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Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016

Marom Bikson [a,*], Pnina Grossman [a], Chris Thomas [a], Adantchede Louis Zannou [a], Jimmy Jiang [a], Tatheer Adnan [a], Antonios P. Mourdoukoutas [a], Greg Kronberg [a], Dennis Truong [a], Paulo Boggio [b], André R. Brunoni [c], Leigh Charvet [d], Felipe Fregni [e], Brita Fritsch [f,g], Bernadette Gillick [h], Roy H. Hamilton [i,j,k], Benjamin M. Hampstead [l,m], Ryan Jankord [n], Adam Kirton [o], Helena Knotkova [p,q], David Liebetanz [r], Anli Liu [s], Colleen Loo [t], Michael A. Nitsche [r,u,v], Janine Reis [f,g], Jessica D. Richardson [e,w,x], Alexander Rotenberg [y,z], Peter E. Turkeltaub [aa,ab], Adam J. Woods [ac]

[a] Department of Biomedical Engineering, The City College of New York, New York, NY, USA
[b] Cognitive Neuroscience Laboratory and Developmental Disorders Program, Center for Health and Biological Sciences, Mackenzie Presbyterian University, Sao Paulo, Brazil
[c] Service of Interdisciplinary Neuromodulation, Department and Institute of Psychiatry, Laboratory of Neurosciences (LIM-27), University of São Paulo, São Paulo, Brazil
[d] NYU MS Comprehensive Care Center, Department of Neurology, New York University School of Medicine, New York, NY, USA
[e] Berenson-Allen Center for Noninvasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA
[f] Department of Neurology, University Medical Center, Freiburg, Germany
[g] BrainLinks-BrainTools Cluster of Excellence, University of Freiburg, Germany
[h] Department of Physical Medicine and Rehabilitation, University of Minnesota Medical School, Minneapolis, MN
[i] Laboratory for Cognition and Neural Stimulation, University of Pennsylvania, Philadelphia, PA, USA
[j] Center for Cognitive Neuroscience, University of Pennsylvania, Philadelphia, PA, USA
[k] Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA
[l] Mental Health Service, VA Ann Arbor Healthcare System, Ann Arbor, MI, USA
[m] Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA
[n] Applied Neuroscience, 711th Human Performance Wing, Air Force Research Laboratory, WPAFB, OH, USA
[o] Departments of Pediatrics and Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
[p] MJHS Institute for Innovation in Palliative Care, New York, NY, USA
[q] Department of Social and Family Medicine, Albert Einstein College of Medicine, The Bronx, NY, USA
[r] Department of Clinical Neurophysiology, University Medical Center, Georg-August-University, Goettingen 37075, Germany
[s] NYU Comprehensive Epilepsy Center, New York University School of Medicine, New York, NY, USA
[t] Psychiatry, Black Dog Institute, Clinical Academic, St George Hospital, University of New South Wales, Sydney, Australia
[u] Leibniz Research Centre for Working Environment and Human Factors at the TU Dortmund, Dortmund, Germany
[v] Department of Neurology, University Medical Hospital Bergmannsheil, Bochum, Germany
[w] Department of Communication Sciences & Disorders, The University of South Carolina, Columbia, SC, USA
[x] Department of Speech and Hearing Sciences, The University of New Mexico, Albuquerque, NM, USA
[y] Berenson-Allen Center for Noninvasive Brain Stimulation, Division of Cognitive Neurology, Department of Neurology, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA, USA
[z] Pediatric Neuromodulation Program, Division of Epilepsy and Neurophysiology, Department of Neurology, Children's Hospital Boston, Harvard Medical School, Boston, MA, USA
[aa] Department of Neurology, Georgetown University, Washington, DC, USA
[ab] Research Division, MedStar National Rehabilitation Hospital, Washington, DC, USA
[ac] Center for Cognitive Aging and Memory, Institute on Aging, Department of Aging and Geriatric Research, McKnight Brain Institute, University of Florida, Gainesville, FL, USA

* Corresponding author. Tel.: 212-650-6791; fax: 212-650-6727.
E-mail address: bikson@ccny.cuny.edu (M. Bikson).

