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Optimal use of EEG recordings to target active brain areas with transcranial electrical stimulation

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ABSTRACT

To demonstrate causal relationships between brain and behavior, investigators would like to guide brain stimulation using measurements of neural activity. Particularly promising in this context are electroencephalography (EEG) and transcranial electrical stimulation (TES), as they are linked by a reciprocity principle which, despite being known for decades, has not led to a formalism for relating EEG recordings to optimal stimulation parameters. Here we derive a closed-form expression for the TES configuration that optimally stimulates (i.e., targets) the sources of recorded EEG, without making assumptions about source location or distribution. We also derive a duality between TES targeting and EEG source localization, and demonstrate that in cases where source localization fails, so does the proposed targeting. Numerical simulations with multiple head models confirm these theoretical predictions and quantify the achieved stimulation in terms of focality and intensity. We show that constraining the stimulation currents automatically selects optimal montages that involve only a few (4–7) electrodes, with only incremental loss in performance when targeting focal activations. The proposed technique allows brain scientists and clinicians to rationally target the sources of observed EEG and thus overcomes a major obstacle to the realization of individualized or closed-loop brain stimulation.

Introduction

The ability to systematically modify observed patterns of neural activity would be highly beneficial on at least two fronts: in basic neuroscience, mapping out the relationship between structure and function is facilitated by causal manipulations of brain activity. Moreover, techniques supporting target engagement provide novel strategies for treating psychiatric and neurological disorders marked by aberrant neural dynamics (Uhlhaas and Singer, 2006, 2012). An intriguing approach is to combine neuroimaging with brain stimulation (Bestmann and Feredoes, 2013; Bergmann et al., 2016; Siebner et al., 2009). The technical capability to perform integrated stimulation-recording of brain activity exists at a variety of scales: invasive microelectrode arrays (Maynard et al., 1997; Jimbo et al., 2003; Dostrovsky et al., 2000), deep brain stimulation (DBS) (Kent and Grill, 2013; Lempka and McIntyre, 2013; Rosin et al., 2011), depth electrodes (Rosenberg et al., 2009), cortical surface electrode arrays (Trebuchon et al., 2012), brain machine interfaces (Guggenmos et al., 2013), and non-invasive scalp electrode arrays that are commonly used in human neuroscience (Thut et al., 2005; Faria et al., 2012; Fernández-Corazza et al., 2016; Wagner et al., 2016b). However, lacking is a general formalism for how to select stimulation parameters given observations of neural activity.

One particularly compelling combination is electroencephalography (EEG) with transcranial electrical stimulation (TES), mirror-symmetric processes related by the long-standing reciprocity principle introduced by Helmholtz (1853). Simply stated, the electrical path from a neural source to a (recording) electrode is equivalent to the electrical path from the (now stimulating) electrode to the location of the neural source (Rush and Driscoll, 1969). Intuition suggests that reciprocity should allow one to leverage the information carried by EEG signals to guide the parameters of the TES. Indeed, recent work has proposed ad hoc rules for distilling EEG measurements to TES configurations ("montages") (Fernández-Corazza et al., 2016; Cancelli et al., 2016). However, these initial efforts have not realized the multi-dimensional nature of the reciprocity principle, and thus have failed to overcome the

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spatial blurring that results from naive implementations of reciprocal stimulation.

Here we develop a general formalism for combined EEG-TES, focusing on the problem of how to select the applied TES currents such that the source of an EEG activation is targeted by the stimulation. By formulating both EEG and TES as linear systems linked by a common transfer matrix, we derive a closed-form expression for the TES electrode configuration ("montage") that generates an electric field most closely matched to the activation pattern. Importantly, we show that source localization of the targeted activation is not required, and that EEG sources may be stimulated using only their projections on the scalp. However, we also derive a duality between EEG localization and TES targeting, showing that the inherent limitations of localization are shared by targeting. In order to guarantee "safe" (i.e., current-limited) and feasible montages, we propose to constrain the L^1 norm of the reciprocal TES solution, and provide a fast iterative scheme to achieve this.

In order to test the proposed approach, we conduct numerical simulations using two magnetic resonance imaging (MRI) based models of the human head. The simulations confirm the main theoretical prediction that in order to target the source of a recorded EEG pattern, the TES currents must be selected as the *spatially decorrelated* vector of measured EEG potentials. The duality between EEG and TES is also validated, and we present a high-noise scenario in which both EEG localization and TES targeting fail. We then demonstrate that the L^1 constrained solution allows for simple montages that increase stimulation intensity while only sacrificing a modest amount of focality. We show that reciprocal stimulation accounts for varying source orientation, in that both radial and tangential sources are effectively targeted. Finally, we evaluate reciprocal TES when active sources are distributed. In summary, we demonstrate that targeted stimulation of neural sources may be achieved by measuring neural activity at a surface array and using these measurements to design spatially patterned electrical stimulation. This approach has application to both basic neuroscience and clinical interventions using neuromodulation.

