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The off-label use, utility and potential value of tDCS in the clinical care of particular neuropsychiatric conditions

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Transcranial direct current stimulation (tDCS) has attracted significant attention from patients and clinicians for its potential to elicit therapeutic benefit in a number of neurological and psychiatric conditions, and to facilitate rehabilitation after neurological injury.¹ Tested indications include recovery of speech and motor loss following stroke,² mitigation of various forms of chronic pain,³ and reduction in signs and symptoms of particular types of depressive and anxiety disorders⁴ (for overview, see Kuo et al., 2014⁵). The mechanisms of transcranial electrical stimulation have been systematically characterized over decades, while the most rigorous clinical trials have considered

¹ Min-Fang Kuo, Walter Paulus & Michael A. Nitsche, *Therapeutic Effects of Non-Invasive Brain Stimulation with Direct Currents (tDCS) in Neuropsychiatric Diseases*, 85 Pt 3 NEUROIMAGE 948–60 (2014); André R. Brunoni et al., *Transcranial Direct Current Stimulation for Acute Major Depressive Episodes: Meta-Analysis of Individual Patient Data*, 208 BR. J. PSYCHIATRY J. MENT. SCI. 522–31 (2016); Andre Russowsky Brunoni et al., *Clinical Research with Transcranial Direct Current Stimulation (tDCS): Challenges and Future Directions*, 5 BRAIN STIMULAT. 175–95 (2012).

² Jodie Marquez et al., *Transcranial Direct Current Stimulation (tDCS): Does it have Merit in Stroke Rehabilitation? A Systematic Review*, 10 INT. J. STROKE 306–16 (2015).

³ Timothy Y. Mariano et al., *Transcranial Direct Current Stimulation (tDCS) Targeting Left Dorsolateral Prefrontal Cortex Modulates Task-Induced Acute Pain in Healthy Volunteers*, 17 PAIN MED. MALDEN MASS. 737–45 (2016).

⁴ Andre R. Brunoni et al., *The Sertraline vs. Electrical Current Therapy for Treating Depression Clinical Study: Results from a Factorial, Randomized, Controlled Trial*, 70 JAMA PSYCHIATRY 383–91 (2013); Brunoni et al., *supra* note 1; Colleen K. Loo et al., *Transcranial Direct Current Stimulation for Depression: 3-Week, Randomised, Sham-Controlled Trial*, 200 BR. J. PSYCHIATRY 52–59 (2012).

⁵ Kuo, Paulus & Nitsche, *supra* note 1.

contexts of use, conditions of test subjects, and ecological variables.⁶ The appeal of tDCS is its ease of application, cost, and ability to be deployed in a range of wide environments⁷ (eg in- and out-patient clinics, mobile/field medical units, etc.).

Importantly, in numerous controlled clinical trials, tDCS has been shown to be effective in reducing clinical features of the aforementioned conditions that are refractory to other treatments⁸ (eg pharmacological agents, physical, and/or cognitive therapy, etc.). However, because clinical trials are inherently restricted in scope, time, and geography, patient access to therapy in trials is often impractical or difficult. Though there are ongoing efforts to establish rigorous methods for remotely supervised clinical trials.⁹ For patients that have completed clinical trials, options for continuity of clinical care are at best limited (if not wholly unavailable), even if patients have proven to be highly responsive. In light of this, patients who may gain clinical benefit from tDCS treatment often are unable to access clinical venues for its safe and apt provision, increasing the burden of disease. If denied access to provision to tDCS under medical care, some patients will then seek alternative resources. One such avenue is the growing body of information available via the internet regarding ‘do-it-yourself’ (DIY) approaches, which may include adaptation of commercially available devices (eg iontophoresis) for transcranial neuromodulation.¹⁰ Furthermore, the issues addressed here are not related to the ethico-legal concerns generated by DIY or direct-to-consumer tDCS,¹¹ but rather refer to consequences of denying patients supervised, well-controlled tDCS clinical care.

