Editorial

Polarizing cerebellar neurons with transcranial Direct Current Stimulation

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In this issue, Parazzini and colleagues (Parazzini et al., 2014), present computational models of brain current flow using transcranial Direct Current Stimulation (tDCS) designed for cerebellum stimulation. Using MRI-derived models of three subjects, they predict that a montage with one 5×9 cm sponge electrode placed roughly over the cerebellum area and an extra-cephalic electrode on the right arm, results in brain current flow that is largely restricted to the cerebellum – though evidently current must exit the brain through deep brain structures. This prediction of relatively targeted stimulation is notable in contrast to imaging studies and modeling predictions using other tDCS sponge-montages that suggest current influences large areas of brain between electrodes (Datta et al., 2009). The possibility of targeted neuromodulation using conventional sponge-tDCS is thus compelling and the cerebellum is a promising target for a range of indications (Ferrucci et al., 2008, 2013; Galea et al., 2009; Hamada et al., 2012; Boehringer et al., 2013; Ferrucci and Priori, 2013).

Like most modeling studies of tDCS, Parazzini et al. (2014) rely on the "quasi-uniform" assumption (Bikson et al., 2013) to suggest electric field (or current density) intensity in any given region indicates the relative neuromodulation of that region. None-the-less, an open question is given that both cortical architecture and cell morphology of the cerebellum differ from cortical targets investigated in a majority of tDCS studies, for example motor regions (Nitsche and Paulus, 2000; Lang et al., 2004). Will the cerebellum respond distinctly to an applied electric field? Indeed, the direction of brain current flow relative to cellular morphology is believed to modulate the direction of induced excitability changes (Bikson et al., 2004; Rahman et al., 2013) while cell morphology is further assumed to determine sensitivity to electric fields (Radman et al., 2009).

We predicted brain current flow using a stand-alone simulation package (HDExplore Version 2.3, Soterix Medical Inc., New York, NY) considering varied deployments of High-Definition (1 cm diameter) electrodes (Fig. 1). Though in each of the four montages selected the region of current flow is restricted to the cerebellum, the direction of current flow across the cerebellum varies. Inward, outward, lateralized left, or lateralized right direction of flow can be achieved by selecting electrode position and polarity. In each case the current flow direction through the cerebellum seems broadly uniform (i.e. local current flow seems largely unaffected by cortical folding and CSF). While high-definition tDCS allows significantly enhanced flexibility in optimization of current flow (Dmochowski et al., 2011), conventional

sponge-tDCS is simpler to apply and Parazzini et al. (2014) demonstrate particularly compelling performance for cerebellum stimulation.

Finite element models of transcranial electrical stimulation thus show diffuse current flow throughout the cerebellum with the direction of current flow guided by a specific montage. How current flow modulates cerebellar activities depends on the physiological and morphological characteristics of neurons in the cerebellum. In vivo and in vitro animal models of transcranial electrical stimulation show that subthreshold DC fields can change membrane excitability, spike timing, and firing rates (Terzuolo and Bullock, 1956; Purpura and McMurtry, 1965; Fröhlich and McCormick, 2010; Reato et al., 2010). These effects are specific for individual neurons with their longitudinal axis oriented along the direction of current flow. Simplistically, current flow along the somato–dendritic axis of a neuron will hyperpolarize membrane compartments proximal to the current source (near anode) and depolarize distal membrane compartments (nearer the cathode; Fig. 2A) (Rahman et al., 2013). Therefore, current flow parallel to the somato–dendritic axis of a cerebellar Purkinje cell can be used to hyperpolarize or depolarize both somatic and dendritic compartments.

