Transcranial Direct Current Stimulation for Major Depression: A General System for Quantifying Transcranial Electrotherapy Dosage

Marom Bikson, PhD
Peter Bulow, MD, MFA
John W. Stiller, MD
Abhishek Datta, MS
Fortunato Battaglia, MD, PhD
Sergei V. Karnup, MD, PhD, DSc
Teodor T. Postolache, MD

Corresponding author
Teodor T. Postolache, MD
Mood and Anxiety Program, University of Maryland School of Medicine, 685 West Baltimore, MSTF Suite 930, Baltimore, MD 21201, USA.
E-mail: Tpostola@psych.umaryland.edu

Current Treatment Options in Neurology 2008, **10:**377–385
Current Medicine Group LLC ISSN 1092-8480

Opinion statement

There has been a recent resurgence of interest in therapeutic modalities using transcranial weak electrical stimulation through scalp electrodes, such as transcranial direct current stimulation (tDCS), as a means of experimentally modifying and studying brain function and possibly treating psychiatric conditions. A range of electrotherapy paradigms have been investigated, but no consistent method has been indicated for reporting reproducible stimulation "dosage." Anecdotal reports, case studies, and limited clinical trials with small numbers suggest that tDCS may be effective in treating some patients with depression, but methods for selecting the optimal stimulation parameters ("dosage") are not clear, and there is no conclusive indication that tDCS is an effective treatment for depression. Larger, controlled studies are necessary to determine its safety and efficacy in a clinical setting.

If tDCS can be established as an effective treatment for depression, it would represent a particularly attractive electrotherapy option, as it is a relatively benign and affordable treatment modality. An accurate system for describing reproducible treatment parameters is essential so that further studies can yield evidence-based guidelines for the clinical use of transcranial current stimulation. Development of appropriate parameters requires a biophysical understanding of how electrotherapy affects brain function and should include different paradigms for different clinical applications. As with any dosage guidelines, such a system does not supersede physician judgment on safety.

Introduction

ELECTROTHERAPY FOR DEPRESSION

Contrary to common perception, the most potent antidepressant agent, in terms of effectiveness and rapidity of onset, is not a pharmacologic agent but an electrical therapy. Electroconvulsive therapy (ECT) is the gold-standard treatment for severe/refractory and psychotic depression, and is highly effective for acutely suicidal patients [1,2, Class I; 3, Class III]. However, the costs of ECT (including anesthesia), unfavorable public perceptions of it, well-documented short-term cognitive deficits, and concerns about permanent cognitive deficits (though ECT protocols can be designed to minimize long-term deficits) support the development of more benign versions of electrical therapy.

Electrotherapy approaches using implanted electrical stimulators, such as deep brain stimulation (DBS) [4, Class III; 5, Class II] and vagus nerve stimulation (VNS) [6, Class I], are increasingly being used to treat neurologic disorders (eg, refractory movement disorders) and psychiatric disorders (ie, severe, refractory mood and anxiety disorders). However, these approaches, being inherently invasive, have manifest limitations related to cost and risk and do not provide the adaptive flexibility of noninvasive approaches.

Noninvasive approaches for brain modulation include magnetic and electrical stimulation through the skull: transcranial magnetic stimulation (TMS) with coils [7, Class I] or transcranial current stimulation (TCS) with electrodes placed on the scalp. TCS is further classified into ECT that necessitates seizure induction under general anesthesia and other, more experimental forms of TCS that deliver significantly less electrical stimulation and do not induce electrographic seizures or require anesthesia. One of these experimental TCS approaches is transcranial direct current stimulation (tDCS).

An ideal electrotherapy treatment would combine ease of administration (ultimately self-administered), effective outcomes through plastic brain changes (not requiring chronic stimulation), low cost, robust safety (noninvasive, with no major risks), and thus, minimal contraindications. From this perspective, tDCS is a highly promising electrotherapy approach [8, Class II; 9••, Class I]. However, questions remain about its clinical efficacy, and there is no consistent system for determining tDCS "dosage," a deficit that fundamentally confounds the further rational development of tDCS treatments [10]. The absence of such a system precludes precise reproduction of stimulation "dosage" across subjects and studies, compromises patient safety, and complicates regulation by the US Food and Drug Administration.

