Modulating oscillatory brain activity correlates of behavioral inhibition using transcranial direct current stimulation

Liron Jacobson, Adi Ezra, Uri Berger, Michal Lavidor

The Gonda Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat Gan, Israel
Department of Psychology, Bar Ilan University, Ramat Gan, Israel
Department of Psychology, University of Hull, UK

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Abstract
Objective: Studies have mainly documented behavioral changes induced by transcranial direct current stimulation (tDCS), but recently cortical modulations of tDCS have also been investigated. Our previous work revealed behavioral inhibition modulation by anodal tDCS over the right inferior frontal gyrus (rIFG); however, the electrophysiological correlates underlying this stimulation montage have yet to be established. The current work aimed to evaluate the distribution of neuronal oscillations changes following anodal tDCS over rIFG coupled with cathodal tDCS over left orbitofrontal cortex (lOFC) using spectral power analysis.

Methods: Healthy subjects underwent sham and real tDCS (15 min, 1.5 mA, anodal rIFG; cathodal lOFC) stimulation conditions in a single-blind, placebo-controlled cross-over trial. Following tDCS session, resting EEG recordings were collected during 15 min.

Results: Analysis showed a significant and selective diminution of the power of theta band. The theta diminution was observed in the rIFG area (represented the anode electrode), and was not found in the lOFC area (represented the cathode electrode). A significant effect was observed only in the theta but not in other bands.

Conclusions: These results are the first demonstration of modulating oscillatory activity as measured by EEG with tDCS over rIFG in general, and documenting theta band reduction with this montage in particular.

Significance: Our results may explain the improvement in behavioral inhibition reported in our previous work, and although this study was conducted with healthy subjects, the findings suggest that tDCS may also modulate electrophysiological changes among ADHD patients, where decreasing theta activity is the target of neuro-feedback methods aimed to improve cognitive control.

1. Introduction
Investigating the effect of a weak electrical current passing through the human’s scalp is now common. In order to understand its effects, researchers have investigated both the behavioral and electrophysiological changes induced by stimulation. Recording electrophysiological changes is of major importance as it enables the understanding of the direct effect of transcranial direct current stimulation (tDCS) over the human brain. The combination of electrophysiological and behavioral data may be the basis for the use of tDCS as a therapeutic tool for psychiatric disorders characterized by abnormalities in these electrophysiological and behavioral parameters.

Electrophysiological changes in EEG oscillations following tDCS have been previously documented. The first to conduct such a study applied the tDCS electrodes over motor areas; Ardolino et al. (2005) reported that cathodal stimulation of the motor cortex increased the power of delta and theta rhythms, while Polania et al.
that anodal tDCS over rIFG can improve healthy subjects’ ability to inhibit responses (Jacobson et al., in press) and we currently tested for changes in the oscillatory activity linked to the behavioral changes induced by this montage of tDCS. Since it has already been suggested by Lansbergen et al. (2007) that lower theta band is associated with a higher probability to inhibit responses, and based on the above ADHD literature, our main hypothesis was that the main stimulation effect would be a reduction in the power of theta band in the rIFG area.

2. Methods

2.1. Participants

The population was composed of 11 healthy participants (6 women, 5 men; mean age, 26.27 ± 4.15 years; age range 23–37 years), who volunteered to take part in the experiment in return for payment. Subjects were informed about all aspects of the experiments and all gave informed consent before taking part in the study, which was approved by the Bar Ilan Ethics committee. All of the subjects were right handed and none of them suffered from any neurological or psychiatric disorder, or had metallic implants/implanted electrical devices. All subjects stated they are not taking medication on a regular basis and they did not take any medication prior the experimental session.

2.2. Transcranial direct current stimulation (tDCS)

Since our previous work showed that cathodal stimulation over rIFG did not modify behavioral inhibition as assessed by the stop signal task, in this study we compared two stimulation conditions: anodal over rIFG coupled with cathodal over IFG, to sham tDCS. A direct current of 1.5 mA was induced by two saline-soaked surface sponge electrodes (25 cm²) and delivered for 15 min by a battery-driven, constant-current stimulator (Rolf Schneider Electronics, Germany). The same stimulation protocol employed in previous studies (Ross et al., 2010) was well tolerated, and a bigger intensity of 2 mA was found to be safe for healthy participants (Iyer et al., 2005).

