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COMMENTARY

Transcranial direct current stimulation and neurovascular modulation

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Regional cerebral blood flow is altered by transcranial direct current stimulation (tDCS) in human as well as animal models, though the nature of responses is brain state and dose dependent [1]. Given the pervasiveness of vascular and brain transport dysfunction across brain disease, the overlap with clinical indications for which tDCS is trialed is not surprising. Is there a further therapeutic mechanisms link?

Gellner et al. [2] systematically document increases in blood flow and permeability of cortical microvasculature, along with increased perivascular microglia activity, in a mouse model of tDCS. Their work shows dose-, time-, and target structure-dependent effects. Gellner et al. [2] contextualize a range of prior work in animal models indicating tDCS can modulate each cell type forming the neurovascular unit including neurons, perivascular astrocytes, microglia, and endothelial cells [3, 4]. Neurovascular-modulation [5] is a framework for explanations for brain stimulation technology, including tDCS, based on neurovascular unit response [5]. Several key neurovascular-modulation considerations are explored in Gellner et al. [2].

A primary consideration in neurovascular modulation is if the direct cellular targets for stimulation are neurons, glia, endothelial cells, or extracellular processes involved in brain transport. Conventional theories of brain stimulation consider only neuron polarization. But in vitro models with isolated glia [4] of endothelial cells [6] show these cell types are also directly stimulated. Precisely because of neurovascular coupling, it is challenging in vivo to untangle which cell type responds first to electrical stimulation and which cell types follow.

A second consideration is to what extent changes in brain vasculature flow and permeability (regardless of which cell type was directly stimulated) underpin the relevant outcomes of brain stimulation. In one extreme, vascular change are just "epiphenomena" of neuronal stimulation – so that hemodynamic response to brain stimulation (e.g., blood oxygen level dependent functional magnetic resonance imaging [BOLD fMRI]) mirrors underlying neuronal activity but has no further explanatory usefulness. This perspective is limited if one gives importance to: (1) neurovascular coupling being bidirectional (i.e., changes in brain transport modulate neuronal activity); and/or (2) brain functions governed by brain transport in health or disease states; and/or (3) functions of non-neuronal cell types or extracellular processes that do not trivially mirror neuronal activity (e.g., clearance of toxins). One approach to disentangle the role of cell types is analysis of the time-course of responses to brain stimulation as considered by Gellner et al. [2].

Gellner et al. [2] contribute to expanding quantification of how non-neuronal cell types and brain transport processes are changed by tDCS. At clinically relevant doses, these changes are non-injurious but potentially profound. Just as the broader outcomes of neuromodulation depend on the stimulation dose, brain state, and other factors, it is important to parse out distinct effects on non-neuronal cell types and brain transport. The translational goal is to develop enhanced neurovascular modulation targeting specific brain (dys)functions. Neurovascular modulation could both engage endogenous systems (directly or by homeostatic responses) or produce supranatural responses (e.g., clearance of brain toxins beyond endogenous capacity), as well as serve as an adjunct therapy, for example, enhancing targeted drug delivery.

CONFLICT OF INTEREST STATEMENT

The City University of New York holds patents on brain stimulation with MB as inventor. MB has equity in Soterix Medical Inc. MB consults, received grants, assigned inventions, and/or served on the SAB of SafeToddles, Boston Scientific, GlaxoSmithKline, Biovisics, Mecta, Lumenis, Halo Neuroscience, Google-X, i-Lumen, Humm, Allergan (Abbvie), Apple, Ybrain, Ceragem, and Remz. MB is supported by grants from Harold Shames and the National Institutes of Health: NIH-NIDA UG3DA048502, NIH-NIGMS T34 GM137858, NIH-NINDS R01 NS112996, NIH-NINDS R01 NS101362, and NIH-G-RISE T32GM136499.

DATA AVAILABILITY STATEMENT

There is no data of any kind or in any sense. Its a comment.

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