Clinical Neurophysiology 131 (2020) 752–754

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Editorial

What it means to go deep with non-invasive brain stimulation

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Whereas the invasiveness of implanted neuromodulation approaches (such as Deep Brain Stimulation) is justified by the need to selectively activate structures deep in the brain, non-invasive brain stimulation (NIBS) approaches have generally targeted superficial cortical regions. Indeed, one of the central challenges in NIBS research is how to achieve stimulation of deep brain regions when desired. The electromagnetic fields applied during Transcranial Magnetic Stimulation (TMS) and Transcranial Electrical Stimulation (TES) fall off in both intensity and focality with increasing depth. The superficial cortex has many regions directly implicated in cognition and behavior, as well as participating in brain wide networks (e.g. circuit therapeutics; Faber et al., 2012; Vaseghi et al., 2015; Cabib et al., 2016; Ironside et al., 2019). Nevertheless, some brain regions strongly implicated in neurological and psychiatric disorders are subcortical, for example the subthalamic nucleus in Parkinson's (Rodriguez-Oroz et al., 2000; Gunalan et al., 2018) or subcallosal cingulate for treatment-resistant depression (Lujan et al., 2013; Holtzheimer et al., 2017). Consequently, the ability to effectively stimulate deep brain regions with NIBS would open new avenues for treating brain disorders and cognitive and behavioral manipulation (Dmochowski and Bikson, 2017). In this issue of *Clinical Neurophysiology*, Gomez-Tames et al. (2020) consider how one NIBS technique, Transcranial Direct Current Stimulation (tDCS, a popular variant of TES where the waveform is constant; (Bikson et al., 2019), may produce reliable "hot spots" in deep brain regions.

Generally, approaches to stimulate deep regions with NIBS either (1) activate deep structures along with superficial cortex or (2) attempt to selectively stimulate deep targets, sparing superficial regions. Approaches for selective targeting include deep High-Definition tES (HD-tES, (Huang and Parra, 2019)), interferential stimulation (Grossman et al., 2017; Rampersad et al., 2019) and ultrasonic neuromodulation (Legon et al., 2018; di Biase et al., 2019; Wang et al., 2019). Approaches to stimulating deep targets alongside superficial regions include "deep" TMS (Salvador et al., 2007; Gomez et al., 2018) and intensity-optimized HD-tDCS that is based on individual MRIs of intact (Dmochowski et al., 2011) or injured brains (Dmochowski et al., 2013). Alongside these customized approaches, conventional tDCS has been shown with modeling (Datta et al., 2009; DaSilva et al., 2012) and intra-cranial recordings (Opitz et al., 2016; Huang et al., 2017; Chhatbar et al., 2018) to generate significant current in deeper regions, with superficial cortical regions also activated. Note that, unlike TMS or ultrasonic neuromodulation, the electrical stimulation dose is inherently bipolar, and the current applied at the anode must return through the cathode. Provided that the two electrodes are sufficiently separated, this dictates that at least some of the applied current will travel broadly through the deeper areas in the brain (Datta et al., 2008; Faria et al., 2011; Dmochowski et al., 2012). However, these areas of increased current flow have generally been viewed as idiosyncratic in location, due to the inter-individual variability in head anatomy that determines the precise distribution of electric field generated during TES. For example, the highly-conductive ventricles may act as current "conduits" to adjacent brain regions creating deep current "hot spots", but it is not clear whether this is a phenomenon that can be exploited at the level of a population (i.e., without a detailed anatomical head model of the subject; (Dmochowski et al., 2011; Huang et al., 2018).

Despite penetration of current to deep brain regions by conventional tDCS, tDCS trials remain interpreted as reflecting cortical stimulation (Lefaucheur et al., 2017; Ekhtiari et al., 2019), with limited exceptions (DaSilva et al., 2012; Chib et al., 2013; Clemens et al., 2014; Hampstead et al., 2014; Fonteneau et al., 2018; Fukai et al., 2019; Meyer et al., 2019; Morya et al., 2019). One reason for this may be the perception that even if tDCS delivers current to both cortical and deep brain regions, only cortical regions are consistently stimulated across subjects. Contrary to this view, Gomez-Tames et al. (2020) employ detailed computational modeling of the head to demonstrate the existence of consistent, group-level hotspots in electric field at deep brain regions such as the caudate and amygdala. The location of these hotspots is dependent on the tDCS montages (positions of the anode and cathode), but within a montage, their existence appears to be relatively robust across individuals.

The presence of reliable deep hot-spots across a population with a fixed montage, means that individual MRI-based modeling is not necessarily required for consistent stimulation of deep region with tDCS; and indeed many past and ongoing trials with tDCS may be consistently activating deep brain structures. The significance of such a finding is that typically detailed, individualized head models are not available for every trial participant or patient. Despite efforts to automate individual modeling (Lee et al., 2017;

https://doi.org/10.1016/j.clinph.2019.12.003

Huang et al., 2019; Saturnino et al., 2019), obtaining high-resolution scans and segmenting head models without error remains a challenge. Therefore, the possibility to employ standardized montages for prescribed deep brain targets is compelling for ongoing NIBS research.

Inevitable variability in the pattern and intensity of current at deep brain regions between subjects should be balanced against variability in cortical regions as well (Datta et al., 2012; Laakso et al., 2015; Gomez-Tames et al., 2019; Mikkonen et al., 2020). Alongside cortical modulation (Radman et al., 2009; Rahman et al., 2013), there is ample cellular-level evidence that deep brain regions are also directly sensitive to DC stimulation (Bikson et al., 2004; Márquez-Ruiz et al., 2012; Chakraborty et al., 2018; Kronberg et al., 2019) and generally to weak electric fields (Francis et al., 2003; Deans et al., 2007; Reato et al., 2010; Kato et al., 2019).

Gomez-Tames et al. (2020) correctly conclude this work supports the notion that tDCS produced "modulation via underlying cortical or subcortical circuits but also modulation of deep brain regions" and these predictions of current flow across "deep brain regions can be used to explain tDCS mechanisms or select the most appropriate tDCS montage". Conversely, studies aiming to implicate a specific cortical target should leverage superficial 4x1 HD-tDCS (Datta et al., 2009; Hampstead et al., 2017; Nikolin et al., 2018; Santos et al., 2018; Lefebvre et al., 2019).

In order to achieve optimal deep stimulation targeting non-invasively, a multi-pronged approach will likely be required (Huang et al., 2018; Rampersad et al., 2019). At the same time, in regard to efficacy (electric field intensity at deep targets), there are ongoing efforts at safely increasing the allowable current injected on the scalp (Reckow et al., 2018; Khadka et al., 2020). The computational approach employed by Gomez-Tames et al. (2020), while demonstrated for conventional tDCS, also applies to these more tailored efforts, with a goal to rationally modulate brain activity in deep brain regions without surgery.

Funding

This research was supported by the National Institutes of Health (NIHNIMH 1R01MH111896, NIH-NIMH 1R01MH109289; NIH-NINDS 1R01NS101362).

Declaration of Competing Interest

The City University of New York (CUNY) has IP on neurostimulation system and methods with Marom Bikson and Jacek Dmochowski as inventors. Marom Bikson has equity in Soterix Medical and served as a consultant for Boston Scientific, Mecta, Halo Neuroscience, X, and GSK.

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Accepted 14 December 2019

Available online 26 December 2019