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Marom Bikson, Dylan Edwards, Emily Kappenman

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Corresponding author
Marom Bikson
bikson@ccny.cuny.edu

The outlook for non-invasive electrical brain stimulation

Over a decade since the initial establishment of modern transcranial direct current stimulation (tDCS), the field of transcranial electrical stimulation (tES) has blossomed to include a range of techniques (e.g., alternating current (tACS), random noise (tRNS), and pulsed current stimulation), and a diverse array of applications (e.g., depression, pain, tinnitus, stroke, and schizophrenia). At the cusp of even broader dissemination of tES as a tool for the treatment and rehabilitation of brain disorders, the study of brain function, and brain enhancement, it is incumbent to consolidate what have we learned and what remains to be addressed. To this end and coinciding with this special issue of *Brain Stimulation*, scientists, clinicians, engineers, program officers, developers, and regulators will converge in New York City in January 2015 for the NYC Neuromodulation conference.

Fifteen years ago, the inflection point in tDCS research was the demonstration that tDCS modulates brain excitability, as evidenced by increased responses of motor cortex to transcranial magnetic stimulation [1]. This neurophysiological evidence was important in establishing the neuromodulatory effects of tDCS, and later, of other low-intensity tES variants. Dozens of clinical neurophysiology and imaging studies [2] [3], animal studies [4], and computational models [5] have validated these initial findings, at the same time demonstrating increased subtlety in the brain's response to tES [6]. These ongoing efforts at explicating the mechanisms through which tES operates in the brain derive not from a lack of confidence that tES changes the brain, but rather from an understanding in the field that advancement in basic science will lead to more robust and long-lasting tES outcomes in cognitive and clinical domains. This includes understanding how changes in excitability relate to higher-level function and how to reduce inter-individual variability in responsiveness to stimulation.

Over the past ten years, a diverse set of human trials have investigated the behavioral efficacy of tDCS and tES variants [7]. Though variability in quality and a 'file-drawer' problem biased toward positive results is typical of an emerging field, rigorously controlled trials of increasing size are building a consensus toward some clinical effectiveness in several indications [8] [9]. State-of-the-art efforts are directed not simply at reproducing effects but rather developing protocols for producing more efficacious and generalizable outcomes. One can hardly expect that the limited range of protocols tested thus far represent the full potential of tES—instead, it is likely that the best uses and applications of tES are only beginning to be realized. Thus, the field of tES is at a critical juncture. On the one hand, new approaches must be tested—debate over average effect sizes in completed clinical trials (e.g., compared to drug therapy; [10]) may be muted by innovative methods that increase efficacy. On the other hand, for many patients, validation of conventional tES therapies through replication cannot come fast enough. The struggle to balancing the testing of new treatment approaches with validating standard methods should be seen as indicative of a field with significant progress and promise for the future.

Starting five years ago, the development of models for designing tES montages coupled with the introduction of high-definition tES approaches (such as the 4x1-Ring; [11]) opened a new frontier in tES. These developments broadened the locus of conventional tES approaches (for example, to include deep brain structures; [3]). Whereas tES was once considered diffuse compared to techniques such at TMS or implanted electrodes, recent theoretical [12] and experimental [12] efforts suggest unrealized opportunities for anatomical targeting. Simultaneously, the field has experienced a deepening appreciation for “functional targeting” approaches, in which brain regions activated by adjunct behavioral therapy become primed for selective neuromodulation with tES—a concept that may even extend to boosting placebo responses [13] [3].

Recent advancements in integrating tES with other technologies—notably, magnetic resonance imaging (MRI; [14] [2] [3]) and electroencephalography (EEG; [15])—have provided a new window into measuring the direct effects of tES and provide possible biometrics to individualize application. Ongoing advances in headgear, electrode design, and adaptive stimulation algorithms [16] are expected to transform the reliability and simplicity of tES. Clinical grade home-based devices are becoming available [17] at precisely the time when trials are increasing in scale and scope. Thus, the inherent advantages of low-intensity tES with regard to cost and deployment may soon be realized.

The NYC neuromodulation 2015 conference provides a forum to examine contemporary approaches in tES, identify existing barriers, and collectively address challenges by encouraging diversity and breadth in solutions. The large number of published manuscripts and registered clinical trials in the field attest to the substantial interest in tES in the scientific and clinical communities, but a cohesive effort by the field is lacking. The increased media, public, and commercial interest in tES has increased the stakes, shining a spotlight on even the choice of language used by researchers. In the face of popular interest, the scientific community can no longer be passive with respect to issues such as regulation, off-label treatment, and neuro-enhancement. Finally, with tES research being conducted at the forefront of cognitive neuroscience and brain therapy, rational design of protocols requires addressing open questions in brain function, disease, and rehabilitation. Rigorous scientific studies and multidisciplinary discussion at meetings like this one will allow scientists and clinicians to use tES to advance our understanding of the human mind and enhance human potential that will galvanize the field.

Marom Bikson*

Dylan Edwards
Emily Kappenman
Scientific Program Directors, NYC Neuromodulation 2015

*Bikson@ccny.cuny.edu

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