LETTERS TO THE EDITOR

Guidelines for precise and accurate computational models of tDCS

To the Editor:

During transcranial electrical stimulation, including transcranial direct current stimulation (tDCS), current is induced in the brain. Because different electrode montages result in distinct brain current flow, researchers and clinicians can adjust montage to target or avoid specific brain regions in an application specific manner. Though tDCS montage design often follow basic rules-of-thumb (e.g., increased/decreased excitability "under" the anode/cathode), computational models of brain current flow during tDCS (also called "forward" models) provide more accurate insight into detailed current flow patterns, and in some cases challenge simplified electrode-placement assumptions. With the increased recognition of the value of computational forward models in informing tDCS montage design and interpretation of results, there have been recent advances in modeling tools and a proliferation of publications.[1-10] In considering new electrode montages, and especially in potentially vulnerable populations,[2,11-13] forward models are the main tool to relate the externally controllable dose parameters (electrode number, position, size, shape, current) with resulting brain current flow–the use and adequacy of these models is considered here.

Computational models of tDCS range in complexity from concentric sphere models to high-resolution models based on individuals MRIs. The appropriate level of modeling detail depends on the clinical question being asked, as well as the available computational resources. Whereas simple geometries (e.g., spheres) may be solved analytically,[14] realistic geometries use numeric solvers, namely, finite element methods (FEM). Regardless of complexity, all forward models share the primary outcome of correctly predicting brain current flow during transcranial stimulation to guide clinical practice. Special effort has been recently directed toward increasing the precision of tDCS models, but complexity does not necessarily equate with accuracy or clinical value.

To meaningfully guide clinical practice, attempts to enhance model precision must rationally balance detail (complexity) and accuracy. (1) Beginning with high-resolution (e.g., 1 mm) anatomic scans, the entire model work flow should *preserve* precision. Any human head model is limited by the precision and accuracy of tissue segmentation ("masks") and of the assigned conductivity values. One hallmark of precision is that the cortical surface used in the final FEM solver should capture realistic sulci and gyri. In addition, with finer segmentation, reliable tissue conductivities at DC frequencies are needed. (2) Simultaneously, a priori knowledge of tissue anatomy and factors known to shape current flow should be applied to further refine segmentation. Particularly critical are discontinuities not present in nature that result from limited scan resolution; notably both unnatural perforations in planar tissues (e.g., holes in CSF where brain contacts skull, misrepresented skull fissures, ventricular architecture…) and microstructures (e.g., incomplete or voxelized vessels) can produce significant aberrations in predicted current flow. Thus addition of complexity without proper parameterization can evidently decrease prediction accuracy.

As there is no standard protocol for tissue imaging or segmentation, diversity in the nature of resulting segmented tissue masks will invariably influence predicted current flow. For reproducibility and interpretability, it is thus valuable to publish each three-dimensional tissue mask and/or classified serial sections, to the extent practical.

When interpreting simulation predictions, it is important to recognize that the intensity of current flow in any specific brain region does not translate in any simple (linear) manner to the degree of brain "activation" or "modulation" (even when further considering current direction[3,8,15]). The absence of a complete understanding of how induced brain currents produce (plastic) functional changes necessitates a simplifying assumption: those regions with more current flow are more likely to be "effected" by stimulation whereas regions with little or no current flow will be spared the direct effects of stimulation. The "Quasi-uniform" assumption considers that if the electric field (current density) is uniform on the scale of a region/neuron of interest, then "excitability" may be modulated with local electric field intensity (see discussion in reference 3).

There is a dearth of experimental data validating direct model predictions of induced brain current flow[14] or relating these predictions to experimental/clinical outcomes.[12,13,16] And there has been no comprehensive effort to differentiate the impact on modeling techniques in regard to their clinical use. Moreover, most modeling studies are published as "case" reports with single head analysis[10,15,17] and thus have limited consideration of variance across individuals—even as increasingly precise patient-specific models[12,13] illustrate the impact of idiosyncratic anatomic differences.

Modeling results can be presented phenomenologically, with current flow maps used by clinicians as a "look-up table" predicting activated and spared regions (given the caveats outlined above). But the applied value of a model follows specific predictions explaining existing data (in ways not obvious) and/or suggesting experimentally testable outcomes (notably when unexpected). In either case explicating hypotheses, including specifying to which populations they apply and underlying assumptions, provides practical insight into clinical decisions.

The increased exploration of tDCS to treat diverse neuropsychiatric diseases and the desire to rationally optimize tDCS dose requires an understanding of which brain regions are targeted. Even working within existing unknown tDCS mechanisms, forward models thus serve as a key framework in developing electrical stimulation strategies and elucidating study outcomes–and indeed may thus provide a substrate for explaining the mechanisms.

Marom Bikson, PhD
Department of Biomedical Engineering
The City College of the City University of New York
New York, NY

Abhishek Datta, PhD
Laboratory of Neuromodulation
Spaulding Rehabilitation Hospital
Harvard Medical School, Boston, MA
E-mail address: abhishek.datta@gmail.com

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Efficacy and safety of bifocal tDCS as an interventional treatment for refractory schizophrenia

To the Editor:

Despite advances in pharmacotherapy, some disabling symptoms remain refractory in 30% of patients with schizophrenia such as auditory hallucinations (AH) and negative symptoms. In this context, peripheral neurostimulation techniques have been proposed to curtail these symptoms by modulating the abnormal cortical activity reported in neuroimaging studies.[1] Thus: (1) "activating" high-frequency repetitive transcranial magnetic stimulation (rTMS) to the left dorsolateral prefrontal cortex (l-DLPFC)