In sum, when considering the possible use of tDCS, it becomes important to address potential harms of both omission and commission. In the former instance, there is defined risk of incurring increased burden of illness by not engaging tDCS to treat patients in whom other interventions have been shown to be ineffective, impractical, or to produce deleterious effects. In the latter, there is theoretical risk of eliciting adverse effects by employing tDCS. We posit that more finely grained assessment of extant information available about tDCS effects and effectiveness under specific conditions and when treating particular types of patients will be essential to establish a more balanced

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- ⁶ John R. Shook, Lucia Galvagni & James Giordano, *Cognitive Enhancement Kept Within Contexts: Neuroethics and Informed Public Policy*, 8 FRONT. SYST. NEUROSCI. 228 (2014); Jay Gill, Priyanka P. Shah-Basak & Roy Hamilton, *It’s the Thought That Counts: Examining the Task-dependent Effects of Transcranial Direct Current Stimulation on Executive Function*, 8 BRAIN STIMUL. 253–59 (2015).
- ⁷ Jared Cooney Horvath, Jason D. Forte & Olivia Carter, *Evidence that Transcranial Direct Current Stimulation (tDCS) Generates Little-to-no Reliable Neurophysiologic Effect Beyond MEP Amplitude Modulation in Healthy Human Subjects: A Systematic Review*, 66 NEUROPSYCHOLOGIA 213–36 (2015).
- ⁸ Marine Mondino et al., *Transcranial Direct Current Stimulation for the Treatment of Refractory Symptoms of Schizophrenia. Current Evidence and Future Directions*, 21 CURR. PHARM. DES. 3373–83 (2015).
- ⁹ Leigh E. Charvet et al., *Remotely-Supervised Transcranial Direct Current Stimulation (tDCS) for Clinical Trials: Guidelines for Technology and Protocols*, 9 FRONT. SYST. NEUROSCI. (2015), <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4362220/> (accessed Nov 10, 2015); Margaret Kasschau et al., *Transcranial Direct Current Stimulation is Feasible for Remotely Supervised Home Delivery in Multiple Sclerosis*, NEUROMODULATION (2016).
- ¹⁰ Anna Wexler, *A Pragmatic Analysis of the Regulation of Consumer Transcranial Direct Current Stimulation (tDCS) Devices in the United States*, 2 J. L. BIOSCI. 669–96 (2016).
- ¹¹ Marom Bikson, Sven Bestmann & Dylan Edwards, *Neuroscience: Transcranial Devices are not Playthings*, 501 NATURE 167–67 (2013); Nicholas S. Fitz & Peter B. Reiner, *The Challenge of Crafting Policy for do-it-Yourself Brain Stimulation*, J. MED. ETHICS 101458 (2013); Anna Wexler, *The Practices of do-it-Yourself Brain Stimulation: Implications for Ethical Considerations and Regulatory Proposals*, 42 J. MED. ETHICS 102704 211 (2015).

stance toward use and non-use, and in this way ameliorate the possibility of both types of harm.

Pursuant to this goal, and with patient care ascendant, we advocate (1) that those tDCS protocols under systematic testing in clinical trials be made available, under limited conditions, in clinical care; (2) that guidelines and regulations for clinical use be focused upon and reflective of realistic assessment of all extant information available to date; (3) ongoing research—under ecologically valid, clinical conditions—be sustained and expanded to inform ongoing care decisions; so as to contribute to (4) developing an iterative, accurate and usable repository of data derived from laboratory studies and practice experiences to guide the safe and sound use of tDCS in defined clinical contexts¹².

