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Research paper

Effects of transcranial direct current stimulation for treating depression: A modeling study

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) above the left dorsolateral prefrontal cortex (lDLPFC) has been widely used to improve symptoms of major depressive disorder (MDD). However, the effects of different stimulation protocols in the entire frontal lobe have not been investigated in a large sample including patient data.

Methods: We used 38 head models created from structural magnetic resonance imaging data of 19 healthy adults and 19 MDD patients and applied computational modeling to simulate the spatial distribution of tDCS-induced electric fields (EFs) in 20 frontal regions. We evaluated effects of seven bipolar and two multi-electrode 4 × 1 tDCS protocols.

Results: For bipolar montages, EFs were of comparable strength in the lDLPFC and in the medial prefrontal cortex (MPFC). Depending on stimulation parameters, EF cortical maps varied to a considerable degree, but were found to be similar in controls and patients. 4 × 1 montages produced more localized, albeit weaker effects.

Limitations: White matter anisotropy was not modeled. The relationship between EF strength and clinical response to tDCS could not be evaluated.

Conclusions: In addition to lDLPFC stimulation, excitability changes in the MPFC should also be considered as a potential mechanism underlying clinical efficacy of bipolar montages. MDD-associated anatomical variations are not likely to substantially influence current flow. Individual modeling of tDCS protocols can substantially improve cortical targeting. We make recommendations for future research to explicitly test the contribution of lDLPFC vs. MPFC stimulation to therapeutic outcomes of tDCS in this disorder.

1. Background

Transcranial direct current stimulation (tDCS) is one of the most widespread non-invasive brain stimulation (NIBS) methods that have been used for alleviating symptoms of major depressive disorder (MDD). During conventional bipolar tDCS, two electrodes, an anode and a cathode, are placed on the head, and the stimulator is set to deliver weak (typically 1 or 2 mA) currents to the brain for 8–20 min (Filmer et al., 2014; Miniussi et al., 2013; Antal et al., 2017). Early animal studies provided evidence that polarizing currents applied to the cortical surface shift the resting membrane potential of pyramidal neurons in a polarity-dependent manner, which in turn can facilitate or inhibit their spontaneous and stimulus-evoked activity under the anode and cathode, respectively (Bindman et al., 1964; Purpura and McMurtry, 1965). In line with these findings, human studies have shown that tDCS induces polarity-specific effects in the motor or sensory cortex, although results are less consistent for prefrontal cortex (PFC) stimulation (Antal et al., 2003; Nitsche and Paulus, 2000; Tremblay et al., 2014).

TDCS is primarily applied above the left dorsolateral prefrontal cortex (lDLPFC) in MDD, a region that was shown to be hypoactive in this disorder (Fales et al., 2008; Grimm et al., 2008; Siegle et al., 2007). In healthy volunteers, anodal tDCS suppressed the evaluation of emotionally negative stimuli (Boggio et al., 2009; Maeoka et al., 2012; Peña-Gómez et al., 2011) and improved frustration tolerance in a demanding cognitive task (Plewnia et al., 2015a). Thus, it is reasonable to

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assume that by increasing excitability in the left DLPFC, dysfunctional control over negative thoughts and attentional bias towards negative stimuli can be restored in MDD patients, leading to significant improvement in symptomatology (Disner et al., 2011; Plewnia et al., 2015b; Rive et al., 2013). In support of this, successful pharmacotherapy, cognitive therapy or invasive brain stimulation have all been associated with normalization (i.e., enhancement) of lDLPFC activity (Bench et al., 1995; DeRubeis et al., 2008; Mayberg et al., 2005).

Since the first report on the clinical efficacy of anodal tDCS over the lDLPFC in MDD (Fregni et al., 2006a), nine double-blind, sham-controlled studies were conducted involving more than 300 patients (Bennabi et al., 2015; Blumberger et al., 2012; Boggio et al., 2008; Brunoni et al., 2013, 2017; Loo et al., 2010, 2012, 2018; Palm et al., 2012). Still, only five studies reported significant improvements in symptoms severity when compared to sham stimulation (Boggio et al., 2008; Brunoni et al., 2013, 2017; Fregni et al., 2006a; Loo et al., 2012), which might be related to different sample sizes, dissimilarities between stimulation protocols, between-patient variations in brain anatomy and/or patient selection criteria. However, a recent meta-analysis that included individual patient data of six randomized, sham-controlled, double-blind trials provided clear evidence for the superiority of active tDCS versus sham stimulation (Brunoni et al., 2016a).

