Running head: tDCS modulation of neural responses

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Title:

Polarity-specific transcranial Direct Current Stimulation effects on object-selective neural responses in the Inferior Parietal Lobe

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Abstract

Neuromodulation techniques such as transcranial direct current stimulation (tDCS) are routinely used for treating neurological and neuropsychiatric disorders, and for enhancement of cognitive abilities. Recently, their effectiveness in modulating behavioral and neural responses has been questioned. Here we use excitatory and inhibitory tDCS prior to a functional magnetic resonance imaging (fMRI) experiment to show that neural responses for an area's preferred stimuli depend on the polarity of stimulation. This is an important, yet overlooked, data point in demonstrating the effectiveness of these stimulation techniques. Our results show that response preferences in the target area are dependent on the polarity of the tDCS session preceding the fMRI experiment – these preferences are less distinct in the cathodal than in the anodal session. As such, we show unequivocally that tDCS modulates neural responses. This result is of the utmost importance in demonstrating the effectiveness of tDCS for clinical and experimental purposes.

Keywords: tDCS, fMRI, Neuromodulation, IPL, Tools

1. Introduction

Non-invasive neuromodulation techniques such as transcranial direct current stimulation (tDCS) have enjoyed a revival in the last few decades because of their putative effectiveness and their non-invasive nature. Specifically, these techniques have been shown to 1) be effective in the treatment of major depressive syndromes (e.g., Nitsche, Boggio, Fregni & Pascual-Leone, 2009), as well as other psychiatric disorders (e.g., Senco et al., 2015); 2) improve neurorehabilitation of brain-lesioned patients (e.g., Fregni et al., 2005); and 3) affect the processing of different types of information in normal participants (e.g., Lupyan, Mirman, Hamilton & Thompson-Schill, 2012). Importantly, this effectiveness has been achieved without compromising safety, and non-invasiveness.

But their neural and behavioral efficacy has recently been challenged (e.g., Buzsáki, 2016; Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016; Horvath, Forte & Carter, 2015a, 2015b; but see Antal, Keeser, Priori, Padberg, & Nitsche, 2015; Joyal & Fecteau, 2016; Kekic, Boysen, Campbell, & Schmidt, 2016; Shin, Foerster, & Nitsche, 2015). Specifically, Buzsáki has suggested that the typical tDCS stimulation parameters used in neuroscientific research are underpowered, as the application of an electric current to the skull of a cadaver, following such parameters, fails to elicit any neural firing in adjacent brain cells (Buzsáki, 2016). Thus, tDCS should not modulate neuronal activity, and consequently affect cognitive and behavioral responses. Moreover, Horvath and colleagues (2015a, 2015b) performed a series of meta-analyses and failed to find effects of tDCS on the majority of neural and behavioral measures they tested. This further puts into question the effectiveness of these techniques in restoring function and treating neuropsychiatric disorders.

Because of the potential role of these techniques in bringing innovation and advances in our understanding of neural and cognitive processing, as well as in the betterment of our tools to intervene and rehabilitate neuropsychiatric disorders, it becomes crucial to unequivocally show that they can modulate neural responses. Here we measured object-selective neural responses while participants took part in an experiment where we coupled offline tDCS stimulation with a typical object processing fMRI experiment. Importantly, we manipulated the polarity of tDCS stimulation (i.e, we used excitatory and inhibitory tDCS), because demonstrating that neural responses change as a reflection of the polarity of stimulation is central in attesting the effectiveness of these non-invasive stimulation techniques.

1.2 Experiment

In our experiment, each participant went through 3 experimental sessions that were separated by at least one week. In the first session, participants went through the fMRI experiment (i.e., the control session), whereas in the second and third sessions participants were first subject to tDCS stimulation outside the MR scanner, and then immediately started the fMRI experiment. The order of the tDCS sessions was counterbalanced across participants. The fMRI experiment consisted of the presentation of a series of visual stimuli belonging to different object categories (e.g., tools, faces). tDCS sessions consisted of anodal (typically thought to increase neuronal excitability) or cathodal (typically thought to decrease neuronal excitability; Nitsche et al., 2009; Senço et al., 2015; Stagg & Nitsche, 2011) stimulation to the left Inferior Parietal Lobule (IPL).