Toward these ends, regulatory oversight will be both important and required, as this is an established protocol for both drug- and device-based interventions to be used to effect medical benefit. Pharmacological compounds are strategically validated by the producing commercial entity, and industry-sponsored research entails formulaic pre-clinical and clinical phases, pursuant to FDA review and ultimate approval. Yet, it is noteworthy that in the United States, a number of compounds are employed ‘off-label’. In its general form, tDCS is not a proprietary technique; tDCS research is ‘investigator initiated’ and thus the extant corpus of completed tDCS studies—many of which appear to demonstrate positive therapeutic outcomes—are heterogeneous with regard to dose, patient selection/inclusion, adjunct treatment(s) and outcome metrics. One salient finding gained from review of these studies is that tDCS effects are relatively selective and specific, as dependent upon context of the intervention and certain neurocognitive characteristics of the subjects involved.¹³ The diversity of these contexts can render it difficult for practitioners to easily and accurately assess both particular effectiveness, and broad clinical benefit with respect to defining patient selection, and treatment parameters. But the development and validation of tDCS is distinct from that conventional proprietary drugs, and so the diversity of tDCS clinical-trial designs (and so outcomes) should be understood to reflect a broad investigator-initiated (and typically government and foundation funded) effort.

At present, tDCS trials are reviewed and conducted in accordance with the ‘Non-Significant-Risk’ designation for medical devices.¹⁴ Typical side effects of tDCS are temporary skin irritation and itching at the sites of electrode placement, with the incidence of other common side effects comparable to sham.¹⁵ It is important to note that, in controlled human trials, no serious adverse effects (ADEs) of tDCS treatment

¹² Lauren Treene, Anna Wexler & James Giordano, *TOWARD AN INTEGRATIVE DATABASE OF/FOR TRANSCRANIAL ELECTRICAL STIMULATION: DEFINING NEED, AND POSITING APPROACHES, BENEFITS AND CAVEATS* (2015), <http://www.neuroethicssociety.org/2015-annual-meeting-abstracts> (accessed August 30, 2016).

¹³ Beatrix Krause & Roi Cohen Kadosh, *Not all Brains are Created Equal: The Relevance of Individual Differences in Responsiveness to Transcranial Electrical Stimulation*, 8 *FRONT. SYST. NEUROSCI.* (2014), <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3932631/> (accessed May 6, 2016); Gill, Shah-Basak & Hamilton, *supra* note 6.

¹⁴ F Fregni et al., *Regulatory Considerations for the Clinical and Research Use of Transcranial Direct Current Stimulation (tDCS): Review and Recommendations from an Expert Panel*, 32 *CLIN. RES. REGUL. AFF.* 22–35 (2015).

¹⁵ Bhaskar Paneri et al., *Tolerability of Repeated Application of Transcranial Electrical Stimulation with Limited Outputs to Healthy Subjects*, 9 *BRAIN STIMUL. BASIC TRANSL. CLIN. RES. NEUROMODULATION* 740–754 (2016), [http://www.brainstimjml.com/article/S1935-861X\(16\)30104-8/references](http://www.brainstimjml.com/article/S1935-861X(16)30104-8/references) (accessed August 30, 2016).

have been reported after greater than 50,000 sessions of tDCS in diverse patient populations at numerous institutions.¹⁶ The risk of tDCS is considered to be so low that routine testing is acceptable in healthy volunteers.¹⁷ Indeed, such considerations are of equal merit when addressing and assessing relative benefits and risks of employing tDCS to treat patients suffering from severe neuropsychiatric disorders.

The official regulatory posture governing the use of tDCS is progressive,¹⁸ with current regulation in the EU supporting the use of tDCS in the treatment of depression and pain. In most cases, the use of tDCS remains investigational or off-label therapy. In the United States, the prescribed use(s) of investigational devices remain highly regulated in compliance with FDA Quality Systems and/or IEC certification standards. When medical devices are used with the intent to treat (outside of the context of a clinical trial), FDA approval is not necessarily required.¹⁹ However, Wexler et al., 2015²⁰ notes that laws regarding consumer safety and advertising still apply to these medical devices when used outside of clinical trials. We agree with Wexler et al. that clinicians currently, and could continue to repurpose iontophoresis devices for 'off-label' tDCS treatments, as such practice is legal in the United States. However, this does not, nor should not suggest cavalier use of tDCS in clinical contexts. A framework of ethical responsibilities, inquiry, and considerations important to the use of any neurotechnology has been proposed, and we advocate that this should be taken into account prior to engaging tDCS in research and practice.²¹ Guidance documents on best practices continue to be updated²² and practitioner certification available.²³ Only medical-grade devices and accessories provide adequate assurance of reliability and reproducibility in the context of clinical care.

