.

Limitations

One limitation is that this study did not compare the effect of unilateral and bilateral anodal stimulation. Therefore, it did not provide data indicating whether the bifrontal stimulation is more or less effective in influencing brain function than unilateral stimulation. The negative findings of real stimulation on n-back task performance did not support our prediction that bilateral anodal stimulation of the prefrontal cortex would enhance working-memory performance. An additional limitation is the relatively small sample size, which may have limited power for detecting between-condition effects.

In summary, participants did not report significant adverse effects after bilateral tDCS using two anodes. They reported attenuated decrements in self-reported vigor-activity during the study session after real relative to sham stimulation. These findings support the feasibility of bilateral anodal stimulation and indicate that this novel electrode arrangement may reduce fatigue as indexed by a vigor-activity subscale in healthy participants. Its potential for helping individuals with substance-use or other neuropsychiatric disorders deserves further study.

Acknowledgments: This study is supported by NIH grant K01DA027750, P20 DA027844, the Wallace H Coulter Foundation and the National Center for Responsible Gaming. We thank Dr. Stephanie O'Malley for her advice about study design.

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