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Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields

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ABSTRACT

Recently, multifocal transcranial current stimulation (tCS) devices using several relatively small electrodes have been used to achieve more focal stimulation of specific cortical targets. However, it is becoming increasingly recognized that many behavioral manifestations of neurological and psychiatric disease are not solely the result of abnormality in one isolated brain region but represent alterations in brain networks. In this paper we describe a method for optimizing the configuration of multifocal tCS for stimulation of brain networks, represented by spatially extended cortical targets. We show how, based on fMRI, PET, EEG or other data specifying a target map on the cortical surface for excitatory, inhibitory or neutral stimulation and a constraint of the maximal number of electrodes, a solution can be produced with the optimal currents and locations of the electrodes. The method described here relies on a fast calculation of multifocal tCS electric fields (including components normal and tangential to the cortical boundaries) using a five layer finite element model of a realistic head. Based on the hypothesis that the effects of current stimulation are to first order due to the interaction of electric fields with populations of elongated cortical neurons, it is argued that the optimization problem for tCS stimulation can be defined in terms of the component of the electric field normal to the cortical surface. Solutions are found using constrained least squares to optimize current intensities, while electrode number and their locations are selected using a genetic algorithm. For direct current tCS (tDCS) applications, we provide some examples of this technique using an available tCS system providing 8 small Ag/AgCl stimulation electrodes. We demonstrate the approach both for localized and spatially extended targets defined using rs-fcMRI and PET data, with clinical applications in stroke and depression. Finally, we extend these ideas to more general stimulation protocols, such as alternating current tCS (tACS).

Introduction

Transcranial current stimulation (tCS) is a noninvasive brain stimulation technique in which weak, constant or slowly varying electrical currents are applied to the brain through the scalp. tCS includes a family of related non-invasive techniques including direct (tDCS), alternating (tACS) and random noise current stimulation (tRNS). These techniques use scalp electrodes with electrode current intensity to area ratios of about 0.3–5 A/m^2 at low frequencies (typically <1 kHz) resulting in weak electric fields in the brain, with amplitudes of about 0.2–2 V/m (see Miranda et al. (2013) and Ruffini et al. (2013) and references therein). The neuromodulatory effect of these fields has been confirmed in many laboratories (Antal and Paulus, 2013; Nitsche and Paulus, 2001, 2000; Terney et al., 2008). In a typical tDCS experiment, a continuous current of 1–2 mA is applied for up to 20 min through two large stimulation electrodes (25–35 cm^2). For therapeutic applications, such as post-stroke rehabilitation (Khedr et al., 2013) or the treatment of depression (Loo et al., 2012), tDCS is usually applied daily for five days, during one or more weeks.

While tCS interventions typically focus on a single cortical target, it is widely recognized today that many behavioral manifestations of neurological and psychiatric diseases are not solely the result of abnormality in one isolated brain region but represent alterations in brain networks (see, e.g., Fox et al. (2012b) and references therein). In this context, and provided a specification for the location and type of stimulation effects is available, brain networks become the target of neuromodulatory interventions. Advances in neuroimaging technology such as positron emission tomography (PET), electroencephalography (EEG), magnetoencephalography (MEG) and resting-state functional connectivity MRI

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(rs-fcMRI) are allowing us to non-invasively visualize brain networks in humans with unprecedented clarity. In a parallel and timely development, technologies have become available today which enable the use of more than two electrodes for stimulation, making possible multifocal stimulation of brain networks. Determining the ideal configuration of a multi-electrode tCS system, however, is complicated by the fact that transcranial brain stimulation effects are largely non-local due to Ohmic propagation effects. For this reason, optimization algorithms based on globally defined, cortical targeting data are needed.

As an especially interesting example, we discuss the use of rs-fcMRI seed maps (Fox et al., 2012b; Shafi et al., 2012) for defining cortically extended tCS targets. In contrast to traditional task-based fMRI, resting state fcMRI examines correlations in spontaneous fluctuations in the blood oxygen level dependent (BOLD) signal in the absence of any explicit input or output, while subjects simply rest in the scanner (see, e.g., Buckner et al. (2013), and references therein). A consistent observation is that regions with similar functional properties, such as the left and right motor cortices, exhibit coherent BOLD fluctuations even in the absence of movement under resting conditions. Negative correlations (anti-correlations) between regions with apparent opposing functional properties have also been observed (Fox et al., 2005). Significant rs-fcMRI abnormalities have been identified across almost every major neurological and psychiatric disease (for a review see Fox and Greicius, 2010), and differences across subjects in rs-fcMRI are reproducible across scanning sessions and have been related to individual differences in anatomical connectivity and behavior.

