Journal of Affective Disorders 167 (2014) 251–258

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research Report

A pilot study of alternative transcranial direct current stimulation electrode montages for the treatment of major depression

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ARTICLE INFO

Article history:
Received 19 March 2014
Received in revised form
12 June 2014
Accepted 12 June 2014
Available online 18 June 2014

Keywords:
Depression
Stimulation
Therapy
Direct current
Computer simulation

ABSTRACT

Background: Typically, transcranial direct current stimulation (tDCS) treatments for depression have used bifrontal montages with anodal (excitatory) stimulation targeting the left dorsolateral prefrontal cortex (DLPFC). There is limited research examining the effects of alternative electrode montages.
Objective/hypothesis: This pilot study aimed to examine the feasibility, tolerability and safety of two alternative electrode montages and provide preliminary data on efficacy. The montages, Fronto-Occipital (F-O) and Fronto-Cerebellar (F-C), were designed respectively to target midline brain structures and the cerebellum.
Methods: The anode was placed over the left supraorbital region and the cathode over the occipital and cerebellar region for the F-O and F-C montages respectively. Computational modelling was used to determine the electric fields produced in the brain regions of interest compared to a standard bifrontal montage. The two montages were evaluated in an open label study of depressed participants ($N=14$). Mood and neuropsychological functioning were assessed at baseline and after four weeks of tDCS.
Results: Computational modelling revealed that the novel montages resulted in greater activation in the anterior cingulate cortices and cerebellum than the bifrontal montage, while activation of the DLPFCs was higher for the bifrontal montage. After four weeks of tDCS, overall mood improvement rates of 43.8% and 15.9% were observed under the F-O and F-C conditions, respectively. No significant neuropsychological changes were found.
Limitations: The clinical pilot was open-label, without a control condition and computational modelling was based on one healthy participant.
Conclusions: Results found both montages safe and feasible. The F-O montage showed promising antidepressant potential.

1. Introduction

Transcranial direct current stimulation (tDCS) is a neuromodulatory technique that involves the passing of a weak electric current to the brain through electrodes placed on the scalp. tDCS modulates cortical activity by polarising the resting membrane potential and influencing the likelihood of neurons firing (Bindman et al., 1964; Purpura and McMurtry, 1965). Studies in the motor cortex have demonstrated that anodal stimulation increases cortical excitability, whereas cathodal stimulation produces the opposite effect, diminishing cortical excitability (Nitsche and Paulus, 2000, 2001). If the stimulation is given at sufficient intensity and duration, effects lasting up to 90 min can be induced after a single session of tDCS (Nitsche and Paulus, 2000, 2001). Repeated stimulation sessions have also been shown to lead to cumulative changes in cortical excitability (Alonzo et al., 2012; Galvez et al., 2013). These principles underlie the therapeutic potential of tDCS which has been studied clinically as a treatment for illnesses and disorders associated with maladaptive cortical functioning (Arul-Anandam and Loo, 2009; Brunelin et al., 2012; Fregni et al., 2005). For example, it has been shown that anodal stimulation of the left dorsolateral prefrontal cortex (DLPFC) can improve symptoms of depression (Arul-Anandam and Loo, 2009; Brunoni et al., 2013; Kalu et al., 2012; Loo et al., 2012).

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http://dx.doi.org/10.1016/j.jad.2014.06.022
0165-0327/

A recent meta-analysis of randomised controlled trials has demonstrated that tDCS results in an average of 29% reduction in the severity of depressive symptoms after 5–15 treatment sessions (Kalu et al., 2012). However, a meta-analysis based on responder numbers failed to find a significant difference between active and sham stimulation (Berlim et al., 2013). Ongoing research efforts to increase the efficacy of tDCS for depression have focused on the use of higher "dosages". There has been a gradual increase in current intensities, stimulation duration and number of stimulation sessions used in clinical trials, though the size of the clinical effect to date has been relatively modest in treatment-resistant samples (Berlim et al., 2013; Blumberger et al., 2012; Kalu et al., 2012; Loo et al., 2012). In fact, a recent study examining excitability in the motor cortex of healthy participants found that longer stimulation durations and stronger current intensities do not necessarily result in greater excitability (Batsikadze et al., 2013), though the applicability of these findings to therapeutic uses in clinical populations is unknown. Further optimisation of stimulation parameters may include increases in stimulus parameters, although increases in current intensity and stimulus durations are limited by tolerability and the risk of skin damage (Rothwell, 2012). As such, alternative methods of optimising treatment efficacy, including alternative electrode montages, must also be considered.

Electrode montage determines current direction and electric field intensities in cerebral tissue (Bikson et al., 2012; Dmochowski et al., 2012). The standard electrode montage used in recent depression trials has involved placing the anode over the left dorsolateral prefrontal cortex (DLPFC; F3 on the 10-20 EEG system). This approach is based on research which suggests that this region has a key modulating role in depression, as treatments using transcranial magnetic stimulation (TMS) to increase activity in this region have been shown to be efficacious (George et al., 2010; O'Reardon et al., 2007; Slotema et al., 2010). The cathode is then either placed over the right supraorbital or lateral orbital (F8) area, or alternatively over the right DLPFC (F4) (Blumberger et al., 2012; Boggio et al., 2008; Brunoni et al., 2013; Fregni et al., 2006; Loo et al., 2012, 2010; Palm et al., 2012). Although to-date modern tDCS montages for depression have focused on anodal stimulation of the left DLPFC, evidence suggests that depression is a systems-wide disorder involving multiple cortical, subcortical and limbic brain regions (Anderson et al., 2012; Bora et al., 2012; Fox et al., 2012). Preliminary data suggests that tDCS given using alternative montages which more widely stimulate the cerebrum, including subcortical regions, may have greater efficacy (Martin et al., 2011).