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ABSTRACT

This review updates and consolidates evidence on the safety of transcranial Direct Current Stimulation (tDCS). Safety is here operationally defined by, and limited to, the absence of evidence for a Serious Adverse Effect, the criteria for which are rigorously defined. This review adopts an evidence-based approach, based on an aggregation of experience from human trials, taking care not to confuse speculation on potential hazards or lack of data to refute such speculation with evidence for risk. Safety data from animal tests for tissue damage are reviewed with systematic consideration of translation to humans. Arbitrary safety considerations are avoided. Computational models are used to relate dose to brain exposure in humans and animals. We review relevant dose–response curves and dose metrics (e.g. current, duration, current density, charge, charge density) for meaningful safety standards. Special consideration is given to theoretically vulnerable populations including children and the elderly, subjects with mood disorders, epilepsy, stroke, implants, and home users. Evidence from relevant animal models indicates that brain injury by Direct Current Stimulation (DCS) occurs at predicted brain current densities (6.3–13 A/m^2) that are over an order of magnitude above those produced by conventional tDCS. To date, the use of conventional tDCS protocols in human trials (≤40 min, ≤4 milliamperes, ≤7.2 Coulombs) has not produced any reports of a Serious Adverse Effect or irreversible injury across over 33,200 sessions and 1000 subjects with repeated sessions. This includes a wide variety of subjects, including persons from potentially vulnerable populations.

Introduction

Scope

The goal of this report is to update the state-of-the-art on the safety of transcranial Direct Current Stimulation (tDCS), based on published Serious Adverse Effects in human trials and irreversible brain damage in animal models. For the purposes of this report, tDCS includes non-invasive transcranial electrical stimulation using direct current with a sustained intensity of a few milliamperes and duration of up to tens of minutes; with specific definitions and inclusion/exclusion criterion defined. Basing our evaluation solely on established evidence, we rely on (1) testing in human trials, including reports of serious adverse events and imaging changes; (2) animal models, including histologically observable tissue; and (3) computational modeling to the limited extent it can inform the interpretation of experimental data. By consensus, we distinguish between adverse *events* (which are potentially coincidental) and adverse *effects* (which are believed to be causally related to stimulation), examining specific case data taken in the context of best experimental practices and all available tDCS data. Tolerability or transient adverse cognitive and behavioral changes that are not associated with Serious Adverse Effects are not taken into account.

Electrical stimulation in animals is referred to as Direct Current Stimulation (DCS; even when epicranial), as opposed to tDCS, to distinguish it from the human stimulation. For human data, the review has the limitation that it relies largely on reports of serious adverse events in published controlled studies in which subjects are not typically exhaustively tested for injury or followed for an extensive period. Prospective studies on tDCS safety are limited in humans [1,2]. For animal data, effort is devoted to understanding the translation of findings (e.g. dose scaling) to humans. Data from translational animal models are taken to support establishing tDCS safety limits only in the context of irreversible brain damage. We avoid speculation regarding *theoretical* risks of tDCS that are based on extrapolation from reports in which no specific link to tDCS has been established (e.g. inferring the potential risks of low intensity direct current based on the known risks of high intensity current).

Exclusion of subjects with preexisting co-morbidities from participation in clinical trials (e.g. exclusion of subject with depression from stroke studies, and exclusion of subjects with stroke from depression studies) reduces the number of complicated cases tested with tDCS. When such exclusion is not explicitly justified for safety reasons then it likely reflects experimental design (e.g. depression post stroke is considered a different illness to depression of another etiology) rather than concern regarding risk. Nonetheless, such "conservative" exclusions, as well as subject-specific safety monitoring protocols applied in the absence of evidence for risk, can be a source of confusion with regards to safety norms and are therefore discussed in this review.

Operator intentions when applying tDCS, the efficacy of tDCS in eliciting desired outcomes [3], and the presumed mechanisms of tDCS are not relevant for the scope of this review [4]. Similarly, potential neuroprotective effects are not within our scope [5], except for instances in which they inform safety. Animal safety data are limited to non-invasive or epicranial electrode techniques, since the safety profile for electrodes that directly contact with brain tissue is distinct (e.g. electrochemical in a way not relevant for non-invasive techniques). This review aggregates and analyzes data relevant to the safety of tDCS and comments on experience in human trials of tDCS to date. It does not make specific recommendations for protocols or serve as a guideline for the design of safety protocols. This review may, however, inform ongoing ethical and regulatory decisions [6].

Definitions and considerations of dose metrics for tDCS safety

For the purposes of this review, tDCS is defined as a technique in which the dose [7] is a waveform of single sustained direct current (DC), with the exception of one ramp-up and one ramp-down period, applied to the head using at least one cephalic electrode. tDCS is non-invasive and requires appropriate electrolyte buffer (conductive gel, paste, or saline) between the electrode and the skin. tDCS thus does not include the use of subdural stimulation electrodes.

While tDCS could technically include any waveform that does not change polarity (e.g. even a monophasic triangle wave), tDCS as used across current human trials involves only fixed sustained direct current. The lower-case "t" in tDCS is thus important to emphasize a proper name that designates a specific stimulation approach. Hence trains of monophasic pulses are not tDCS as defined here (but rather transcranial Pulsed Current Stimulation, even when a DC offset is included). Similarly neither oscillating transcranial direct current stimulation (a monophasic square waveform) nor a rectified or monophasic sinusoidal waveform is included in tDCS as defined here.