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A computational modelling study of transcranial direct current stimulation montages used in depression

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ABSTRACT

Transcranial direct current stimulation (tDCS) is a neuromodulatory technique which involves passing a mild electric current to the brain through electrodes placed on the scalp. Several clinical studies suggest that tDCS may have clinically meaningful efficacy in the treatment of depression. The objective of this study was to simulate and compare the effects of several tDCS montages either used in clinical trials or proposed, for the treatment of depression, in different high-resolution anatomically-accurate head models. Detailed segmented finite element head models of two subjects were presented, and a total of eleven tDCS electrode montages were simulated. Sensitivity analysis on the effects of changing the size of the anode, rotating both electrodes and displacing the anode was also conducted on selected montages. The F3–F8 and F3–F4 montages have been used in clinical trials reporting significant antidepressant effects and both result in relatively high electric fields in dorsolateral prefrontal cortices. Other montages using a fronto-extracephalic or fronto-occipital approach result in greater stimulation of central structures (e.g. anterior cingulate cortex) which may be advantageous in treating depression, but their efficacy has yet to be tested in randomised controlled trials. Results from sensitivity analysis suggest that electrode position and size may be adjusted slightly to accommodate other priorities, such as skin discomfort and damage.

Introduction

Transcranial direct current stimulation (tDCS) is a neuromodulatory technique which involves passing a mild electric current to the brain through electrodes placed on the scalp. This direct constant flow of current modulates underlying cortical activity with specific outcomes related to anodal or cathodal stimulation (Nitsche and Paulus, 2000, 2001). The relative position (electrode montage) and size of the anode and cathode determine the distribution of current density throughout the brain (Bikson et al., 2010; Datta et al., 2011; Lee et al., 2012; Miranda et al., 2009; Wagner et al., 2007). Thus there is potential for stimulation to be focussed on specific cortical brain regions for therapeutic or investigative purposes or more diffuse effects can be produced if widespread activation of brain regions is desired.

A key application of tDCS has been investigated in the treatment of depression. Several recent open label and placebo-controlled trials, and a meta-analysis of mean change in depression scores from placebo-controlled studies suggest that tDCS may have clinically meaningful efficacy (Boggio et al., 2008; Brunoni et al., 2011; Fregni et al., 2006a, 2006b; Kalu et al., 2012; Loo et al., 2012; Martin et al., 2011; Palm et al., 2011). These studies focused on anodal stimulation of the left dorsolateral prefrontal cortex (DLPFC), based on observations that this area has been associated with underactivity in depression (Grimm et al., 2008). However, studies differed in the location of the cathode, i.e. the return electrode — right supraorbital, right lateral orbitofrontal, right DLPFC or in an extracephalic position. Though the anodal left DLPFC electrode is often considered the "active" electrode, the placement of the cathode is important for several reasons: shunting of much of the current over the scalp may occur if the inter-electrode distance is too close (Datta et al., 2008; Miranda et al., 2006; Weaver et al., 1976), current density under the anode is affected by the placement of the reference or "return" electrode (Bikson et al., 2010; Datta et al., 2011), and the pattern of brain areas stimulated will be determined by the overall montage. All of these factors may have important therapeutic implications.

Pathophysiological changes in depression are system-wide, involving a network of various cortical and limbic structures rather than a solitary brain region such as the left DLPFC (Mayberg, 2007). Hypoactivity in cortical regions and hyperactivity in subcortical and limbic regions is often associated with symptoms of depression (Fitzgerald et al., 2008; Mayberg, 1997). Meta-analyses have identified frontal and temporal

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cortices, the insula and cerebellum as regions of hypoactivity while subcortical and limbic regions tend to be hyperactive. This distributed network of structures includes the DLPFC, medial prefrontal cortex (MPFC), orbitofrontal cortex (OFC), as well as the anterior cingulate cortex (ACC), insula and hippocampus (Fox et al., 2012; Mayberg, 2003). Most recently, functional connectivity studies have suggested altered activity at a network level during the resting state (Carballedo et al., 2011). In particular, there is increased functional connectivity in the subgenual anterior cingulate (sgACC), thalamus and OFC in people with depression (Greicius et al., 2007). Further, overactivity in the sgACC has been shown to be strongly negatively correlated with resting state underactivity in the left DLPFC (Fox et al., 2012).

Studies of deep brain stimulation (DBS) in depression have also provided insight into the critical regions involved in depression. Consistent with imaging studies, DBS interventions targeted at the sgACC have demonstrated efficacy in reducing symptoms of depression (Lozano et al., 2012; Mayberg et al., 2005). DBS to specific regions of the basal ganglia such as the nucleus accumbens (NAcc) and the ventral capsule/ventral striatum (VC/VS) have also been found to have significant antidepressant effects (Anderson et al., 2012; Bewernick et al., 2010, 2012; Malone et al., 2009).