The left IPL was chosen as the target area because it is highly accessible to these non-invasive neuromodulation techniques, and because it is known to respond more to images of tools than images of stimuli from other categories (e.g., Almeida, Fintzi, &

Mahon, 2013; Chao & Martin, 2000; Garcea, Kristensen, Almeida, & Mahon, 2016; Kristensen, Garcea, Mahon, & Almeida, 2016; Mahon, Kumar, & Almeida, 2013). The current understanding of how tDCS works assumes that tDCS modulates the polarity of the resting membrane and the synaptic strength of neurons (e.g., Fertonani & Miniussi 2016; Stagg & Nitsche, 2011), but does not, in and of itself, elicit action potentials. By virtue of this mechanistic understanding of tDCS, we expect there to be modulation of the responses of those neurons already engaged in (cognitive) processing. As such, because in our experiment neurons within the left IPL will be engaged in processing tool stimuli, we will be able to test whether tDCS can modulate neural responses, and in particular tool-preferences, in IPL.

Importantly, if the stimulation parameters used in our sessions, which are similar to those typically used in regular tDCS experiments, are sufficient for modulating neural activity, then, activity in the left IPL for tools, when compared to activity for a control category (e.g., faces; henceforth tool-specificity), should be dependent on the polarity of the tDCS stimulation. Specifically, there should be a decrement of tool-specific responses in the left IPL when we inhibit this area (i.e., in the sessions in which we apply cathodal tDCS), when compared to when we excite it (i.e., in the sessions in which we apply anodal tDCS). That is, BOLD signal coming from the left IPL as a response to the presentation of tool images should be modulated by whether we excite or inhibit this area before the fMRI session.

2. Material and Methods

2.1 Participants

Ten healthy right-handed adults (mean age = 23.0 years, SD = 4.5 years, range = 18 – 33 years; five females, and five males) participated in the experiment. Participants

were part of the student population of the Faculty of Psychology and Educational Sciences of the University of Coimbra, and received course credit for their participation. The study adhered to the Declaration of Helsinki and was approved by the Ethical Committee of the Faculty of Psychology and Educational Sciences of the University of Coimbra. All participants gave written informed consent after a detailed description of the complete study. Because of the use of tDCS, and the collection of fMRI data, there were clear exclusion criteria that included cardiovascular or neurological disorders, brain injury, pregnancy, lifetime and current substance abuse or dependence, any mental disorder, and metallic implants.

2.2 Procedure

2.2.1 fMRI experiment.

In the fMRI experiment we used grayscale photographs of tools, animals, famous faces, and famous places, plus phase-scrambled versions of these stimuli as experimental stimuli (for more details on materials, see Fintzi & Mahon, 2014). Stimuli were 400x400 pixels in size and were presented on a gray background using an Avotec projector with 60 Hz refresh rate. To control stimulus presentation we used "A Simple Framework" (Schwarzbach, 2011) under MATLAB R2014a (The MathWorks Inc., Natick, MA, USA). Stimuli were back-projected on a screen that participants viewed with a mirror attached to the head coil. Participants viewed the images passively in a block design. Each run was divided into 6-second miniblocks. In each miniblock, twelve stimuli of the same category were presented for 500 ms without any inter-stimulus interval. Each of these miniblocks was followed by a 6-second fixation block. Eight miniblocks of intact images (two per category), and four miniblocks of the phase-scrambled versions of the images were presented per run. Within each run, miniblocks were pseudo-randomized. All

participants completed five runs of this experiment which resulted in 455 functional volumes – 91 functional volumes per run. One run lasted 3 minutes and 6 seconds.

2.2.2 tDCS sessions.

A tDCS 1-channel stimulator (TCT Research Limited, Hong Kong) was used to elicit a direct current via a pair of rectangular-shaped rubber electrodes (surface: 24.75 cm^2) placed inside sponges and kept in place using non-conductive tissue straps. The sponges were soaked in a 0.9% sodium chloride solution before application. The current was set to 2.0 mA delivered for 20 minutes. In the cathodal stimulation sessions, the cathode electrode was placed above the left IPL, and the anode electrode was placed on the participant's contralateral deltoid muscle. In the anodal stimulation sessions, the electrodes were reversed. In the control sessions, no electrodes were placed as no electrical stimulation was applied.

To locate the stimulation site for each participant we used one of two possible strategies that emulate what has been used in neuromodulation research hitherto – the use of the 10/20 EEG system, and the use of neuronavigation over native anatomical and functional MRI data. In 6 participants we used the 10/20 EEG system to define left IPL, and chose the location of the electrode P3 as our target area (e.g., Herwig, Satrapi, & Schönfeldt-Lecuona, 2003). For the remaining participants, we first defined IPL in each participant's native space by using functional data from control sessions. Specifically, we contrasted the responses for tool and animal stimuli, and then used neuronavigation (Brainsight, Rogue Research) to set the stimulation site. tDCS was delivered directly before the fMRI experiment, outside of the MR scanner. The electrodes were removed when participants entered the scanner.