SYSTEM FOR REPORTING TCS DOSAGE

To accurately describe electrical therapy "dosage" for tDCS (and more broadly, TCS), it is important to have a basic understanding of the terminology (system of metrics) that is used to define and differentiate the various practical aspects of TCS. This is of pivotal importance because even subtle differences in electrical therapy dosage paradigms can fundamentally affect treatment outcome and safety. This article presents a comprehensive system that can be used to characterize TCS dosage paradigms and can be applied to current and past tDCS protocols.

TCS encompasses all research and clinical technology to modulate brain function by passing current through at least one electrode placed on the scalp. Modern clinical TCS approaches to treat depression have been broadly classified based on the stimulation paradigm used and the therapeutic approach. The tDCS protocol involves relatively weak (≤ 2 mA) direct-current stimulation for several minutes. Cranial electrotherapy stimulation (CES) encompasses a range of pulsed protocols (> 1 Hz) with intensities nominally less than 5 mA. ECT involves relatively strong (> 0.9 A) pulsed waveforms, sufficient to induce electrographic seizures. The tDCS and CES protocols are both subconvulsive. The potential range of electrotherapy stimulation paradigms extends well beyond the limited set currently described by tDCS, CES, and ECT. However, clinical treatment with TCS generally has been restricted to this limited set of stimulation protocols, reflecting both safety concerns restricting innovation and limitations of common clinical stimulation devices.

This article focuses on clinical experience with tDCS for depression. Even within a specific therapy classification such as tDCS, however, "dosage" variables will fundamentally affect clinical outcome. Across TCS studies, descriptions of electrotherapy dosage are inconsistent, and essential information necessary to reproduce and compare results is often omitted.

For any TCS research or therapeutic application, the electrotherapy paradigms (dosage) will be fully described by the following system of seven independent metrics. This system is based on clinical experience with factors found to affect outcome, and on in vivo and in vitro animal and human studies of stimulation mechanisms [10–22]. The TCS device consists of a programmable stimulator (metrics 1, 4, and 5) connected via leads to electrodes placed on the body (metrics 2 and 3). In some stimulation paradigms, multiple stimulation devices may be simultaneously activated; if so, the stimulation parameters (metrics 1 through 6) may be "mirrored" (the same stimulation protocol but opposite hemispheres) or distinct for each device.

Metric 1: Exposure duration

A single exposure is defined in the context of the outputs of an electrical stimulator being energized (turned from functionally OFF to ON) and then being turned OFF after a user-determined exposure duration. When the

stimulation is OFF, no current/voltage is being applied. When stimulation is turned ON, it is assumed that metrics 2 through 5 below are fixed for the duration of any given exposure (eg, electrodes are not moved during an exposure). If exposure duration is adjusted across patients (metric 7), the range must be indicated.

Metric 2: Electrode number, connectivity, and position on body

It is assumed that the default stimulation device has two output wires and each electrode is connected to only one of these two wires. There may be more than two electrodes per stimulation device, so that multiple electrodes are connected to the same output wire. The connectivity and the position of every electrode on the surface of the body must be indicated. The position of all scalp electrodes and extracephalic electrodes must be accurately reported. It is not sufficient to indicate only the presumed "active" electrodes. In case of tDCS, each electrode can be designated as either an anode or a cathode, which indicates connectivity to the respective stimulator output terminal.

Metric 3: Electrode size/shape, electrode material, and contact/skin conditions

The geometry (shape) and size of every electrode can fundamentally affect therapy outcome [18]. The electrode material should be indicated, as well as the use of any specific electrolyte gel and sponge (including the salinity/conductivity of sponge fluid [23]). The use of conductive solution or gel may change the effective area of the electrode. The preparation of the skin should also be described (eg, no preparation, cleaning the skin with alcohol, or use of an abrasive).

