Archival Report

Biological Psychiatry

Online Effects of Transcranial Direct Current Stimulation in Real Time on Human Prefrontal and Striatal Metabolites

Antoine Hone-Blanchet, Richard A. Edden, and Shirley Fecteau

ABSTRACT

BACKGROUND: Studies have reported that transcranial direct current stimulation (tDCS) can modulate human behaviors, symptoms, and neural activity; however, the neural effects during stimulation are unknown. Most studies compared the effects of tDCS before and after stimulation. The objective of our study was to measure the neurobiological effect of a single tDCS dose during stimulation.

METHODS: We conducted an online and offline protocol combining tDCS and magnetic resonance spectroscopy (MRS) in 17 healthy participants. We applied anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC) and cathodal tDCS over the right DLPFC for 30 minutes, one of the most common montages used with tDCS. We collected MRS measurements in the left DLPFC and left striatum during tDCS and an additional MRS measurement in the left DLPFC immediately after the end of stimulation.

RESULTS: During stimulation, active tDCS, as compared with sham tDCS, elevated prefrontal *N*-acetylaspartate and striatal glutamate + glutamine but did not induce significant differences in prefrontal or striatal gamma-aminobutyric acid level. Immediately after stimulation, active tDCS, as compared with sham tDCS, did not significantly induce differences in glutamate + glutamine, *N*-acetylaspartate, or gamma-aminobutyric acid levels in the left DLPFC.

CONCLUSIONS: These observations indicate that tDCS over the DLPFC has fast excitatory effects, acting on prefrontal and striatal transmissions, and these effects are short lived. One may postulate that repeated sessions of tDCS might induce similar longer lasting effects of elevated prefrontal *N*-acetylaspartate and striatal glutamate + glutamine levels, which may contribute to its behavioral and clinical effects.

Keywords: Dorsolateral prefrontal cortex, Glx, Magnetic resonance spectroscopy, *N*-acetylaspartate, Striatum, Transcranial direct current stimulation

http://dx.doi.org/10.1016/j.biopsych.2015.11.008

Studies have reported that transcranial direct current stimulation (tDCS) can noninvasively modulate human behaviors in vivo. Applied over the dorsolateral prefrontal cortex (DLPFC), tDCS can influence mood, emotional perception, and various cognitive processes including decision making (1), problem solving (2), and working memory (3). However, recent meta-analyses questioned some of these effects of tDCS (4,5). Some of these questions raised the issue that most studies have tested the effects of tDCS on behavioral and clinical outcomes. The neurophysiologic mechanisms of action of tDCS remain relatively unknown. The few studies that tested the effects of tDCS on neural outcomes used offline designs, measuring and comparing neural substrates before and after stimulation (6). Although these studies greatly contributed to elucidating the neural effects of tDCS, they were limited to reporting neural differences after tDCS delivery. There is still a need to demonstrate whether tDCS instantaneously changes neural substrates during stimulation. Such a demonstration would provide evidence that tDCS directly modulates the brain.

Characterization of the neural effects of tDCS is also important to further investigate the clinical potentials of tDCS (7,8). The possibility of modulating the brain and consequently inducing behavioral and cognitive changes indicates therapeutic potential for tDCS. Most studies modulating behaviors and cognition in healthy volunteers reported such effects with a single tDCS session, and therapeutic potential has mainly been reported when repetitive sessions of tDCS were applied over the DLPFC. Studies reported reduction of depressive symptoms in patients with major depressive disorders (9,10), positive symptoms in patients with schizophrenia (11), and craving in patients with substance use disorders (12). Again, how the brain is modulated when tDCS induces such clinical benefits is largely unknown. Better characterization of the neural effects of tDCS over the DLPFC would likely contribute to identifying optimal parameters to enhance clinical outcomes.

The goal of this study was to develop an online design using tDCS and magnetic resonance spectroscopy (MRS) to characterize the simultaneous and subsequent neurometabolism