Apart from the DLPFC, research interest has focused on regions such as the anterior cingulate cortex (ACC), in particular the subgenual ACC (sgACC), as well as the nucleus accumbens, insula, hippocampus, ventral capsule and striatum (Anderson et al., 2012; Fox et al., 2012; Mayberg, 2009). For example, imaging studies have demonstrated overactive metabolic activity in the sgACC, with normalisation following clinical response to treatment (Bewernick et al., 2010; Mayberg et al., 2000). Further, studies using the more invasive technique of deep brain stimulation (DBS) have demonstrated clinical efficacy through targeting the sgACC and other sub-cortical structures (Bewernick et al., 2010; Holtzheimer and Mayberg, 2012; Lozano et al., 2012; Malone et al., 2009). There is additionally increasing suggestion that the cerebellum may also play a role in emotion dysregulation and depressive pathophysiology (Fitzgerald et al., 2008; Hoppenbrouwers et al., 2008; Schutter and van Honk, 2005), thus offering another potential target for novel therapies. While originally thought only to be involved in motor function, the cerebellum is now thought to play a role in mood regulation through its functional and structural connections with the prefrontal cortex, brain stem and limbic structures (Beyer and Krishnan, 2002; Bostan et al., 2013; Konarski et al., 2005). Further, increased cerebral blood flow in the medial cerebellum and vermis have been associated with depression and have been found to decrease following successful treatment (Konarski et al., 2005; Videbech et al., 2001).

This pilot study aimed to examine the feasibility and safety of two alternative tDCS electrode montages (fronto-occipital, F-O; fronto-cerebellar, F-C), and provide preliminary data on the therapeutic potential of these two montages for the treatment of depression. The electrode montages were designed to target the midline and deep brain structures including the sgACC, nucleus accumbens and basal ganglia, while also delivering anodal left frontal stimulation. The rationale was that these electrode configurations would result in the greatest current flow through midline structures implicated in depression, with the F-C montage also aimed to modulate maladaptive cerebellar activity.

The clinical potential of these new montages was first tested by modelling the electric-fields (E-fields) that would result in key brain regions, and comparing this to our previously used F3–F8 montage (Loo et al., 2012, 2010). Following this, an open-label clinical pilot study of the montages was then conducted.

2. Method

2.1. Computational modelling

T1-weighted 3T MRI head scans of a healthy 35-year-old Asian male subject were obtained from Neuroscience Research Australia, and segmented into several tissue compartments using BrainSuite (Shattuck and Leahy, 2002) and ScanIP (Simpleware Ltd., UK) segmentation software. These tissue compartments included the skin, skull, cerebrospinal fluid (CSF), cerebrum, cerebellum and brainstem (Bai et al., 2014). The skull was further segmented into compact bone tissue (the innermost and outermost layers) and spongy bone tissue (the middle layer). The cerebrum was also segmented into grey matter and white matter. Several brain regions of interest (ROIs), considered important in tDCS therapeutic effects, were further segmented from the brain masks. ROIs examined were cerebellum, brain stem, bilateral DLPFC, bilateral orbitofrontal cortex (OFC), bilateral ACC and bilateral hippocampus. Most compartments of the head models were considered to be electrically homogeneous and isotropic, except the white matter. Electrical conductivities of the tissues can be found in Bai et al. (2014). All head compartments in the tDCS simulations were formulated as passive volume conductors using $\nabla \cdot (-\sigma \nabla \phi) = 0$, where ϕ is the electric potential, σ is the electric conductivity tensor, and ∇ is the del partial derivative operator given by $(\partial/\partial x, \partial/\partial y, \partial/\partial z)^T$. The electric field (E-field) vector was calculated from the negative gradient of potential according to $E = -\nabla\phi$. The model was solved using the COMSOL Multiphysics (v4.3a, COMSOL AB, Sweden) finite-element software package on a standard desktop PC with 24G RAM. Simulation results were analysed by comparing the average E-field magnitude $\overline{E}$ in several ROIs in the brain. Brain E-field distributions (magnitude and direction) with three montages were also investigated. For more detailed methodology, refer to Bai et al. (2014).

2.2. Electrode montages

As shown in Fig. 1, for F-O tDCS, the anode ($5 \times 7\ cm^2$) was placed horizontally over the left supraorbital region, using the AFz and FP1 positions on the 10-20 EEG system as the left and bottom edge boundaries of the electrode. The anode was over the left supraorbital region rather than in the centre of the forehead to avoid shunting of the current along the superior sagittal sinus (Neuling et al., 2012). The cathode was placed with the bottom edge over O1 and O2 ($10 \times 10\ cm^2$). A large cathode was used to reduce the cathodal effects of the stimulation and ensure broad stimulation of the midline structures. The anode was placed in the