Metric 4: Stimulation peak intensity (stimulation peak amplitude)

Indicate whether the stimulation device is "current-controlled" or "voltage-controlled." Indicate the peak intensity of the stimulation as the maximum amplitude of current (for current-controlled devices) or voltage (for voltage-controlled devices) applied to the electrodes during the entire exposure. For tDCS, peak intensity is nominally the intensity of the DC stimulation. If peak intensity is adjusted across patients (metric 7), indicate the range.

Metric 5: Waveform

The stimulation waveform fully describes the output of the stimulation device during the entire exposure duration (from turning stimulation ON to turning it OFF, including any designed or undesired transients). No aspect of the waveform can be ignored or omitted, including initial transients. The waveform describes how the current (for current-controlled devices) or voltage (for voltage-controlled devices) applied to the electrodes changes over time, never exceeding the peak intensity. Often the waveform can be described using simple mathematical functions such as ramps, sinusoids, or pulses. Any change in polarity must be indicated in describing waveforms. In tDCS, the waveform does not change polarity (in a given exposure) and remains DC for most of the exposure duration, but the initiation and termination of stimulation may be associated with other waveform components such as on/off ramps.

Metric 6: Exposure number and interval

Metrics 1 through 5 fully describe the stimulation paradigm ("dose") used for a single exposure, but it is also necessary to describe the total number of exposures and the interval between them. For multiple exposures, metrics 1 through 5 may change for each exposure. Because tDCS may have prolonged effects on neuronal excitability [24] and mood, repeated exposures may interact in a complex fashion. This is of particular clinical significance, as repeated exposure of the same polarity may lead to cumulative effects, whereas alternating polarity may interfere with net effects (Table 1).

Metric 7: Patient selection and contraindications, empiric paradigm adjustment

Simply on the basis of gross morphologic differences (eg, skull dimensions), TCS effects will vary across subjects. Subject age and sex provide a minimal baseline for considering these differences. As with drugs, clinical history also may affect treatment outcome. Patient medication should be indicated, in case of drug/stimulation interactions. Stimulation paradigms may also be adjusted by feedback specific to the group or patient, including changes in perception (eg, pain), behavior, and EEG (eg, seizure thresholds). If such empiric adjustments of dosing occur, the optimization methods should be outlined, even though the final selected paradigm will still be described using metrics 1 through 6. In some cases, protocols may also be adjusted based on predictive computer simulations. Exclusion criteria and contraindications should be clarified and clearly reported. Reporting empiric adjustment methods (eg, peak intensity titration) is not a substitute for full reporting of the stimulation parameters ultimately used (metrics 1–6).

ADDITIONAL TCS TERMINOLOGY AND CONVENTIONS

Each commercial clinical stimulator produces a limited range and combination of intensities and waveforms, and specific electrode configurations are often recommended. Theoretically, if all the above factors are controlled for, the specific manufacturer or model of stimulation device and electrodes will not affect therapy outcome (no more than if two companies produced chemically identical drugs). However, therapeutic devices may not perform ideally (eg, in delivering the peak intensity indicated), so report-

Table 1. Comparisons of transcranial direct current stimulation paradigms (stimulation "dosage") for treatment of depression*

