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Modulation of cortical responses by transcranial direct current stimulation of dorsolateral prefrontal cortex: A resting-state EEG and TMS-EEG study

Pedro Caldana Gordon [a, b], Christoph Zrenner [a], Debora Desideri [a], Paolo Belardinelli [a], Brigitte Zrenner [a], André Russowsky Brunoni [b, c], Ulf Ziemann [a, *]

[a] Department of Neurology & Stroke, Hertie Institute for Clinical Brain Research, University of Tübingen, Hoppe-Seyler-Straße 3, 72076, Tübingen, Germany
[b] Service of Interdisciplinary Neuromodulation, Laboratory of Neuroscience (LIM27) and National Institute of Biomarkers in Psychiatry (INBioN), Department and Institute of Psychiatry, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, R. Dr. Ovídio Pires de Campos, 785, 01060-970, São Paulo, Brazil
[c] Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University, Leopoldstr. 13, 80802, Munich, Germany

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique with potential for cost-effective therapeutic neuromodulation. Although positive therapeutic effects were found by stimulating the dorsolateral prefrontal cortex (DLPFC), few studies have investigated physiological effects of DLPFC-tDCS.
Objectives: To investigate effects of tDCS with different parameter settings applied to the left DLPFC on cortical responses, measured by resting-state electroencephalography (rs-EEG) and transcranial magnetic stimulation (TMS)-evoked/induced EEG responses.
Methods: 22 healthy subjects underwent 5 tDCS sessions with different tDCS parameter settings in a double-blinded randomized crossover design (1: 1.5 mA, anode left-DLPFC, cathode right-DLPFC; 2: 1.5 mA, cathode left-DLPFC, anode right-DLPFC; 3: 0.5 mA, anode left-DLPFC, cathode right-DLPFC; 4: 1.5 mA, anode left-DLPFC, cathode left deltoid muscle; 5: sham stimulation). Rs-EEG and TMS-EEG were recorded before and after tDCS.
Results: Rs-EEG power spectrum analysis showed no difference comparing baseline with post stimulation in any of the tDCS conditions. TMS-EEG evoked potential amplitude decreased in parietal cortex after 1.5 mA left-DLPFC anodal tDCS, and TMS-induced gamma and theta oscillations decreased after all conditions using left-DLPFC anodal tDCS. Left-DLPFC cathodal tDCS did not lead to significant change. None of the post-intervention changes was different when comparing the effects across conditions, including sham.
Conclusions: Our study does not provide evidence that a single tDCS session results in significant changes in rs-EEG, using the current stimulation parameters. Significant changes in EEG responses to TMS pulses were observed following the anodal 1.5 mA tDCS interventions, although these changes were not statistically significant in a group comparison.

1. Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that has gained much attention due to its potential clinical applications [1], coupled with low cost and favorable safety profile [2,3]. The prospect of a highly cost-effective neuromodulation tool has led to the investigation of numerous possible usages of this technique. Nevertheless, only a few clinical conditions, such as major depressive disorder, have been shown to consistently improve following tDCS treatment [4,5]. The neuromodulatory potential of tDCS has also been investigated in cognitive tasks, with reports of increased working memory performance after tDCS [6], although only few experiments consistently showed a lasting effect of tDCS on cognition [7]. The lack of consistency of

* Corresponding author.
E-mail address: ulf.ziemann@uni-tuebingen.de (U. Ziemann).

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reported effects derived from tDCS trials has been partially attributed to high variability of stimulation parameters across studies, as well as other factors, such as age, gender, and brain state during neuromodulation [7,8].

The basic operation of tDCS involves the induction of a low-intensity electrical field in the brain by injecting electrical current, usually between 1 and 2 mA, through a set of electrodes placed on the subject's scalp [9]. It has been hypothesized that the electric field induced by tDCS shifts the polarity difference between the intra- and extracellular space, which either increases neuronal firing rate (anodal stimulation) or decreases it (cathodal stimulation) [10,11]. In human studies, tDCS applied over motor cortex was shown to modulate motor evoked potentials (MEP) elicited by transcranial magnetic stimulation (TMS), with anodal stimulation increasing MEP amplitude and cathodal stimulation decreasing it [12,13]. Although changes in MEP amplitude after a single session tend to be short lasting, longer duration of tDCS led to longer lasting after-effects [14], supporting the idea that repetitive sessions of tDCS would lead to more stable and enduring neuroplasticity [15,16]. However, the effects of tDCS on cortical modulation were found to be less predictable than expected, as changes of stimulation parameters would promote significant shifts in expected cortical responses. In the motor cortex, a 26-min session (vs. 13 min) led to effects opposite from the expected, with anodal tDCS of motor cortex decreasing MEP amplitude [16]. Cathodal tDCS over motor cortex, initially believed to induce MEP amplitude reduction [12], led to MEP increase when a higher current intensity (2 mA rather than 1 mA) was applied [17]. Brain state was also observed to impact the effects of tDCS, as the same stimulation parameters led to different results, depending on whether subjects were at rest or performing a cognitive task during stimulation [18].