Results

TES delivers electric currents to the brain via an array of scalp electrodes, while EEG records voltages on the scalp generated by neural current sources in the brain. The goal of reciprocal TES is to select the stimulation currents on the scalp such that they reproduce the neural current sources in the brain. We provide the mathematical theory to optimally achieve this goal, while deferring proofs to the Methods. To test the theoretical predictions (Figs. 1–3), we employ a simple 3-compartment boundary element model (BEM) of the human head based on a tissue segmentation derived from MRI (see Methods for details). To estimate the performance of reciprocal TES in practice (Figs. 4–7), we make use of a more detailed finite element model (FEM) with 6 compartments that captures idiosyncrasies in human head anatomy (Huang et al., 2015). These head models allowed for the estimation of stimulation currents in the brain as well as simulation of voltage recordings due to neural currents.

EEG lead field and TES forward model are symmetric

Consider an array of N electrodes that is capable of both recording (neurally-generated) electric potentials and stimulating the brain with applied electrical currents. The recorded voltages, denoted by N-dimensional vector V (units of V), are a linear superposition of M neural current source vectors whose activity is represented by $3M$-dimensional vector J (units of A·m):

$$V = RJ, \tag{1}$$

where N-by-$3M$ matrix R (units of Ω/m) is the so-called "lead field" matrix (Sarvas, 1987; Hämäläinen and Ilmoniemi, 1994) that quantifies the voltages generated on the scalp by unit currents at various source locations and orientations in the brain ($M \gg N$). One example is given in Fig. 1A, which shows a localized source of activity on the cortical surface. Note that the voltage recordings on the scalp are blurred due to volume conduction. The stimulation currents applied to the electrode array, denoted by N-dimensional vector I (units of A), generate an electric field E (units of V/m) inside the brain:

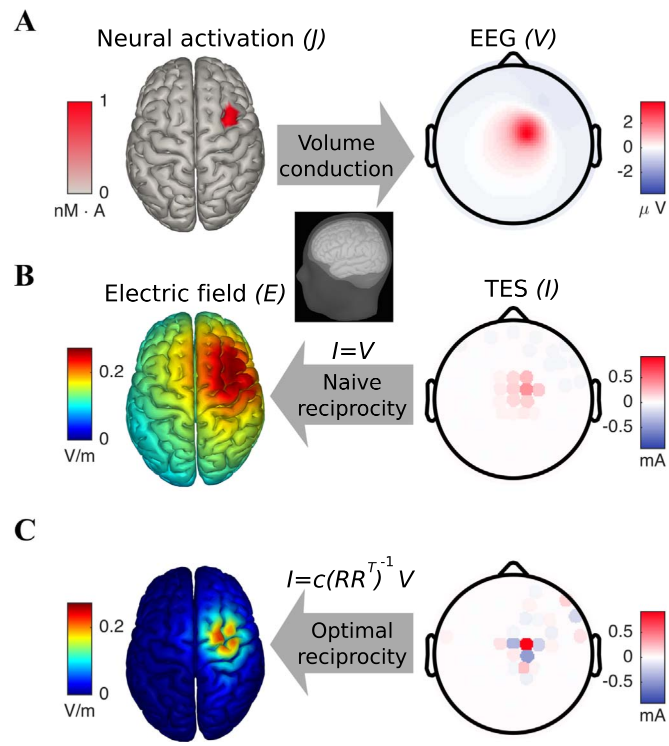

Fig. 1. Reciprocal stimulation produces an electric field focused on the site of neural activation. **(A)** Focal neural activation of the right frontocentral cortex produces a radially-symmetric pattern of electric potentials on the scalp. Inset: BEM head model employed to simulate EEG activations and electric fields during TES. **(B)** By patterning the stimulation currents according to the observed scalp activity (i.e., $I \propto V$), "naive" reciprocity generates a diffuse electric field that is strong at the site of activation but also over expansive regions of cortex. **(C)** Applying TES in proportion to the spatially decorrelated EEG (i.e., $I = c(RR^T)^{-1}V$) yields focal stimulation at the neural activation. Note that the injected reciprocal currents are both positive ("anodal") and negative ("cathodal") over the scalp regions marked by positive EEG potentials.

$$E = SI, \tag{2}$$

where E is a vector of dimension $3M$ that spans the three Cartesian dimensions and matrix S (units of Ω/m) is the $3M$-by-N "forward model" (Dmochowski et al., 2011) that quantifies the electric field generated in the brain for a unit current applied to each of the stimulation electrodes. In this multiple electrode context, reciprocity leads to a symmetry relationship among R and S:

$$R^T = S, \tag{3}$$

where ^{T} denotes matrix transposition. This formulation of reciprocity is novel in that it describes the relationship between *multiple* neural sources and *multiple* electrode pairs. Reciprocity for individual sources and a single pair of recording electrodes in a non-uniform medium such as the brain has been known for decades (Rush and Driscoll, 1969), and linear superposition of multiple sources has been previously leveraged for current flow modeling (Hallez et al., 2007; Huang et al., 2015; Wagner et al., 2016b), but a compact formulation as in Equation (3) was lacking. We provide a derivation for this multi-dimensional reciprocity in the Methods. In the next section, we exploit multi-dimensional reciprocity to, for the first time, selectively target active