Study	*N*	Population class	Study design, class	Electrode shape/size, surface conditions	Electrode number, connectivity, positions	Intensity, *μA*	Exposure duration	Exposure sessions (polarity changes)	Outcome
Lippold and Redfearn [25]	32	Adults, variable diagnosis	Double-blind, Class III	Head: 0.5-in chlorided silver disks covered in saline-soaked gauze. Cambridge electrode jelly on skin. Leg: "similar" but "larger"	2 supraorbital (same polarity), right knee (return)	100–500†	1–5 h†	Same day, alternate polarities	26 of 32: improved mood (anode), quietness (cathode); 6 of 32: opposite directions
Redfearn et al. [22]	29	Depression with variable diagnosis, not responsive to drugs or ECT; age 18–70 y	Open case reports, Class III	Same as [25]	2 supraorbital (anode), leg (cathode)	20–250† per anode	Up to 8 h	Variable†	> 50% "some" or "considerable" value
Costain et al. [26]	24	Depression, in/outpatients, excluding suicidal; no antidepressive drugs	Double-blind, Class I	Same as [25]	2 supraorbital (anode), leg (cathode)	Increased to 250 per supraorbital electrode during first 2 d	~ 8 h	Daily for 5 consecutive weekdays, total 12 exposures	Improved mood
Sheffield and Mowbray [27]	6	Normal men, mean age 21 y	Double-blind, Class II	Head: 0.5-in chlorided silver disks covered in saline-soaked lint. Leg: 0.75-in disks	"As close as possible" to [25]	< 250† "per lead"	~ 3 h	Daily (alternating anodal/cathodal) × 5 d	No change
Carney [28]	4	Manic, ages 27–65 y	Open, Class III	Cathode electrodes covered in saline-soaked gauze and electrode jelly	Cathodes on "inner end of each eyebrow"; anode on knee	250	2–3 h	2–6 sessions per wk "according to need" for 6 mo	3 of 4: "calming effect"
Arfai et al. [24]	19	Female inpatients, "depressive states"	Double-blind, Class I	–	2 supraorbital (anode), 2 thighs (cathode)	250 per supraorbital electrode	8 h	Daily 6 d/wk for 2 wk	No change

*Heterogeneity of procedures and the spottiness of published documentation regarding stimulation parameters complicates direct comparison of outcomes and reproduction of protocols.
†Parameters that were adjusted empirically (within the range indicated) based on patient-specific feedback.
DLPFC—dorsolateral prefrontal cortex; ECT—electroconvulsive therapy; HAM-D—Hamilton Depression Rating Scale.

Table 1. Comparisons of transcranial direct current stimulation paradigms (stimulation "dosage") for treatment of depression* (*Continued*)

Study	*N*	Population class	Study design, class	Electrode shape/size, surface conditions	Electrode number, connectivity, positions	Intensity, μA	Exposure duration	Exposure sessions (polarity changes)	Outcome
Nias and Shapiro [29]	2	Subject 1: Male, age 37 y, atypical depression with underlying schizophrenia, on medication	Class III	–	2 supraorbital (same polarity), 2 right leg (returns)	400–500	3–4 h	Daily (alternating anodal/cathodal), 20 sessions	Subject 1: "improve" (cathode)
		Subject 2: Male, age 57 y, depression, on medication							Subject 2: "improve" (anode)
Fregni et al. [8]	10	Depression	Double-blind randomized, Class II	Saline-soaked sponge, 7 × 5 cm	DLPFC, F3 (anode), right supraorbital (cathode)	1000	20 min	Daily, 5 sessions	4 of 5: 50% HAM-D drop
Boggio et al. [9••]	40	Major depression; women age 50 ± 7 y. Antidepressant-free for 2 mo; other psychotropic meds allowed	Double-blind randomized, Class I	Saline-soaked sponge, 7 × 5 cm	DLPFC (anode), right supraorbital (cathode)	2000	20 min	10 d (Monday–Friday, 2 consecutive wk)	40% HAM-D drop

*Heterogeneity of procedures and the spottiness of published documentation regarding stimulation parameters complicates direct comparison of outcomes and reproduction of protocols.
†Parameters that were adjusted empirically (within the range indicated) based on patient-specific feedback.
DLPFC—dorsolateral prefrontal cortex; ECT—electroconvulsive therapy; HAM-D—Hamilton Depression Rating Scale.

ing the device used and device settings will allow for post hoc correction of unintended device performance.

Just as with pharmaceutical clinical trials, the methods and controls used will determine how each specific electrical therapy trial is interpreted. Particularly in psychiatric trials, special consideration must be given for potential placebo effects related to device operation (eg, beeping) and electricity sensation. The particular clinical trial design will determine what electrical therapy paradigms are tested. As with pharmaceutical trials, a dose-response study may be indicated under certain circumstances; each electrical "dosage" metric (metrics 1–6) may be changed independently. However, as in a fixed-dose pharmaceutical study, the electrotherapy dosage (metrics 1–6), once standardized, needs to be administered reproducibly for any meaningful conclusions to be drawn about efficacy and safety.