In the real tDCS condition (anodal), the anode electrode was positioned over the region of interest – the rIFG, and the cathode electrode served as a reference electrode, and was placed over the left orbitofrontal cortex (IOF). Localization was established using the 10–20 EEG technique; the rIFG was identified as the crossing point between T4-Fz and F8-Cz, based on Monti et al. (2008) who localized the homologue IFG between T3-Fz and F7-Cz. The IOF electrode was positioned above the left eyebrow (Nitsche and Paulus, 2000). In the sham condition, the current was applied for 30 s and then turned off automatically. Because most subjects feel an itching sensation only initially during tDCS, this procedure prevents awareness of the stimulation conditions (Gandiga et al., 2006; Nitsche et al., 2008). Stimulation sessions were counterbalanced and were administered at about a 1 week interval between them.

2.3. Data acquisition

EEGs (ASA ANT system) were recorded for 15 min in a resting state, about 5 min after finishing the stimulation sessions (anodal, sham). This experimental design was chosen based on two top priority issues: causing less discomfort to the participants and collecting the most refined EEG data. EEGs were recorded against an average of two reference electrodes (right and left ear lobes) in the following 27 positions: Fp1, Fpz, Fp2, AF7, AF3, AFz, AF4, A8, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FCz, FC2, FC4, FC6, FT8 and Cz, using Ag/AgCl electrodes; electrode impedance was monitored throughout the experiment to be less than 5 kΩ.
Data was acquired at sampling rate of 2048 Hz and was filtered online with an anti-aliasing filter; a low pass filter with a cut-off frequency of 555 Hz, after acquisition data was down-sampled to 256 Hz for further analysis. Recording was conducted in a sound-attenuated room where subjects sat in a comfortable reclining chair. During the EEG recording, subjects were instructed to keep their eyes closed and remain calm and alert. After the recording, participants were asked if they were alert during recording.

2.4. Data analysis and statistics

Data analysis was performed offline using EEGLAB (Delorme and Makeig, 2004), the MATLAB 7 (The MathWorks Inc., Natick, MA, USA) toolbox for electrophysiological research and custom written scripts. The two raw EEG data sets (anodal, sham) for each participant were split into 1 s segments (900 segments in total). Before analysis, manual artifact detection was conducted by an unbiased analyzer over all the EEG channels; all EEG segments containing eye or muscle artifacts were excluded, an artifact in one channel lead to the exclusion of the whole 1 s segment.

A fast Fourier transform (FFT) was computed on the raw EEG data, 1 s segments, multiplied by a Hamming window moving half a second at a time, which yielded the absolute power spectra for each segment. The segments were then averaged for each subject in each condition (anodal, sham), and in order to evaluate any induced changes in cortical activity, the mean spectral amplitude was obtained, in four frequency ranges: theta band frequency (4–7 Hz), alpha band frequency (8–12 Hz), beta band frequency (13–30 Hz) and gamma band frequency (31–45 Hz).

Since our region of interest cannot be specified by a single electrode, we divided the channels into clusters, such that two of them will represent the two regions of interest, two will represent the two contralateral areas and the other clusters will be grouped based on proximity and symmetry; the 27 channels were divided into seven clusters (Fig. 1). The region of interest was the rIFG area, over which the anode electrode was positioned which is represented by the following four channels: FC2, FC4, FC6, FT8. The cathode electrode which was positioned over the IOFC is represented by the following four channels: F7, AF7, FP1, FPz. The two contralateral clusters were: [FT7, FC5, FC3, FC1]; [FP2, AF8, F8]; represent the contralateral area to the IOFC, and the additional three clusters were: [AF3, F5, F3, F1]; [AFz, Fz, FCz, Cz]; [AF4, F2, F4, F6].

