NeuroImage 181 (2018) 560–567

Contents lists available at ScienceDirect

NeuroImage

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

On the importance of precise electrode placement for targeted transcranial electric stimulation

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A B S T R A C T

Transcranial electric stimulation (TES) is an increasingly popular method for non-invasive modulation of brain activity and a potential treatment for neuropsychiatric disorders. However, there are concerns about the reliability of its application because of variability in TES-induced intracranial electric fields across individuals. While realistic computational models offer can help to alleviate these concerns, their direct empirical validation is sparse, and their practical implications are not always clear. In this study, we combine direct intracranial measurements of electric fields generated by TES in surgical epilepsy patients with computational modeling. First, we directly validate the computational models and identify key parameters needed for accurate model predictions. Second, we derive practical guidelines for a reliable application of TES in terms of the precision of electrode placement needed to achieve a desired electric field distribution. Based on our results, we recommend electrode placement accuracy to be < 1 cm for a reliable application of TES across sessions.

1. Introduction

Transcranial electric stimulation (TES), including transcranial direct current (tDCS) or alternating current (tACS) stimulation, is an increasingly popular method for non-invasive modulation of neural activity in humans (Paulus, 2011). Typically, weak electric currents (e.g. 1 mA) are passed through two or more electrodes attached to the scalp creating a low amplitude electric field in the brain. Repeat administration of these currents is increasingly considered as a potential therapeutic modality for psychiatry due to the ability to produce sustained changes in neural function, possibly by inducing neuroplastic changes (Kuo et al., 2014). As TES moves towards the clinical realm, the need for consistent, reliable administration of TES across sessions and individuals becomes increasingly important.

A common practice in the application of TES is to equate the placement of electrodes across individuals using anatomical landmarks defined using a reference system, such as the International 10–20 system (Woods et al., 2016). However, intracranial electric field measurements have shown that the spatial distribution of the electric fields (including orientation and strength) during TES can have intricate patterns (Huang et al., 2017; A. Opitz et al., 2016a), which significantly increases the difficulty of creating reliable stimulation protocols. In this regard, current practices tend to rely on consistent placement of reference systems for the identification of anatomical landmarks to guide the targeting of stimulation; however, there have been only limited efforts to establish acceptable tolerance limits for variation in placement across administrations.

Realistic computational models of the brain offer a potential solution for increasing the spatial accuracy of targeting for stimulation. In addition to accounting for the impact of the expected variations in anatomy among individuals, they provide a medium for making predictions about the influences of anatomical factors that can vary across the lifespan, or can be affected by disease processes (e.g., Alzheimer's disease). Examples of such factors include gyral folding, CSF thickness, and skull composition (Opitz et al., 2015). Additionally, they can provide insights into the impact of commonly overlooked technical factors, such as skin conductance and electrode size (Saturnino et al., 2015). Researchers are increasing the use of realistic brain models to devise electrode montages, and to interpret variations in TES outcomes within and across studies investigating differences in electric field spread and strength across

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https://doi.org/10.1016/j.neuroimage.2018.07.027
Received 3 October 2017; Received in revised form 13 June 2018; Accepted 12 July 2018

1053-8119/

individuals (Laakso et al., 2015).

Here, we leverage individual-specific realistic brain models to inform our understanding of variations in the electric field generated by differences in electrode placement from administration to administration, and generate practical guidelines for decreasing this variability. We: a) carry out a validation for the specific realistic brain modeling framework used in the present work; this work confirms the findings of an initial validation effort recently carried out in ten neurosurgical patients (Huang et al., 2017) and extends it to provide an understanding of the impact of skull defects and surgical materials on findings, and b) use the validated model to establish estimates of the tolerance limits for the placement of electrodes; tolerance is determined with respect to the consistency of the spatial distribution of the electric field and that of the electric field strength generated. This allows us to derive an estimate of the minimal accuracy needed for electrode placement to reliably administer targeted transcranial electrical stimulation.

2. Methods

2.1. Participants

2.1.1. Model validation

Experimental data was obtained from a 29-year-old male patient and a 35-year old female patient with refractory epilepsy who underwent presurgical monitoring at North Shore University Hospital. The experimental protocol was approved by the Institutional Review Board of the Feinstein Institute for Medical Research; the patients gave informed consent in accordance with the ethical standards of the Declaration of Helsinki and monitored by the local Institutional Review Board. *Generalization to neurotypical participants*. To generalize findings from the patient, anatomical MR data from 25 participants of the Human Connectome Project were used to create individual realistic FEM models.

2.1.2. Electrode placement

The male patient was implanted with left subdural grid, strip, and depth electrodes (Integra Lifesciences Corp.). The female patient was implanted with bilateral s-EEG electrodes (Adtech Medical Instrument Corp.). The number and placement of electrodes were determined solely by clinical requirements. Electrode positions were identified on a post-implantation CT scan and registered in a two-step procedure - first to the post-implantation MR and then to the pre-implantation MR. The patients were monitored until sufficient data was collected to identify the seizure focus for 8 days. Continuous intracranial video-EEG monitoring was performed with standard recording systems (XLTEK EMU 128 LTM System) with a sampling rate of 500 Hz.