2.3 *Image acquisition*

All MRI data were acquired on a 3T MAGNETOM Trio whole body MR scanner (Siemens Healthineers, Erlangen, Germany) using a standard 12-channel head coil. Structural MRI data were acquired using a T_1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence (repetition time (TR) = 2530 ms, echo time (TE) = 3.29 ms, flip angle (α) = 7°, field of view (FoV) = 256 × 256, matrix size = 256 × 256, bandwidth (BW) = 200 Hz/px, parallel acquisition technique GRAPPA acceleration factor 2). For fMRI data, a T_2*-weighted gradient echo echo planar imaging (EPI) sequence (TR = 2000 ms, TE = 30 ms, FoV = 256 × 256, matrix size = 64 × 64, α = 90°, BW = 1562 Hz/px) was used. Each image volume consisted of 30 contiguous transverse slices recorded in interleaved slice order oriented parallel to the line connecting the anterior commissure to the posterior commissure covering the whole brain. Before pre-processing, the first two volumes of each run were discarded to allow for T_1 saturation effects.

2.4 Analysis

Preprocessing, single subject and group analyses were conducted with Statistical Parametric Mapping software (SPM12 (v6685), Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, UK) implemented on MATLAB R2013a. Functional volumes were slice time corrected to reference slice 1 (middle slice in time) and realigned to the third volume by minimizing the mean square error (rigid body transformation) in order to correct for head movement. Six measurements were removed because of excessive motion estimates (greater than 2.5 mm in translation and 3° in rotation), resulting in a final sample of 24 measurements. The created mean image was coregistered to each participant's MPRAGE which was normalized into standard stereotactic space (Montreal Neurological Institute, Quebec, Canada) using tissue probability maps in SPM12. The nonlinear transformation

parameters were then applied to the functional images. To reduce spatial noise, the images were smoothed with an 8 × 8 × 8 mm^3 full-width at half-maximum Gaussian kernel. To remove low-frequency noise, a high-pass filter (cutoff 1/128 Hz) was included and the time series were corrected for serial autocorrelations using first-order autoregressive models (AR(1)).

For each of the 24 measurements, a fixed effects analysis was performed independently by setting up a general linear model (GLM) including the following experimental conditions: tools, animals, faces, places, phase-scrambled pictures and fixation. These inputs were convolved with a canonical hemodynamic response function (first order expansion) to create the design matrix. The six parameters describing the rigid body transformation were implemented as confound variables in the statistical analyses to covary out signal correlated with head motion.

On a second-level analysis, individual contrasts *tools* > *phase-scrambled* and *tools* > *faces* were employed using a GLM flexible factorial design (two-stage procedure as described in Henson & Penny, 2013) with participant, session and contrast as main factors and session-by-contrast as the interaction term. Results were considered significant at $p < 0.05$ on a voxel-level, whole-brain corrected for multiple comparisons using a family-wise error rate. Peak voxel selection and extraction of evoked BOLD responses were done using Anatomical Automatic Labeling2 (Tzourio-Mazoyer et al., 2002) and rfxplot (Gläscher, 2009) toolboxes for SPM12, respectively. For extraction of evoked BOLD responses, a search volume (10 mm sphere) was defined based on the second level analysis contrast control session-by-*tools* > *faces*. Within this search volume, individual peaks were selected for visualization of group inference data by rfxplot.

3. Results

As can be seen in Figure 1, the activation of the left IPL for tools is dependent on whether the fMRI experiment was preceded by an anodal or cathodal tDCS session – tool-specificity is more distinct in the anodal session when compared to the cathodal session ($t(21) = 7.81$, $p < 0.05$). Interestingly, the anodal session did not differ statistically from the control session ($t(21) = 1.37$, $p > 0.05$), whereas the cathodal session led to less explicit tool-related responses than the control session ($t(21) = 6.93$ $p < 0.05$; corrected for multiple comparisons using a Family-wise error rate; see Fig. 1B). In fact, the effect of tDCS is clearly stronger over the BOLD responses for the category of tools, as compared to the other experimental conditions (see Fig. 1C).