It is useful to clarify how electrical therapy terms are used (sometimes inconsistently) in the literature. Stating that a protocol employs DC stimulation indicates that the stimulation remains at the peak intensity for the duration of the exposure. However, as mentioned previously, current and voltage may be "ramped" on or off during an exposure; this must be indicated. *Monophasic* stimulation indicates that for the entire exposure, though the intensity may vary, only one polarity is applied (ie, current is passed in only one direction). *Biphasic* and *alternating current (AC)* stimulation indicate that the polarity is reversed at some point in the course of an exposure. In the context of electrical stimulation, an *anode* electrode is at a positive voltage relative to a *cathode* electrode, so that positive current will move from the anode electrode to the scalp, whereas positive current will move from the scalp to a cathode electrode. In monophasic stimulation such as tDCS, the anodes and cathodes are well defined. In biphasic stimulation, the anode and cathode are technically changing between phases; in this case, one electrode may be arbitrarily defined as mathematically "positive" relative to the other, and applied waveform current/voltage can be described as "positive" or "negative" based on this arbitrary referencing system. The terms *anodal stimulation*, *cathodal stimulation*, *bipolar*, and *unipolar* may be ambiguous and should be defined in the context of the given study.

There have been considerations in the clinical literature to summarize the dosage of a complete stimulation paradigm using a single "reduced" metric. Examples of reduced metrics include peak electrode current density (the peak current divided by the area of a selected electrode) or charge-per-phase (the average current in a specific pulse times the duration of the pulse). Working with limited stimulation paradigm constraints (eg, DC stimulation through large scalp electrodes), these single metrics provide general guidelines in normalizing the effects of therapy across subjects and studies (eg, maintain current density across electrode sizes). However, these reduced metrics do not necessarily serve as absolute normalizing factors for efficacy and safety; simply reporting these metrics does not fully describe the stimulation paradigm, and it is not possible to determine or reproduce the stimulation paradigm given only a reduced metric.

From the perspective of normalizing stimulation across patients (including efficacy and safety aspects) current-controlled stimulation is preferable to voltage-controlled stimulation. Although voltage-controlled stimulation remains "grandfathered" into some stimulation technology, the electric field induced intracranially (which ultimately determines therapy effects) is not controlled across patients with voltage control [11], and it will vary in an unpredictable fashion depending on electrode size and material and skin properties.

Even within the limited reports on tDCS for treatment of mood disorders, there is a lack of consistency and completeness in describing stimulation paradigms (dosage) (Table 1). As emphasized above, this issue is very important, as any change in stimulation paradigms (eg, change in position or number of electrodes, exposure interval, or polarity) may fundamentally affect clinical outcome.

SPECIAL ASPECTS AND SAFETY FACTORS

Several interrelated factors affect electrical stimulation safety with each stimulation modality (TCS, TMS, DBS, VNS) to different extents: 1) electrochemical reactions at the electrode-electrolyte (tissue) interface, 2) excitotoxic neuronal activation, 3) electroporation and electropermeation of barriers, 4) tissue heating (burning), and 5) undesired plastic changes in brain function (eg, memory disruption, seizure kindling). Safety guidelines for TCS must be cognizant of each of these factors [11,17].

During TCS, because the electrodes are not in contact with the brain, hazards associated with electrochemical reactions and heating are presumably minimized and any acute irritation is restricted to the skin. Thus, TCS is a special modality, allowing the safe application of subthreshold paradigms that incorporate long, monophasic (eg, tDCS) or brain-derived (simple oscillation or "played back EEG") waveforms. These waveforms may be particularly suited to induction of "functionally targeted" plastic changes in brain function. Use of subthreshold fields prevents painful shocks (as are induced during high-intensity transcranial electrical stimulation) but may still be associated with scalp sensation and mild discomfort. Scalp discomfort and hazards to brain function are not necessarily linked [18,23].

When an extracephalic electrode is used, a portion of the applied electricity will flow across the neck and brainstem. Injuries have not been reported with relatively low currents (< 1 mA), but one anecdotal report suggests that higher current (> 3 mA) through the brainstem may transiently disrupt breathing (Bindeman L, personal communication).

