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Cranial electrotherapy stimulation and transcranial pulsed current stimulation: A computer based high-resolution modeling study

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ABSTRACT

The field of non-invasive brain stimulation has developed significantly over the last two decades. Though two techniques of noninvasive brain stimulation — transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) — are becoming established tools for research in neuroscience and for some clinical applications, related techniques that also show some promising clinical results have not been developed at the same pace. One of these related techniques is cranial electrotherapy stimulation (CES), a class of transcranial pulsed current stimulation (tPCS). In order to understand further the mechanisms of CES, we aimed to model CES using a magnetic resonance imaging (MRI)-derived finite element head model including cortical and also subcortical structures. Cortical electric field (current density) peak intensities and distributions were analyzed. We evaluated different electrode configurations of CES including in-ear and over-ear montages. Our results confirm that significant amounts of current pass the skull and reach cortical and subcortical structures. In addition, depending on the montage, induced currents at subcortical areas, such as midbrain, pons, thalamus and hypothalamus are of similar magnitude than that of cortical areas. Incremental variations of electrode position on the head surface also influence which cortical regions are modulated. The high-resolution modeling predictions suggest that details of electrode montage influence current flow through superficial and deep structures. Finally we present laptop based methods for tPCS dose design using dominant frequency and spherical models. These modeling predictions and tools are the first step to advance rational and optimized use of tPCS and CES.

Introduction

The field of non-invasive brain stimulation has developed significantly during the last two decades. The use of neurophysiological, neuroimaging and computer-based modeling tools have contributed to this increased interest and development of this field. As a consequence, techniques that have been explored and used in the past are now being re-explored, with different, optimized parameters of stimulation. Transcranial direct current stimulation is one such example. The use of neurophysiological markers such as transcranial magnetic stimulation-induced cortical excitability and computer-based modeling has optimized parameters of stimulation such as electrode montage, intensity and duration of stimulation (Brunoni and Fregni, 2011; Datta et al., 2008, 2010; Miranda et al., 2006; Nitsche and Paulus, 2000; Wagner et al., 2006, 2007) One highly used method of noninvasive transcranial electrical stimulation — cranial electrotherapy stimulation (CES), with relatively broad clinical use, has not been fully explored.

CES has had relatively broad clinical use following FDA clearance in 1978, and is historically a derivative of neuromodulation approaches dating to the early 20th century including cranial electrostimulation therapy (CET) and electrosleep (ES). CES devices use transcranial pulse current stimulation with dose parameters typically 50 μA to 5 mA intensity, around 100 Hz, typically applied over a session (around 30 min) using surface electrodes on the infra- or supra-auricular structures (Zaghi et al., 2010). Although the CES technique has been used for several decades (Edelmuth et al., 2010) and has been reported to be effective for the treatment of insomnia, depression and anxiety (FDA label indications) in several clinical studies, the mechanisms of action remain unknown. Due to its effect mainly on vegetative symptoms of psychiatric disorders such as sleep, impaired attention and fatigue, it is purported that the application of CES through the maxillo-occipital junction causes current to reach the sub-cortical and brain stem structures. It has been shown that stimulation of these structures causes increased secretion of neurotransmitters, namely serotonin,

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beta endorphin, and norepinephrine (Shealy, 1989); thus being potentially involved with the mechanisms underlying the behavioral effects of CES (Schroeder and Barr, 2001).

In one of the few controlled studies where the physiologic mechanism of action of CES was investigated, electroencephalographic (EEG) changes were reported (Schroeder and Barr, 2001). CES led to changes in alpha and beta frequency ranges suggesting potential neuroplastic and cognitive effects of this technique. Interestingly, similar changes in alpha and beta bands were shown to be associated with a reduction in the emotional-cognitive aspects of pain in a study using transcranial direct current stimulation, which is another type of non-invasive brain stimulation (Maeoka et al., 2012). Though these results are promising, additional studies must be done due to the lack of mechanistic studies, particularly in CES (Edelmuth et al., 2010). Table 1 includes a summary of the most recent studies with CES therapy published in the past 15 years. Moreover a recurring point of contention over the years has been whether low current CES applied through the electrode sites (ear lobes, mastoid processes or the temporal areas) can even reach the underlying cortex to influence neural activity. In fact very limited effort has been invested to quantify the spatial distribution of currents within the human brain using this technique.