In a seminal series of papers, Chan, Nicholson and colleagues (Chan and Nicholson, 1986; Chan et al., 1988; Lopez et al., 1991) used isolated turtle cerebellum to quantify Purkinje and stellate cell polarization under DC and low-frequency sinusoidal electric fields. These studies identified morphological determinants of neuron sensitivity to externally applied electric fields. Purkinje cells polarized linearly along the somato–dendritic axis (pia proximal to the current source; Fig. 2B) (Chan et al., 1988) and their results support the concept that current flow that depolarizes the soma leads to excitation while current flow that hyperpolarizes the soma leads to inhibition of firing (Chan and Nicholson, 1986). Pharmacological blockade of active conductances and synaptic transmission revealed passive membrane polarization by the field (thus depending simply on the resistive and capacitive properties of the cell membrane) underlying active voltage-dependent responses. Chan et al. (1988) also report Purkinje cells will polarize by 0.2 mV per 1 V/m applied electric field, which is within the 0.03–0.49 mV per V/m range reported for layer V/VI pyramidal cells (Radman et al., 2009).

Further evidence for the morphological dependence of cerebellar cells to DC stimulation effects is given by the variety of stellate cells in the cerebellum. While the geometry and orientation of the dendrites of stellate cells of the lower molecular layer (distal to the
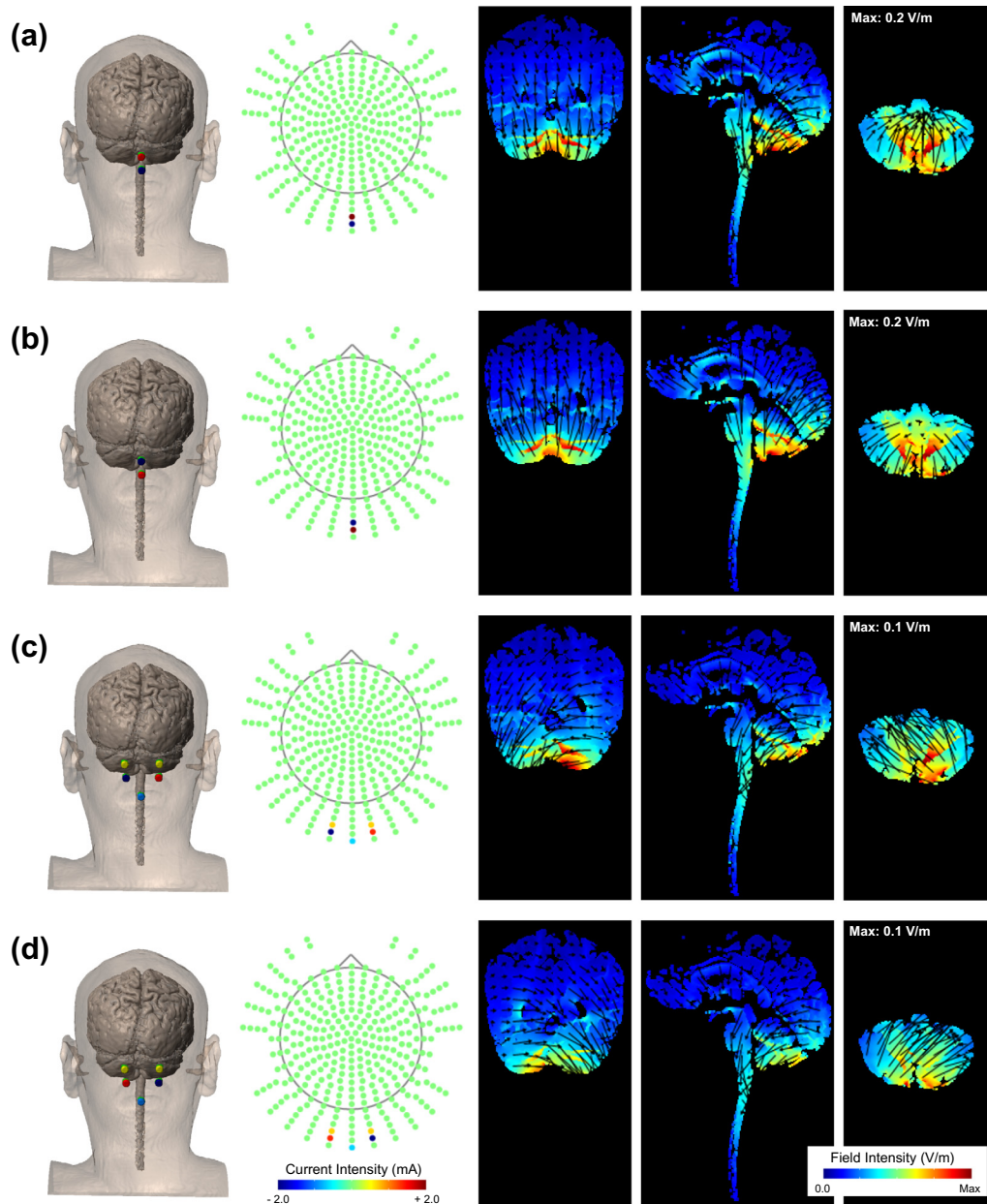
Fig. 1. Prediction of brain current flow using high-definition tDCS optimized for cerebellum targeting. Models were generated using a stand-alone graphic-user-interface software designed to allow rapid screening of stimulation montages removing the need for specialized computer resources. Four models were generated with distinct, quasi-uniform orientation of current flow across the cerebellum. Slices across models intersect at MNI coordinate (2, −71, −29).