Treatment

Electrical therapy

- Two recent studies of tDCS in the treatment of major depressive disorder are summarized here. The complete reporting of stimulation protocols in both of these studies allows the direct comparison of the complementary but distinct stimulation paradigms and illustrates that even slight deviations in protocols can produce significant differences in electrical stimulation "dosage."
- The study by Boggio et al. [9••, Class I] used a common tDCS electrode configuration: one surface cranial anode electrode positioned over the dorsolateral prefrontal cortex, and one cathode electrode over the contralateral eyebrow.
- The second study, by Bulow et al. (2008, in progress), used one anode electrode placed similarly over the left dorsolateral prefrontal cortex and a cathode electrode on the contralateral arm; earlier investigators favored this use of an extracephalic electrode. These small differences in electrical stimulation paradigms result in different electrical dosages being tested (Fig. 1).

tDCS for Depression Stimulation Paradigm I (Boggio et al. 2008)

Stimulation metrics

1. **Exposure duration:** 20 minutes.
2. **Electrode number, connectivity, and position on the body:** 1 anode, left dorsolateral prefrontal cortex (F3); 1 cathode, contralateral supraorbital area.
3. **Electrode size/shape, electrode material, skin/contact conditions:** 7 × 5 cm square sponge electrodes (metal mesh back), saline-soaked (impedance not excessively large).
4. **Peak intensity:** 2 mA (current-controlled).
5. **Waveform:** DC.
6. **Exposure number and interval:** 10 sessions (Monday–Friday of 2 consecutive weeks).
7. **Patient selection and contraindications, empirical paradigm adjustment:** Adult, no neurologic illness.

Main drug interactions None reported.

Main side effects None reported.

Special points Custom simulator. Controls include sham stimulation (stimulation for 30 sconds only) and active control with occipital tDCS.

tDCS for Depression Stimulation Paradigm II (Bulow et al. 2008)

Stimulation metrics

1. **Exposure duration:** 20 minutes.
2. **Electrode number, connectivity, and position on the body:** 1 anode, left dorsolateral prefrontal cortex (F3); 1 cathode, contralateral arm.
3. **Electrode size/shape, electrode material, skin/contact conditions:** 7 × 7 cm square sponge electrodes (metal mesh back), dampened with tap water.
4. **Peak intensity:** 1 mA (current-controlled).
5. **Waveform:** DC.
6. **Exposure number and interval:** Daily treatment sessions (Monday–Friday) for total of 10 sessions (sham group) or 20 sessions (active group).
7. **Patient selection and contraindications, empirical paradigm adjustment:** Adult.

Main drug interactions None reported.