To analyze the difference between the two stimulated regions, i.e., the rIFG (anode electrode) and the IOFC (cathode electrode), we compared the channels that represent the anode electrode [FC2, FC4, FC6, FT8] to those represent the cathode electrode [F7, AF7, FP1, FPz] for each band by repeated measures ANOVA. To do that, we calculated a measurement that represents the percent change (the difference between sham to anodal divided by sham) for each channel and band, and then summed the results twice, for the two sets of four channels represent the anode and the cathode electrodes.

To analyze whether effects were consistent with all four channels represent the tDCS electrodes, or perhaps derived from a single channel, an additional repeated measures ANOVA was conducted between the two tDCS conditions and the four channels for the recognized, selective and significant effect found in the initial analysis.

To investigate the selectivity of the effect we conducted further t-maps for each of the clusters, for each of the four analyzed bands. We averaged the activity for each bands, each of the seven clusters and for the two tDCS conditions and conducted t-tests (corrected for multiple comparisons between anodal and sham stimulation conditions for each band and cluster.

3. Results

There was no significant difference between the numbers of epochs in the anodal (659.722 ± 143.862) and sham (670.545 ± 136.400) stimulation conditions (t (11) = .276, p = .789; mean ± SD), which enables a comparison between the two tDCS conditions.

The repeated measures ANOVA for the percent change [(sham-anodal)/sham] yielded a significant interaction (F (3, 30) = 3.378, p = .031) between band (theta, alpha, beta, gamma) and area (anode-rIFG area, cathode-IOFC area), and insignificant main effects (F (3, 30) = .640, p = .565; F (1, 10) = .294, p = .600 respectively). To define the source of interaction, post-hoc comparisons were run for each of the bands (theta, alpha, beta, gamma). The difference between the two areas (anode-rIFG area, cathode-IOFC area) for the power of theta band was significant (t (10) = 2.306, p = .044), whereas no significant differences were evident in any of the other bands (alpha: t (10) = 1.695, p = .121; beta: t (10) = .152, p = .882; gamma: t (10) = −.818, p = .432). The significant effect of the power of theta band in the rIFG area was due to a reduction in the power following anodal condition compared to sham, the effect was consistent for all participants and the average (±SEM) percent change was about 27.5% (±5.88; Fig. 2a).

In order to confirm that the significant effect of theta band was consistent with each of the four channels that represent the rIFG area (where the anode electrode was positioned), a repeated measures ANOVA was conducted between the two tDCS conditions (anodal, sham) and each of the four channels that represent the rIFG area (FC2, FC4, FC6, FT8). Significant main effects were yielded for tDCS conditions (F (1, 10) = 10.597, p = .009), and for channels (F (3, 8) = 25.458, p < .001), whereas the interaction was not significant (F (3, 8) = 2.914, p = .101), which confirm the consistency of the tDCS effect over the four channels in the power of theta band (Fig. 2b).

T-maps were conducted to confirm that the reduction of the power of theta band was selective to the rIFG area. Analysis revealed a significant difference between anodal and sham stimulation conditions in the power of theta band in the rIFG area (t (10) = 3.37, p = .007), while no additional significant difference was found for the additional clusters, nor for the additional bands (Fig. 3).
4. Discussion

In the present study we applied tDCS (anodal over rIFG; cathodal over lOFC) and recorded EEG oscillation following real stimulation and sham. Corroborating our a priori hypothesis, we demonstrated that this stimulation montage led to a significant and selective reduction among all subjects in the power of theta band in the rIFG area, as no such change was evident in the other recorded areas and none of the other analyzed bands were significantly affected by the stimulation. Additionally the effect was consistent with the four channels that represent the rIFG.