pia) is similar to Purkinje cells, stellate cells of the upper molecular layer (closer to the pia), however, show less susceptibility to polarization primarily due to their horizontally branched dendrites (Chan and Nicholson, 1986). Furthermore, the complexity of cerebellar folding (Fig. 2D) will also contribute to the diverse polarization profiles that are expected (Fig. 2B). The angle between the electric field and the somato-dendritic axis will strongly influence both the magnitude and polarity of somatic membrane potential changes (Fig. 2C).

Considering the diffuse current flow, variety of cell types, morphologies, active membrane properties, and excitatory–inhibitory synaptic interactions of cerebellar neurons (Chan and Nicholson, 1986), further analysis is warranted to predict how any given sub-region will be functionally affected by a

polarizing electric field. Given the diverse orientations of cerebellar neurons we considered montages producing orthogonal current flow (Fig. 1). The cerebellum is a potentially promising target for tDCS as current flow can be focalized; moreover, the directionality of the current can be controlled over the cerebellum. Further refinement of stimulation protocols is needed to characterize the electrophysiological responses to cerebellar stimulation with respect to field orientation. In the four simulated montages, the resulting current flow is largely uniform in direction thereby producing an alternating direction of polarization across the convoluted cerebellum architecture (Fig. 2D). We further predict that maximal polarization of cerebellar neurons is comparable to pyramidal neurons of the motor cortex for the same electric field.