4. Discussion

Our data unequivocally shows that applying tDCS (within the range of stimulation parameters typically used) does modulate neural activity at the target area. Consequently, these data favor the idea that tDCS can modulate behavior, and hence fulfill the promising role of tDCS as a technique to be used both in understanding the human mind, as well as in improving our ability to treat neural and psychiatric disorders.

This is important because the efficacy of tDCS in modulating behavior and ameliorating neurological and neuropsychiatric conditions has been recently challenged. For instance, in Horvath and colleagues' systematic reviews (2015a, 2015b; see also Dedoncker et al., 2016) reliable effects of tDCS were obtained only over a peripheral neurophysiological measure – motor evoked potentials – but not on more central measures such as in fMRI or EEG data. However, other systematic reviews highlight the potential efficacy of tDCS in a variety of measures and conditions (e.g., Joyal & Fecteau, 2016; Kekic et al., 2016; Shin et al., 2015). In fact, there have been some indications that tDCS may modulate neural activity. For instance, Callan and colleagues

(Callan, Falcone, Wada, & Parasuraman, 2016; see also Keeser et al., 2011; Merzagora et al., 2010; Pena-Gomez et al., 2012; Polanía, Nitsche, & Paulus, 2011) showed that tDCS stimulation over right posterior parietal cortex altered resting state connectivity. Moreover, Schestatsky, Morales-Quezada and Fregni (2013; see also Antal et al., 2015; Jacobson, Koslowsky, & Lavidor, 2012) compared the EEG signal before and after tDCS stimulation, and showed attenuation of cortical activity in parietal cortex as a result of tDCS stimulation.

Similarly, the efficacy of tDCS in clinical settings has also been systematically explored, with overall promising results (e.g., Cappon, Jahanshahi, & Bisiacchi, 2016; Kekic et al., 2016; Lefaucheur et al., 2017). For instance, Lefaucheur and colleagues (2017) found that while there may be limited evidence for making any Level A recommendation (definite efficacy) for the use of tDCS in any clinical condition, Level B recommendation (probable efficacy) is suggested for some neurological and psychiatric disorders (e.g., non-resistant major depression).

Importantly, our data expands these extant results because we show that we can alter neural activity within the target area for specific experimental conditions (e.g., in a domain-specific way; Caramazza & Shelton, 1998; see also e.g., Almeida 2007; Almeida et al, 2013; Marques, Raposo, & Almeida, 2013), and that this modulation is dependent on the polarity of the stimulation used. Furthermore, the fact that these effects were obtained in an experimental situation where the target area was already engaged in processing one of its preferred stimuli (i.e., tools), is in line with the idea that tDCS effects are activity-dependent (e.g., Fertonani & Miniussi, 2016; Fregni et al., 2005; Gill, Shah-Basak & Hamilton, 2015; Senço et al., 2015; Stagg & Nitsche, 2011). That is, tDCS is effective in modulating the response of neurons that are at or within close-range of their firing threshold. It may well be this mechanistic property of tDCS

that explains why no neural firing was elicited after the application of tDCS in an inert neural system (Buzsáki, 2016), as this system's biochemical and biophysical properties, as well as threshold activity, are not comparable to a living and engaged tissue.

Finally, our results stress the importance of making particular experimental design options when implementing tDCS, in line with previous proposals (e.g., Brunoni et al., 2012; Martins, Fregni, Simis, & Almeida, 2016). In particular, selection of experimental designs that take into consideration the putative cognitive processes happening within the target areas is of the utmost importance, perhaps extending the recommendations and considerations put forth by Horvath and colleagues (2015a, 2015b).

Despite the potential implications of the results presented herein, there are some aspects of our experimental set up that may limit our conclusions. For instance, we do not have data regarding the effects of this same stimulation, and concomitant modulation of neural activity, on behavioral performance. Nevertheless, it may be reasonable to assume that these parameters would affect performance on tasks that are dependent on tool processing. Moreover, in this study we were limited to a relatively small sample of participants. While this is a weakness of our study, and a result of the complexities associated with multiple-session and multimodal research, the effects obtained are reliable even under strict multiple comparison corrections.

To sum up, this study provides important data on the efficacy of tDCS by showing that the use of tDCS can modulate neural activity, does so in a polarity-specific way, and its effects seem to be stronger over cognitive processes already at play at the target area.