The current study used a stimulation protocol that had been proved to be successful in improving behavioral inhibition (Jacobson et al., in press), and here revealed its electrophysiological correlates, which are assumed to derive from the rIFG area, as suggested by Asada et al. (1999) and Ishii et al. (1999). They suggested that the theta rhythm may derive from prefrontal regions; however due to EEG characteristics we can only refer to electrode locations and not to brain locations. The integration of the current electrophysiology study with our previous work (Jacobson et al., in press) provides evidence that anodal tDCS over the rIFG is able to affect behavioral inhibition as well as to modulate cortical activity; i.e., the electrophysiological correlates of behavioral inhibition, and it appears that the changes in the ability to inhibit responses achieved by tDCS may account for a reduction in the power of theta band. The present study is the first to demonstrate a significant and selective reduction in the power of theta band following anodal stimulation over the rIFG compared to sham stimulation.

The neuronal effect of tDCS has been investigated in a few animal-based studies. For example, Bindman et al. (1964) reported that when a positive stimulation (i.e., anode) is applied, a depolarization of the resting membrane potential occurs, which increases
neuronal excitability and therefore increases spontaneous cell firing. Inversely, when a negative stimulation (i.e., cathode) is applied, a hyperpolarization occurs, which decreases neuronal excitability and decreases spontaneous cell firing. This effect was afterwards replicated by Nitsche and Paulus (2000), who applied the tDCS electrodes over human motor cortex. The effects of a single session of tDCS last for a few minutes after stimulation and the assumption is that after-effects following stimulation are enabled by modulation of LTP/LTD mechanisms (Nitsche et al., 2003). To extend these data, there is still a need to use brain imaging techniques to better determine the cortical changes induced by stimulation. Although there is considerable literature on the ability of tDCS to modulate behavior when applied over the cortex, the associated changes in brain activity following stimulation have yet to be fully established.

The current study contributes to the growing list of electrophysiological documented changes induced by tDCS applied over the cortex. tDCS over motor areas has been found to: induce changes in functional connectivity patterns (Alon et al., 2011; Polania et al., 2011) and in delta and theta rhythms (Ardolino et al., 2005), promote an increase in regional cerebral blood flow (Lang et al., 2005), and cathodal tDCS over sensorimotor area has resulted in a global decrease of the mean number of activated pixels (Baudewig et al., 2001). tDCS over DLPFC has been found to induce changes in current densities of delta band (Keesser et al., 2011) and in theta and alpha bands (Zaehle et al., 2011). The novelty of the current study is in the broad perspective provided by the combination of the current electrophysiology study, and our previous behavioral study applied the same montage of tDCS. Previously we demonstrated behavioral inhibition modulation (Jacobson et al., in press), and here we demonstrated an electrophysiology modulation which may be the basis underpinning the previous behavioral findings.

The decrease in the power of theta band which is associated with a better ability to inhibit responses following anodal stimulation over the rIFG is consistent with the literature about ADHD, a common psychiatric disorder which is primarily characterized by a behavioral inhibition deficit (Barry, 1997). People with ADHD, compared to control groups, have been characterized as having increased levels of theta band activity (Clarke et al., 1998, 2001; Capute et al., 1968; Chabot and Serfontein, 1996). The standard pharmacological treatment – MPH – has been found to decrease levels of theta band, according to the above literature, may be used as a therapeutic tool to improve behavioral inhibition in healthy and genetically impaired populations.

Several limitations of the current study must be acknowledged. Only some of the possible montages of prefrontal regions were tested; in addition, it would be worthwhile to conduct EEG recordings during stimulation as well and not only off-line protocols. Nevertheless, these findings have significant theoretical and practical implications. At the theoretical level, the results suggest that cortical oscillatory changes are induced by tDCS, which may account for the observed behavioral changes. They also have practical implications for the development of interventions to benefit individuals with various types of attentional deficits. For the participants in the current study who were in their twenties and thirties, the effect of stimulation, while significant, was relatively modest. It is likely that older adults or people with attention impairments seen in conditions such as ADHD would show greater effects. We hope that in future studies the potential of tDCS with attention – challenged populations such as ADHD would be investigated.

5. Conclusion

Anodal tDCS over the rIFG decreased the power of theta band in the rIFG area selectively among healthy participants. These results may suggest that the use of tDCS would be beneficial as a therapeutic tool for improving behavioral inhibition deficits in populations such as ADHD.

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References