As the therapeutic potential of tDCS in psychiatric disorders is further explored, information on how different electrode arrangements determine current density in key brain regions, is essential. This study compared the effects of several DCS montages, with realistic head models reconstructed from MRI head scans, by investigating the brain electric field (E-field) distribution and the average E-field in various brain regions. tDCS montages modelled were those used in recent tDCS depression studies: the F3–supraorbital (F3–SO) montage first used when interest was rekindled in tDCS from 2006 onwards (Boggio et al., 2008; Fregni et al., 2006a, 2006b; Loo et al., 2010; Palm et al., 2011), and modified approaches in which the cathode was moved more laterally to reduce shunting, F3–F8 (Loo et al., 2012), to the right DLPFC, F3–F4 (Brunoni et al., 2011, 2013; Dell'Osso et al., 2012; Ferrucci et al., 2009a, 2009b), or to an extracephalic position to achieve a more widespread pattern of brain activation, F3–extracephalic (F3–EC, brain sites based on the 10–20 EEG system; Martin et al., 2011). The bilateral supraorbital–extracephalic (SO–EC) montage most commonly used in earlier, pre-2000 studies, involving two small anodes at the frontal poles and an extracephalic cathode was also modelled (Arul-Anandam and Loo, 2009; Lippold and Redfearn, 1964; Redfearn et al., 1964). In addition, several hypothetical montages were modelled: supraorbital–occipital (SO–OCC), premised on maximal stimulation of the sgACC and other central and midline subcortical structures; temporal–extracephalic (TMP–EC), prioritising temporal lobe stimulation as neurotrophic changes in this region may have a key role in the pathophysiology of depression (Pittenger and Duman, 2007), and supraorbital–cerebellum (SO–CB), as abnormal cerebellar modulation of the cerebello-thalamo-cortical pathway has been implicated in the mood and cognitive symptoms associated with several psychiatric disorders, including bipolar disorder and depression (Hoppenbrouwers et al., 2008).

The montages were modelled in two subjects — one male and one female — to examine the extent to which inter-individual differences in head anatomy affect variation in electric field with different montages. Finally, a sensitivity analysis was performed to examine the effects of displacing the anodal electrode by ~1 cm, to inform on the likely importance of accuracy in electrode placement in clinical applications.

Methods

Image segmentation and mesh generation

Two different high-resolution computational head models were reconstructed from human subjects. One subject was a 35-year-old Asian male whose MRI head scan, labelled "Msub" (short for male subject), was truncated at the level of cervical vertebra 6. The other was a 42-year-old Caucasian female, labelled "Fsub" (female subject, Fig. 1S in Supplementary data): her scan was truncated at the level of the atlas-axis, i.e., cervical vertebrae 1–2. T1-weighted MRI scans of both subjects were obtained from Neuroscience Research Australia. The scans were sagittally-oriented with voxel resolution of 1 mm × 1 mm × 1 mm. The images of Msub were later down-sampled to 1.5 mm in every dimension.

Head tissue masks were obtained using a combination of automated and manual segmentation softwares. Automated mask generation was performed using BrainSuite, an open-source package from the Laboratory of NeuroImaging at the University of California (Shattuck and Leahy, 2002). Thus, tissue compartments including skin, skull, cerebrospinal fluid (CSF), grey matter (GM) and white matter (WM) were generated from the MRI data. The segmented masks were exported from BrainSuite as grayscale images, and imported into ScanIP (Simpleware Ltd., UK) for manual correction and further processing. The five original masks were hence divided into more compartments:

- masks representing eyes, paranasal sinuses, larynx and cervical vertebrae were separated from the skin and skull, as shown in Fig. 1a. In addition, the major foramina of the skull were included in the skull mask, including the superior orbital fissure, optic canal, foramen ovale and foramen magnum;
- the skull was divided into the cranium and jaw. The cranium was then subdivided into three layers, with spongy bone tissue as the middle layer, and compact bone tissue as the outermost and innermost layers. The jaw was considered compact. These skull compartments are shown in Fig. 1b;
- the brain masks consisted of GM, WM, cerebellum (CB, with brainstem) and the cervical spinal cord (SC), as well as the ventricular system which was later assigned to the CSF mask;
- several brain regions of interest (ROIs), considered important in tDCS therapeutic effects, were further segmented from the GM mask as shown in Fig. 1c — anterior cingulate cortices (ACCs), amygdalae, hippocampi, dorsolateral prefrontal cortices (DLPFCs) and orbitofrontal cortices (OFCs).

In the head models, fat and muscle were included in the skin compartment, due to the fact that their conductivities are of the same order of magnitude as skin conductivity (Gabriel et al., 1996). Similarly, the venous sinuses and cranial arteries were included in the cerebrospinal fluid compartment. Finally, any remaining blank voxels were manually assigned to the most appropriate neighbouring mask.

To examine the effect of an extracephalic clinical electrode montage used in some tDCS studies (Martin et al., 2011; Moliadze et al., 2010), a synthetic upper torso attached to the segmented head was manually painted in ScanIP up to the level above the axilla based on anthropometric measurements (Dreyfuss and Tilley, 1993), as shown in Fig. 1d. A similar approach was used in other studies (Borckardt et al., 2012; Datta et al., 2011, 2012; Mendonca et al., 2011).

The +FE Free meshing algorithm in the +FE module of ScanIP (v4.3) was selected to generate the tetrahedral mesh elements for the high-resolution head models, with a compound coarseness of -30. The meshes were then imported into the COMSOL Multiphysics FE solver (v4.2).

Tissue conductivities

Most compartments of the head models were considered to be electrically homogeneous and isotropic. The electrical conductivity of paranasal sinuses (and larynx) was set to zero. Conductivities of the scalp, compact and spongy bones of the skull, CSF, GM and WM, were assigned mean values from multiple studies (Akhtari et al., 2000, 2002; Baumann et al., 1997; Geddes and Baker, 1967; Gonçalves et al., 2003; Gutierrez et al., 2004; Lai et al., 2005; Oostendorp et al., 2000).