 ISSN: 0006-3223

differences induced by tDCS using ^{1}H MRS. Our hypotheses were that tDCS would 1) elevate glutamate + glutamine (Glx) levels in the left DLPFC (under the anode electrode) and left ventral striatum, 2) elevate *N*-acetylaspartate (NAA) levels in the left DLPFC, and 3) decrease gamma-aminobutyric acid (GABA) levels in the left DLPFC. Furthermore, it was hypothesized that these neurometabolic differences in the left DLPFC would be observed during and after delivery of tDCS. To test these hypotheses, we simultaneously delivered anodal and cathodal tDCS over the left and right DLPFC, respectively, and measured total Glx, GABA, and NAA concentrations in the left DLPFC and left striatum with MRS. We selected this electrode montage (anodal tDCS over the left DLPFC and cathodal tDCS over the right DLPFC) because these regions are the most targeted areas to modulate behaviors and cognition and to alleviate neuropsychiatric symptoms. We studied metabolites in the left DLPFC and left striatum because of the importance of corticostriatal fibers as connections within the forebrain and to probe potential subcortical effects of tDCS. We studied Glx and GABA because the effects of tDCS are primarily thought to be ascribable to local differences in cortical excitability, implicating glutamate (13) and GABA transmissions (14). We also measured NAA, a metabolite implicated in neuronal regulatory processes such as protein synthesis and lipid production (15) and an indicator of neuronal viability and metabolism activity (16). Finally, we also focused on these neurotransmitters because they have been shown in numerous articles to be affected in the aforementioned pathologic conditions (17) in which tDCS has shown some clinical potential.

METHODS AND MATERIALS

This study used a randomized, crossover, sham-controlled, blinded at three levels design (participant, MRS experimenter, data analysis conductor). Each participant took part in two experimental sessions: one with active tDCS and one with sham tDCS. The order of the tDCS sessions was randomized with a Latin square (eight participants received active tDCS first and sham tDCS second). Sessions were separated by 7 days to minimize potential carryover effects of tDCS.

Participants

We recruited 17 healthy participants through the electronic mail distribution service of Université Laval. The local institutional review board committee (Institut de Réadaptation en Déficience Physique de Québec) approved the study. We obtained informed written consent from all participants and screened them for neurologic, medical, and psychiatric conditions. Two participants demonstrated moving artifacts during scanning and were omitted from further analysis. The remaining 15 participants (eight men) had an average age of 27 years (range, 21–41 years) and were right-handed as assessed by the Edinburgh Handedness Inventory. Table 1 summarizes participant characteristics.

Table 1. Participant Characteristics

Participant No.	Sex	Age, Years	Handedness[a]
1	Male	31	80
2	Female	27	50
3	Male	29	100
4	Male	22	80
5	Female	41	100
6	Female	27	100
7	Male	23	90
8	Male	23	100
9	Female	24	50
10	Female	23	100
11	Female	28	60
12	Female	21	88
13	Male	28	78
14	Male	26	100
15	Male	33	100

[a]Scores on the Edinburgh Handedness Inventory.

tDCS Parameters

We delivered stimulation using a magnetic resonance imaging–compatible DC-STIMULATOR (neuroConn GmbH, Ilmenau, Germany). We placed the anode electrode over the left DLPFC (F3) and the cathode electrode over the right DLPFC (F4) using the electroencephalography 10-20 system. We used 35-mm^2 electrodes, and electrode positioning was verified on T1-weighted scan. Active stimulation was delivered for 30 minutes at a current intensity of 1 mA. Sham stimulation was delivered for 30 minutes following standard procedure with a ramp up and a ramp down of 30 seconds with the remaining time with no active current (18). Participants and the MRS experimenter completed a questionnaire on the stimulation conditions for each session to test the integrity of blinding at the end of the study. Of 15 participants, 11 guessed which tDCS session (active or sham) was conducted with a confidence level of 55% determined on a visual analog scale. The MRS experimenter (AH-B) had minimal interaction with the participants and remained fully blinded to the tDCS conditions (active vs. sham; delivered by SF), with a confidence level of 100%, until the interpretation of results.

tDCS and MRS Design

We delivered tDCS during MRS scanning (Figure 1). We started tDCS 5 minutes before acquiring the first spectroscopy scan. To the best of our knowledge, no studies reported online neural effects of tDCS when targeting the DLPFC. However, results of studies reported that tDCS over the primary motor cortex had to be delivered for 5 minutes to induce significant differences in the amplitude of motor evoked potentials as captured by electromyography (19). We are aware that the effects of tDCS over the DLPFC or the primary motor cortex may have a different timeline, but we also made this choice of starting the MRS scan after 5 minutes of stimulation because the most likely side effect of tDCS is an itching sensation during ramp periods (the first and last 30 seconds of tDCS delivery), which might cause head movement and affect data quality. Each scanning period lasted 50 minutes at our facility. Following the acquisition of the 7-minute anatomic magnetic resonance imaging scan and the 30-minute tDCS/MRS session, we had time for only one poststimulation measurement. Because the main goal of our study was to capture the effect