Since it is technically difficult to directly assess current flow in structures within the human head, simulations of current flow via computer modeling can be used to predict the intensity and spatial distribution of current flow during transcranial stimulation. Concentric-sphere models have previously been used to calculate CES induced electric fields (Ferdjallah et al., 1996). In recent years, advances in modeling and imaging tools have allowed the development of models with increased realism and precision, resulting in high-resolution (1 mm^3) MRI derived head models that capture gyri/sulci anatomical details (Datta et al., 2009) as well as examine current density distributions through sub-cortical target regions (Dasilva et al., 2012; Parazzini et al., 2012).

We adapted a previously developed high-resolution individualized model of tDCS (Datta et al., 2009) for simulating the effects of CES. We modeled the conventional ear-clip electrode montage and compared it with several novel montages (Brain Gear, Switzerland). We determined induced surface cortical electrical field (EF) to predict spatial focality. In addition, sub-cortical and brain-stem structures implicated in the purported CES beneficial effects were individually analyzed.

Methods

In order to better understand which brain regions are modulated during cranial electrotherapy stimulation (CES), we carried out a high-resolution finite element (FE) model analysis. For comparison, we showed the effects of conventional therapy using ear-clip electrodes versus multiple novel montages like the in-ear, ear-hook and the over-the-ear montages.

MRI derived high-resolution model

The human head model was derived from a high spatial resolution (1 mm^3) 3 T MRI of a male adult healthy subject with no neurological pathologies. Using a combination of tools from FMRIB Software Library (FSL) and Simpleware, the head model was segmented into tissue compartments representing the scalp, skull, CSF, eye region, muscle, gray matter, white matter, and air respectively. In addition to analyzing current flow patterns through structures thought to be implicated in the beneficial effects of CES, structures such as cingulate cortex, thalamus, insula, pituitary gland, pineal gland, hypothalamus, midbrain, pons, and medulla oblongata were also segmented. The head model was limited to the masks being directly derived from the MRI acquisition volume. An artificial neck and shoulder region was thus fused onto the existing segmented head. Stimulation electrodes of various sizes (as mentioned below) were imported as CAD models and placed onto the existing segmented volume to model the different CES montages. The entire model (head and the electrodes) were meshed and exported to a commercial FE solver (COMSOL 3.5a) for final computation of current flow patterns.

Electrode montages

We modeled the following CES montages representing the conventional and the novel montages (see Fig. 1):

1) Conventional ear-clip montage (montage 1):The stimulation electrodes were placed mimicking conventional CES stimulation using ear-clip electrodes. The left ear-clip electrode was energized to a normal current density boundary condition corresponding to 1 mA total injected current. The right ear-clip electrode was applied as the ground boundary condition. All other external surfaces were treated as insulated.
2) Novel in-ear electrode montage (montages 2 and 3):Stimulation electrodes were placed resembling the in-ear headphone locations. The left in-ear electrode was energized to a normal current density boundary condition corresponding to 1 mA total injected current. The right in-ear electrode was applied as the ground boundary condition. All other external surfaces were treated as insulated. In addition, the In-Ear electrode montage was also solved at 150 Hz (montage 3).
3) Novel ear-hook electrode montage (montage 4):Stimulation electrodes were placed resembling the ear-hook headphone locations. The left ear-hook electrode was energized to a normal current density boundary condition corresponding to 1 mA total injected current. The right ear-hook electrode was applied as the ground boundary condition. All other external surfaces were treated as insulated.
4) Novel over-the-ear electrode montage (4 contacts) (montage 5): Stimulation electrodes were placed resembling the over-the-ear

Table 1
Summary of randomized CES trials.

Author	Year	Patient#	Design	Sham controlled	Blinded	Clinical effects
Rose	2009	44	Parallel Randomized Trial	Yes	Double blinded	The CES group showed improvements in sleep disturbance, and depression though neither was statistically significant.
Schroeder	2001	12	Cross-over Trial	Yes	Double blinded	.5 and 100 Hz CES elicited frequency distribution shifts. 100 Hz CES produced greater overall change. These results suggest beneficial changes in mental state.
Southworth	1999	52	Parallel Randomized Trial	Yes	Not Stated	CES significantly improved attention and concentration in a normal adult population.
Scherder et al.,	2006	21	Parallel Randomized Trial	Yes	Blinded	No significant improvements on cognition and (affective) behavior were found between CES treatment and control groups.

Abbreviations: CES: cranial electrical stimulation; TCES: transcutaneous cranial electrical stimulation; CBF: cerebral blood flow.