One of the most valuable clinical uses of rs-fcMRI may be to predict how focal brain stimulation will propagate through networks, thus informing the ideal site for stimulation (Fox and Greicius, 2010; Fox et al., 2012b). Recently, Fox et al. (2012b) used rs-fcMRI to identify differences in functional connectivity between effective and less effective DLPFC stimulation sites (M. Fox et al., 2012; Fox et al., 2012b). Significant differences in connectivity were seen with the subgenual cingulate (SG), a region repeatedly implicated in antidepressant response and an effective DBS target (Drevets et al., 2008; Mayberg, 2009; Mayberg et al., 2005). Based on this finding, Fox et al. used rs-fcMRI with the SG to identify theoretically optimal TMS target coordinates in the left DLPFC (Fox et al., 2012a). A similar strategy can be applied to other neurological diseases with effective or potentially effective DBS sites including Parkinson's disease, dystonia, essential tremor, Alzheimer's disease, and even minimally conscious state. An important challenge with this approach is that rs-fcMRI with an effective DBS site does not identify just a single cortical site, but many. In fact, it provides a continuous pattern across the cortical surface of regions that are both positively and negatively correlated with the deep brain stimulation site of interest. Realizing the full potential of this targeting approach thus requires the ability to simultaneously excite or inhibit multiple sites across the surface of the cortex. As we will see below, the same occurs with targets from other imaging techniques, such as PET. While conventional TMS and tDCS technologies allow for only one or two stimulation sites, the multi-electrode approach perfectly complements this scientific and therapeutic need.

The mechanisms underlying the after-effects of tDCS are still the subject of investigation, but in all cases these local changes are brought about by the accumulated action of the applied electric field over time, directly or indirectly. For this reason we focus here on electric field optimization. Moreover, given that there are strong directional effects in the interaction of electric fields and neurons, i.e., neurons are influenced mostly by the component of the electric field parallel to their trajectory (Bikson et al., 2004; Fröhlich and McCormick, 2010; Ranck, 1975; Rattay, 1986; Roth, 1994; Rushton, 1927), and that the effects of tDCS depend on its polarity, knowledge about the orientation of the electric field is crucial in predicting the effects of stimulation. The components of the field perpendicular and parallel to the cortical surface are of special importance, since pyramidal cells are mostly aligned perpendicular to the surface, while many cortical interneurons and axonal projections of pyramidal cells tend to align tangentially (Day et al., 1989; Fox et al., 2004; Kammer et al., 2007). Thus, an important element in modeling is to provide the electric field distribution and orientation relative to the gray matter (GM) and white matter (WM) surfaces (the latter might be important to study the possibility of polarizing corticospinal axons, their collaterals and other projection neurons). In order to do this, we work here with a realistic head model derived from structural MRI images (Miranda et al., 2013) to calculate the tCS electric field components rapidly from arbitrary EEG 10–20 montages. Importantly, this modeling approach allows for fast calculation of electric field components normal and parallel to the GM and WM surfaces.

In what follows, we show how to use neuroimaging data to specify a target map on the cortical surface for excitatory, inhibitory or neutral stimulation, and how, given constraints on the maximal number of electrodes and currents, a solution can be produced with the optimal electrode currents and their locations. The main differences of our approach with other recent efforts stem from a) the overall concept of working with extended, weighted cortical pattern target maps based on fMRI, PET, EEG, MEG or other data, b) the emphasis on optimization of an electric field component as opposed to its magnitude or intensity (as in, e.g., Sadleir et al. (2012)), c) the definition of targets based on a coordinate system relative to the cortical surface, with targets for normal ($E^{\perp}$) and tangential ($E^{||}$) components of electric field (as opposed to "radial or normal to the skull" as in Dmochowski et al. (2011), and d) the use of advanced algorithms to optimize not only currents but also the number and location of electrodes given appropriate constraints. Finally, in the discussion section we address the generalization of these methods to tACS, although in a more exploratory fashion.

Methods

General statement of the problem

The non-invasive stimulation problem can be loosely classified as follows: a) single localized target, b) bipolar or, more generally, multi-polar localized targets and c) pattern targeting. With the single target case an issue that typically arises is how to deal with the return current, since the laws of physics require current conservation and thus a minimum of two electrodes need to be applied. The return (or "reference") electrode is normally positioned in an area which is presumed not to play a role (e.g., "over the contralateral orbit"), and sometimes it is chosen to have a larger area than the "active" one so that its effects diffuse (Nitsche et al., 2007). More modern approaches include the so-called "high-definition tDCS", where a return arrangement of electrodes is placed close to the active electrode (see, e.g., Dmochowski et al. (2011), and references therein) or more general quasi-monopolar montages such as the one described below, which employ an array of optimally-placed return electrodes (see Targeting localized cortical regionssection and Fig. 1).

In bipolar or multi-polar targeting, two or more discrete targets are actually sought, some excitatory (anodal) and others inhibitory (cathodal) (as in, e.g., Chib et al. (2013), Ferrucci et al. (2009), Lindenberg et al. (2010) and Mahmoudi et al. (2011)). This situation will normally require the use of small electrodes, as electric field defocusing may be an issue if large electrodes are used. An example is provided below (see Targeting localized cortical regions section and Fig. 2).

More generally, we have the possibility of global cortical targeting designed to achieve a more effective neuromodulatory outcome. In the case of tDCS, such a map may just be a specification of the areas to excite, inhibit, or leave unaffected, with a particular weighting map for each of them. We provide examples on the use of PET and rs-fcMRI generated target maps in sections Cortical pattern target from PET and Cortical pattern target from rs-fcMRI respectively.

In the following, and without loss of generality, we make the discussion concrete by adopting the *StarStim* device specifications (produced

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