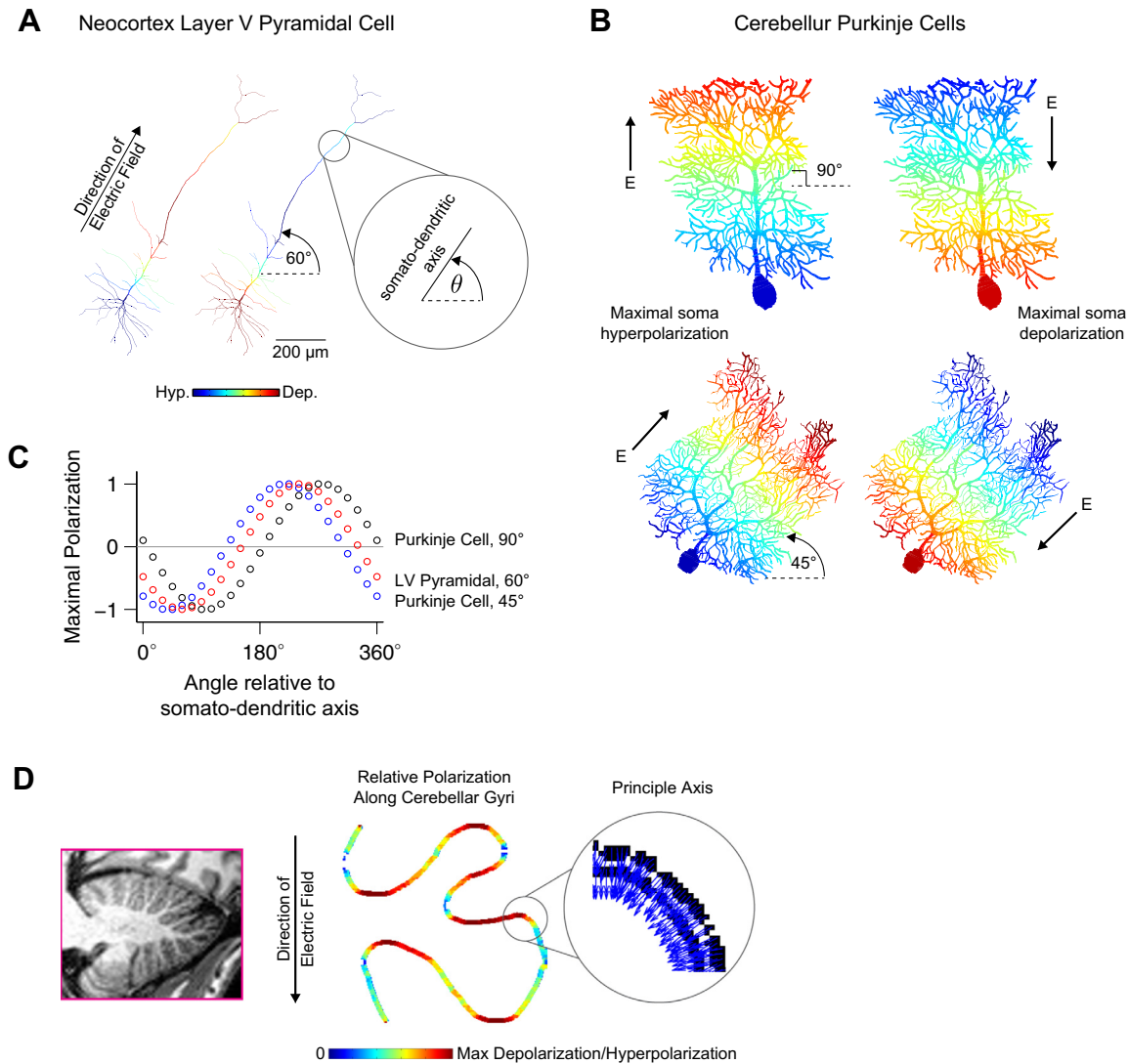
Fig. 2. Simulations of morphologically reconstructed Purkinje cells with passive membrane properties in a uniform electric field. (A) Compartment model showing the polarization profile (hyperpolarization to depolarization) of a cortical layer V pyramidal cell illustrates current flow along the somato–dendritic axis will differentially polarize distal and proximal membrane compartments. (B) Passive compartment models of morphologically reconstructed Purkinje cells confirm the apparent linear polarization along the somato–dendritic axis depends on the orientation of the cell to current flow. (C) Neuronal orientation relative to current flow influences how the soma will polarize. The change in membrane potential at the soma is normalized by the maximal polarization at the optimal angle such that maximal depolarization corresponds to 1 and maximal hyperpolarization corresponds to −1. (D) Cerebellar folding will influence polarization along the gyri. The principal axis of Purkinje cells along a trace of cerebellar gyri are subject to an electric field (assuming maximal polarization as $V = E\lambda \cos(\theta)$, Rahman et al., 2013). The resulting polarization (maximal hyperpolarization or depolarization) is indicated in false color along the trace.

Conflict of interest

The City University of New York has brain stimulation patents with Marom Bikson as inventor. Marom Bikson has equity in Soterix Medical, Inc.

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