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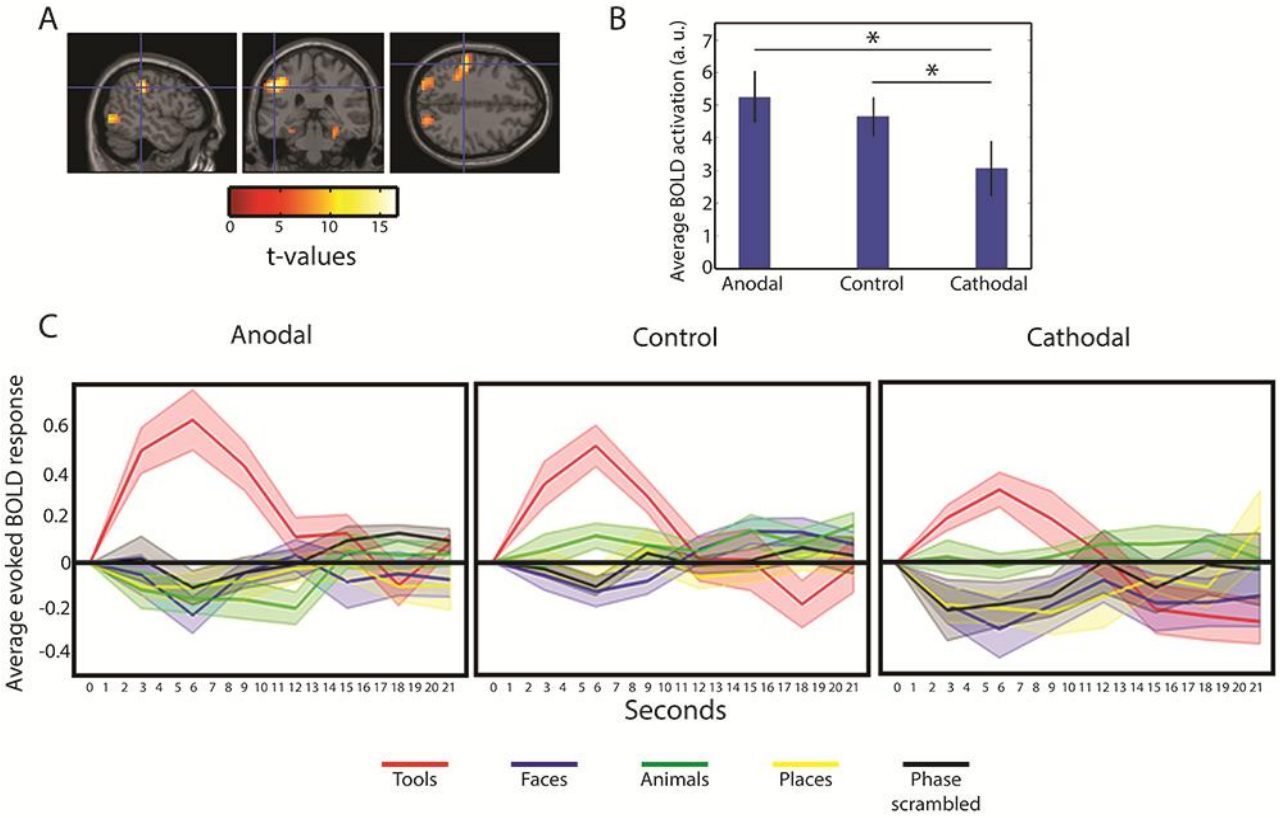
7. Figures

Figure 1. Modulation of neural activity by tDCS session.



8. Figure Legends

Figure 1. Modulation of neural activity by tDCS session. (A) Overlay of *t*-map on SPM T_1-template image with activation patterns at left Inferior Parietal Lobule (x = -50, y = -32, and z = 38 according to Anatomical Automatic Labeling Atlas, coordinates in Montreal Neurological Institute space notation). Activation denotes the interaction term session-by-contrast for contrast *tools* > *faces* in the control session. Results are whole-brain corrected for multiple comparisons using a Family-wise error rate ($p < 0.05$, voxel-level). Note that colors indicate *t*-scores. (B) Average BOLD activation for the contrast *tools* > *faces* across tDCS sessions at the crosshair location in A. There is a reduction in tool-specific activation in the cathodal session when compared to the anodal and control sessions. The error bars denote the standard error of the mean. * $p < 0.05$, FWE corrected. (C) Visualization of the average evoked BOLD response for each experimental conditions (i.e., tools, faces, animals, places and phase-scrambled images). There is a reduction in the average evoked BOLD response for tools in the cathodal session when compared to the average evoked BOLD response for tools in the anodal and control sessions. The shaded areas denote the standard error of the mean.