2.1.3. Transcranial electrical stimulation

TES measurements for model validation were conducted in a single session for each patient. Two circular saline-soaked sponge electrodes (25 cm^2 surface area) were attached to the scalp over the left and right temple (bilateral montage). The electrode montage was chosen to maximize electric field strength in areas with best coverage of recording contacts. A 1 Hz alternating current of 1 mA was applied (Starstim, Neuroelectrics) for 2 min with a ramp up/down of 10 s. The locations of stimulation electrodes were recorded with photographs.

2.2. In vivo field measurements

The measurement of intracranial electric fields generated by TES is central to model validation. In order to estimate electric fields from the recorded potentials we performed the following analysis steps: From each channel we subtracted the mean voltage over a time interval of 1s preceding stimulation onset to correct for baseline differences between channels and bandpass filtered the recorded voltages between 0.5 Hz and 1.5 Hz. To estimate the electric field strength during TES, we calculated the numerical gradient of the recorded voltages using the symmetric difference quotient. The numerical gradient was calculated along the implanted electrodes at the peak up-phase of the recorded voltages. For the central region covered with grid electrodes two gradients were computed along both grid axes and combined by vector addition. To enhance robustness of the electric field estimates we calculated the mean electric field over five stimulation cycles. The computation of the electric field along the electrodes measures the projection of the electric field along a vector spanned by the contacts.

3. Data analysis and modeling

3.1. Realistic brain model generation

To identify those factors that most impact the findings generated using realistic brain models, we created four distinct FEM head models of increasing complexity in multiple steps (see Fig. 1). First, we reconstructed WM, GM, ventricles and skin surfaces from the high-resolution pre-implantation T1 using Simnibs (Thielscher et al., 2015; Windhoff et al., 2013). The skull was segmented based on intensity thresholding and manual corrections from the co-registered CT image. Most importantly, the skull reconstruction included small openings present from the surgery (Fig. 1B, upper left panel). The inner skull surface marks the beginning of the CSF and the outer skull surface the transition to the skin. To estimate the effect of accurate skull modeling on the estimation of TES electric fields we created a second skull model in which the skull openings were removed manually in the surface reconstruction (Fig. 1B, upper

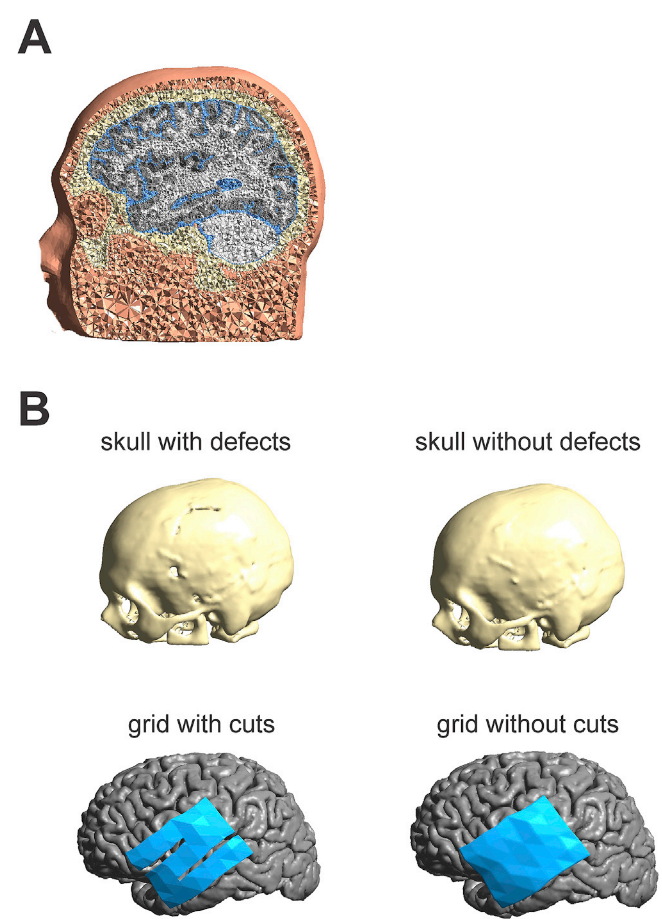

Fig. 1. A) Illustration of the FEM head model including scalp, skull, CSF, GM and WM. B) Illustration of four different models investigated. 1. Skull reconstructed from a CT image (upper left). Small skull defects from the surgery were included in the skull model. 2. Skull model with surgical defects closed (upper right). Model with ECOG grid exhibiting small cuts from the surgery (lower left). Model with closed ECOG grid (lower right).