Furthermore, most studies investigating tDCS effects on the human brain targeted the motor cortex. This is a relevant limitation for the application of tDCS in clinical practice, as most cortical targets in neuropsychiatry and cognition are non-motor areas [5,7]. Also, given the high variability of cortical reactivity in response to tDCS protocols on motor cortex, there is little reason to expect that tDCS of non-motor cortex will follow a simple “anode-facilitation cathode-inhibition” model. Moreover, an important limitation of neurophysiological studies in non-motor cortical areas is the absence of a direct read-out of cortical excitability, easily accessed in motor cortex through MEP amplitude. An alternative way to quantify cortical modulation in non-motor areas is by means of measuring scalp potentials with electroencephalography (EEG). Rs-EEG signal analysis has been used to investigate effects of tDCS applied to the frontal cortex. The available studies have described diverse changes in the EEG signal following tDCS to the prefrontal cortex, such as increase in medial prefrontal theta power [19], or change in the mean frequency index [20], while other studies found no change of rs-EEG following tDCS [21,22], indicating an overall lack of evidence for an effect of tDCS on rs-EEG [23]. TDCS-related changes in cortical excitability were also probed using TMS-EEG (transcranial magnetic stimulation coupled with EEG), a complementary technique that allows direct analysis of TMS-evoked/induced cortical responses to stimulation of any cortical area [24]. Several authors [25–27] investigated the effects of tDCS over the motor cortex with TMS-EEG, and reported a significant amplitude increase of TMS evoked EEG potentials (TEPs) after anodal tDCS, and a decrease after cathodal tDCS, both concomitant with the expected changes in MEP amplitude. A further study of tDCS over the parietal cortex also showed modulation of cortical excitability measured with TMS-EEG, with increased TEP amplitudes after anodal tDCS [28]. Finally, a study using bipolar vs. high-definition tDCS (HD-tDCS), targeting the dorsolateral prefrontal cortex (DLPFC), found significant modulation of cortical excitability measured with TMS-EEG [29].

Despite these initial findings, it is not yet clear how the DLPFC reacts to different tDCS settings. A careful appraisal of the difference in cortical responses to varying tDCS parameters, analogous to motor cortex [16,17], would provide relevant information of the DLPFC responsivity to tDCS. To this aim, we have tested the effects of 4 different set of tDCS parameters over the DLPFC, and investigated the changes in cortical activity and response using rs-EEG and TMS-EEG. Considering previous findings regarding cortical excitability of the motor cortex, our aims were to address in the DLPFC: (1) polarity-dependent effects by testing anodal (associated with increased cortical excitability) vs. cathodal tDCS (associated with decreased cortical excitability); (2) current-strength-dependent effects, by testing 0.5 mA (associated with decreased cortical excitability) vs. 1.5 mA anodal tDCS (associated with increased cortical excitability) and; (3) the influence of the placement of the return electrode, by testing a cephalic vs. extra-cephalic montage.

2. Materials and methods

2.1. Subjects

22 healthy right-handed volunteers (12 females, mean age: 26.9 ± 8.2 years) completed all sessions and their data were included in the present study. Right-handedness was confirmed using the Edinburgh Handedness Inventory (laterality score $\geq$75%) [30]. Exclusion criteria were prior history of psychiatric or neurological disease, current treatment with drugs acting on central nervous system, presence or prior history of alcohol or illicit drugs abuse, and current pregnancy. The study was approved by the local Ethics Committee of the Medical Faculty of the Eberhard-Karls-University Tübingen, and all subjects provided written informed consent prior to participation.

2.2. Design

The study followed a randomized, sham-controlled, double-blinded, repeated measures design. Each subject underwent 5 sessions, with a one-week lapse between sessions. Each session consisted of baseline measurements (BASELINE) followed by tDCS intervention, and immediately followed by outcome measurements (POST). Measurements consisted of resting state EEG (rs-EEG) and TMS evoked responses, as described below. For a given subject, all sessions were conducted on the same week day and time of day.

2.3. Transcranial direct current stimulation

tDCS was applied using a DC stimulator (DC-Stimulator Plus, neuroCare Group GmbH, Germany). The five sessions involved the following parameter settings: #1: 1.5 mA, anode left-DLPFC, cathode right-DLPFC; #2: 1.5 mA, cathode left-DLPFC, anode right-DLPFC; #3: 0.5 mA, anode left-DLPFC, cathode right-DLPFC; #4: 1.5 mA, anode left-DLPFC, cathode left deltoid muscle; #5: sham stimulation (Fig. 1B). The order in which these sessions were delivered to each subject was randomized. All tDCS interventions lasted 14 min each, including 30 s of electric current ramp-up at the beginning of the stimulation and 10 s ramp-down at the end. In the sham condition the current was reduced to zero after the 30-s ramp-up. This procedure was shown to effectively simulate an active tDCS session, thus assuring that subjects remained blinded to the stimulation condition [31].

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