Studies reviewed so far offer a relatively straightforward model for understanding the clinical effects of tDCS in MDD: (1) in the healthy, the lDLPFC is involved in suppressing the influence of negative emotional stimuli on behavior, (2) the lDLPFC is hypoactive in depression, (3) processes linked to lDLPFC are implicated in the psychopathology of MDD, and (4) successful treatment normalizes lDLPFC activity in MDD. Due to the fact that several studies have successfully used tDCS to influence neurophysiological and/or behavioral outcomes by placing the electrodes above the region of interest (Antal et al., 2003; Meinzer et al., 2012; Nitsche et al., 2007; Nitsche and Paulus, 2000), it is usually assumed that the primary effects of tDCS are manifested under the electrode pads. However, the spatial resolution of tDCS is rather poor: Given that the current flows from the anode towards the cathode, substantial effects should also be expected in brain areas situated between the two electrodes. This assertion was confirmed by modeling and neuroimaging studies, with stimulation-induced electric fields (EFs) and hemodynamic responses being very strong in regions between the electrodes (Antal et al., 2011; Bai et al., 2014; Baudewig et al., 2001; Bikson et al., 2010a; Datta et al., 2009; Datta, 2012; Laakso et al., 2016; Lang et al., 2005; Miranda et al., 2013; Seibt et al., 2015). These results raise the possibility that tDCS-associated behavioral effects might also be linked to the stimulation of regions that are not intentionally targeted.

In this study, we used computational modeling to analyze the spatial distribution of EFs in realistic head models created from structural magnetic resonance imaging (MRI) scans of 19 healthy adults and 19 MDD patients. Simulations were performed on a relatively large cohort of participants because inter-individual differences in head and brain anatomy were shown to significantly influence current flow (Datta, 2012; Laakso et al., 2016; Opitz et al., 2015; Seibt et al., 2015). Given the evidence for systematic anatomical alterations in MDD (Bora et al., 2012; Kempton et al., 2011; Price and Drevets, 2010; Schmaal et al., 2017), we also included head models created from patient data to assess whether and to what extent healthy individuals and MDD patients differ in terms of the spatial distribution of tDCS-induced EFs in the brain. We compared the effects of five montages used in the six studies included in a recent meta-analysis because, when merged together in the individual patient data approach, these were shown to be significantly superior to sham stimulation in MDD (Brunoni et al., 2016a). In addition, we simulated the protocols of the two most recent double-blind randomized studies involving the largest patient groups so far (Brunoni et al., 2017; Loo et al., 2018). Based on earlier studies that implicated stronger EFs in regions between electrode pads, we expected to find robust stimulation-related effects outside the DLPFC (Bikson et al., 2010a; Datta et al., 2009; Miranda et al., 2013; Seibt et al., 2015). Finally, we simulated the effects of two 4×1 tDCS montages to make recommendations for an improved protocol with more selective targeting of MDD-associated areas (Datta et al., 2008, 2009).

2. Methods and materials

2.1. Participants

High-resolution head models were created from T1-weighted anatomical images that were collected in a separate functional MRI study (Lepping et al., 2016). The data was obtained from the OpenfMRI database (https://openfmri.org/; accession number: ds000171). Structural scans of 19 healthy adult participants with no history of depression or other psychiatric disorders (11 females; mean ± SD age: 28.79 ± 10.86) and 19 unmedicated patients formerly diagnosed with MDD and experiencing a depressive episode at the time of the scanning (11 females; mean ± SD age: 33.52 ± 13.35) were used.[2] For full details regarding demographic data, we refer to the original paper (Lepping et al., 2016).

2.2. Creation of head models

The workflow for data extraction is shown in Fig. 1. Except for four manual steps (see Supplementary methods), all procedures were done in a fully automated manner, using a pipeline developed in Nipype (http://nipype.readthedocs.io/en/latest/) (Gorgolewski et al., 2011). Automated tissue segmentation was performed in SPM12 (Friston et al., 1994) for skin, skull, eyeballs and CSF, and in FreeSurfer (Fischl et al., 1999) for gray and white matter. We used an extended version of SimNIBS 2.0 (Thielscher et al., 2015), a freely available software package for simulating the effects of NIBS techniques (www.simnibs.org/) for creating the final head models. Head meshes consisted of approximately 3,200,000 tetrahedral elements, assigned to six tissue types (Supplementary Fig. 1).

2.3. TDCS simulations and data extraction

TDCS electrodes for the seven bipolar montages were sized and positioned as described in the original papers (Table 1). Electrode parameters and orientations are presented in Supplementary methods. Head models for all participants and the consistency of electrode placement for one montage are shown in Supplementary Fig. 2. For 4×1 montages, four surrounding cathodes were positioned around the central anode to form a circle with a radius of approximately 7 cm (Villamar et al., 2013). The central electrode was placed above the target region, which was either the lDLPFC (electrode F3) or the medial prefrontal cortex (MPFC; electrode Fz). The MPFC was chosen because our analysis for the bipolar montages indicated especially strong tDCS fields in this region.

After setting the current intensities for all montages[3] (Table 1), we ran field calculations based on the Finite Element Method (FEM) (Saturnino et al., 2015). Tissue conductivities are shown in Supplementary Table 1. The resulting spatial maps of tDCS-induced EF distributions for each participant and montage were saved as two-dimensional maps corresponding to the middle of the cortical sheets of individual head models, registered to the average surface ('fsaverage') of FreeSurfer. These reconstructed cortical surfaces were used for atlas-based automated parcellation of the frontal lobe into 20 regions (10 labels per hemisphere: primary motor cortex, lateral premotor cortex,

[2] Data of one control participant ("sub-control20") was excluded due to technical problems with head model creation.

[3] In the montage used by Palm et al. (2012), the stronger stimulation intensity of 2 mA was applied because this was associated with slightly better clinical outcome.