Physicians remain obligated to obtain and employ the most current knowledge about the product (including if it is manufactured to medical device standards), and subject-specific dose and treatment profiles.²⁴ Such knowledge should be based upon both scientific rationale and sound medical evidence (eg clinical trials, reports of investigator-initiated research, empirical laboratory studies relevant to the focus and scope of intended use-in-practice, and evidence-based reviews), and in this light, there is an equally strong imperative to stringently maintain medical records of use,

¹⁶ Andre Russowsky Brunoni et al., *A Systematic Review on Reporting and Assessment of Adverse Effects Associated with Transcranial Direct Current Stimulation*, 14 INT. J. NEUROPSYCHOPHARMACOL. 1133–45 (2011).

¹⁷ Brian A. Coffman, Vincent P. Clark & Raja Parasuraman, *Battery Powered Thought: Enhancement of Attention, Learning, and Memory in Healthy Adults using Transcranial Direct Current Stimulation*, 85 NEUROIMAGE 895–908 (2014).

¹⁸ Fregni et al., *supra* note 13.

¹⁹ Office of the Commissioner, SEARCH FOR FDA GUIDANCE DOCUMENTS-, <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm> (accessed Apr. 27, 2016).

²⁰ Wexler, *supra* note 9.

²¹ James Giordano, *Conditions for Consent to the Use of Neurotechnology: A Preparatory Neuroethical Approach to Risk Assessment and Reduction*, 6 AJOB NEUROSCI. 12–14 (2015); James Giordano, *A Preparatory Neuroethical Approach to Assessing Developments in Neurotechnology*, 17 VIRTUAL MENTOR 56–61 (2015).

²² Alexandre F. DaSilva et al., *Electrode Positioning and Montage in Transcranial Direct Current Stimulation*, J. VIS. EXP. (2011), <http://www.jove.com/index/Details.stp?ID=2744> (accessed May 24, 2016); A. J. Woods et al., *A Technical Guide to tDCS, and Related Non-Invasive Brain Stimulation Tools*, 127 CLIN. NEUROPHYSIOL. 1031–48 (2016).

²³ NYC tDCS Fellowship 2016, <http://neuromodex.com/event/nyc-tdcs-fellowship-2016/> (accessed May 24, 2016).

²⁴ Giordano, *supra* note 19.

therapeutic outcomes and any and all side effects, so as to contribute to the body information available to guide current and future use.²⁵ Patients should be fully informed of known effects, effectiveness, and limitations, so as to insure probity of consent. And continued clinical care should be made available and accessible to patients should treatment be ineffective or elicit any side effects that would require mitigative intervention even if there are no established hazards.²⁶

In conclusion, we argue that the information about the efficacy, effectiveness and safety of tDCS available to date defensibly supports our position that:

- tDCS is broadly considered safe for routine application even in healthy subjects, and investigator-initiated controlled clinical trials have suggested effectiveness in reducing particular symptoms of defined neuropsychiatric disorders/conditions.
- To withhold treatment of patients in acute need, pending resolution of all mechanistic questions, completion of pivotal trials that exactly overlap the subject disease etiology, and/or explicit approval from regulatory agencies will effectively prohibit a majority of patients from the possibility of a demonstrably safe, and potentially beneficial treatment.
- The study of tDCS should continue in order to develop and fortify the database of information regarding the potential viability, utility, and value of this treatment, in the spirit and tenor of responsibility to/of clinical equipoise.
- Any and all such research and clinical interventions should be conducted under the purview and auspices of an ethically sound framework of preparation, review and execution. tDCS interventions should only be applied in accordance with best practices and published guidelines in regards to both equipment and practitioner training.
- The off-label use of tDCS does not and should not in any way reduce manufacturers' responsibility to meet medical device design guidelines, or physicians' adherence to technically apt and ethically sound treatment practices.

²⁵ Treene, Wexler & Giordano, *supra* note 11.

²⁶ Giordano, *supra* note 19.