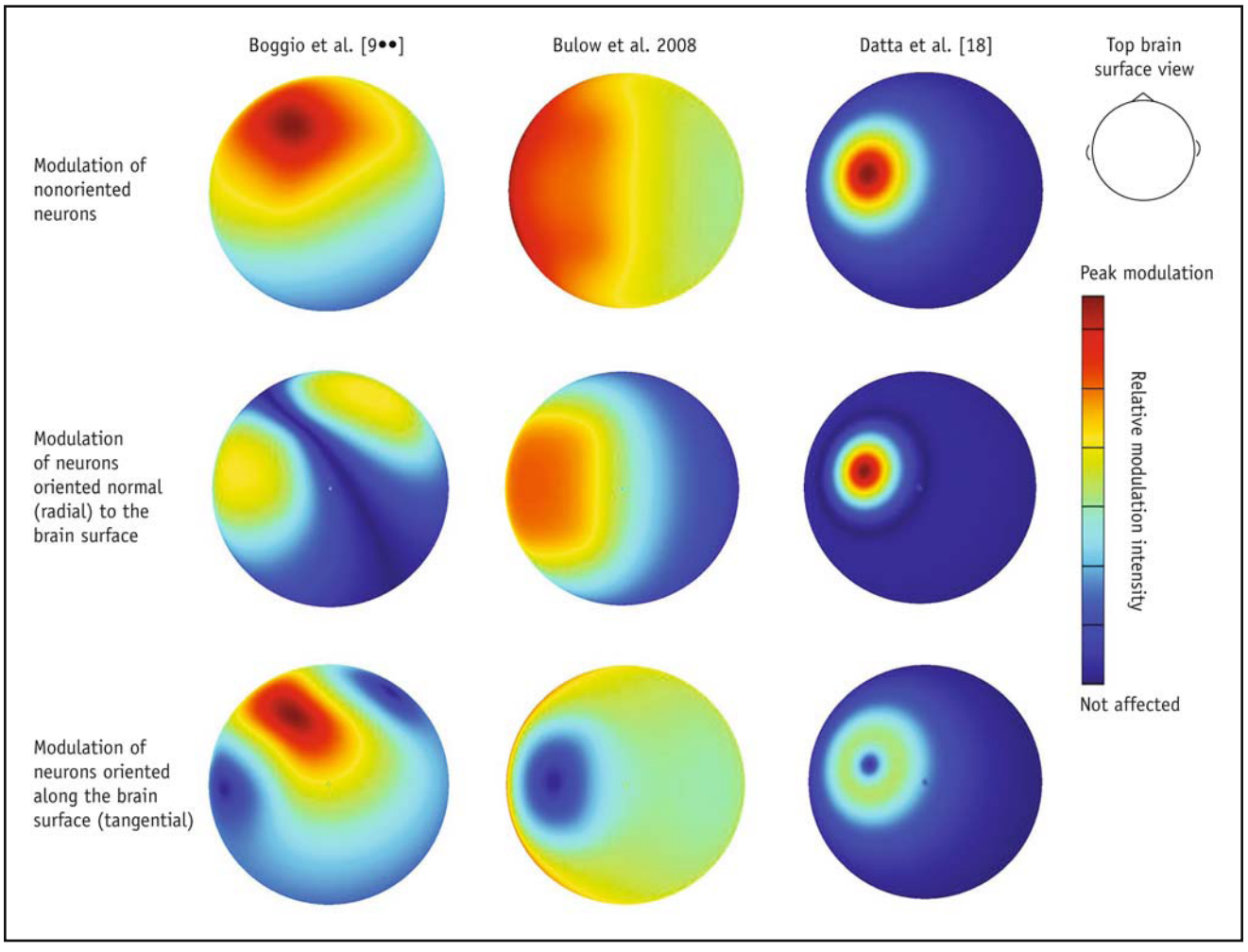

Figure 1. Comparison of predicted brain modulation by different electrotherapy paradigms. The false color maps provide different indicators of brain modulation and were generated using finite-element computer head models of transcranial direct current stimulation (tDCS). Different electrical therapy "dosage" results in divergent brain modulation and thus may result in different therapeutic outcomes. These computational predictions require further experimental and clinical validations. Nonetheless, the substantive differences in predicted brain modulation between different electrical stimulation protocols highlight the need to fully control and report electrical therapy paradigms.

Main side effects	Mild headache, nausea in some patients. Tingling/itching under the electrodes for most patients. Mild burns under anodal electrode after one session in one subject, apparently due to insufficient wetting of sponges; the problem resolved when the sponges were kept very moist.
Special points	Stimulator: Phoresor II (Iomed, Salt Lake City, UT). Electrodes: rubber pad with sponge insert (2-A103, Amrex, Carson, CA); effective immersion covers sponge and rubber.

Acknowledgments

The authors are grateful to Sarah Lisanby, Walter Paulus, and Michael Nitsche for valuable comments on an earlier version of the manuscript and to Sarah Zimmerman for help with references and overall formatting.

Disclosures

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently,
have been highlighted as:

- • Of importance
- •• Of major importance

1. Lisanby SH, Maddox JH, Prudic J, et al.: **The effects of electroconvulsive therapy on memory of autobiographical and public events.** *Arch Gen Psychiatry* 2000, **57:**581–590.
2. Sackeim HA, Prudic J, Devanand DP, et al.: **A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities.** *Arch Gen Psychiatry* 2000, **57:**425–434.
3. Lisanby SH: **Electroconvulsive therapy for depression.** *N Engl J Med* 2007, **357:**1939–1945.
4. Aouizerate B, Cuny E, Martin-Guehl C, et al.: **Deep brain stimulation of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression.** *J Neurosurg* 2004, **101:**682–686.
5. Greenberg BD, Malone DA, Friehs GM, et al.: **Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder.** *Neuropsychopharmacology* 2006, **31:**2384–2393.
6. Rush AJ, Marangell LB, Sackeim HA, et al.: **Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial.** *Biol Psychiatry* 2005, **58:**347–354.
7. O'Reardon JP, Solvason HB, Janicak PG, et al.: **Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial.** *Biol Psychiatry* 2007, **62:**1208–1216.
8. Fregni F, Boggio P, Nitsche M, et al.: **Treatment of major depression with transcranial direct current stimulation.** *Bipolar Disord* 2006, **8:**203–204.
9. •• Boggio PS, Rigonatti SP, Ribeiro RB, et al.: **A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression.** *Int J Neuropsychopharmacol* 2008, **11:**249–254.

A controlled study of tDCS in depression.

10. Bikson M, Radman T, Datta A: **Rational modulation of neuronal processing with applied electric fields.** *Conf Proc IEEE Eng Med Biol Soc* 2006, **1:**1616–1619.
11. Merrill DR, Bikson M, Jefferys JG: **Electrical stimulation of excitable tissue: design of efficacious and safe protocols.** *J Neurosci Methods* 2005, **141:**171–198.
12. Bikson M, Inoue M, Akiyama H, et al.: **Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro.** *J Physiol* 2004, **557:**175–190.
13. Miranda PC, Lomarev M, Hallett M: **Modeling the current distribution during transcranial direct current stimulation.** *Clin Neurophysiol* 2006, **117:**1623–1629.
14. Nitsche MA, Paulus W: **Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation.** *J Physiol* 2000, **527:**633–639.
15. Nitsche MA, Paulus W: **Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans.** *Neurology* 2001, **57:**1899–1901.
16. Nitsche MA, Nitsche MS, Klein CC, et al.: **Level of action of cathodal DC polarization induced inhibition of the human motor cortex.** *Clin Neurophysiol* 2003, **114:**600–604.
17. Nitsche MA, Liebetanz D, Lang N, et al.: **Safety criteria for transcranial direct current stimulation (tDCS) in humans.** *Clin Neurophysiol* 2003, **114:**2220–2222.
18. Datta A, Elwassif M, Battaglia F, et al.: **Transcranial current stimulation focality using common and novel electrode configurations: FEM analysis.** *J Neural Eng* 2008, **5:**163–174.
19. Rush S, Driscoll DA: **Current distribution in the brain from surface electrodes.** *Anesth Analg* 1968, **47:**717–723.
20. Iyer MB, Mattu U, Grafman J, et al.: **Safety and cognitive effects of frontal DC brain polarization in healthy individuals.** *Neurology* 2005, **64:**872–875.
21. McCreery DB, Agnew WF, Yuen TG, et al.: **Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation.** *IEEE Trans Biomed Eng* 1990, **37:**996–1001.
22. Redfearn WT, Lippold J, Costain R: **Preliminary account of the clinical effects of polarizing the brain in certain psychiatric disorders.** *Br J Psychiatry* 1964, **110:**773–785.
23. Dundas JE, Thickbroom GW, Mastaglia FL: **Perception of comfort during transcranial DC stimulation: effect of NaCl solution concentration applied to sponge electrodes.** *Clin Neurophysiol* 2007, **118:**1166–1170.
24. Arfai E, Theano G, Montagu JD, et al.: **A controlled study of polarization in depression.** *Br J Psychiatry* 1970, **116:**433–434.
25. Lippold OCJ, Redfearn JWT: **Mental changes resulting from the passage of small direct currents through the human brain.** *Br J Psychiatry* 1964, **110:**768–772.
26. Costain RJW, Redfearn JW, Lippold OC: **A controlled trial of the therapeutic effect of polarization of the brain in depressive illness.** *Br J Psychiatry* 1964, **110:**786–799.
27. Sheffield LJ, Mowbray RM: **The effects of polarization on normal subjects.** *Br J Psychiatry* 1968, **114:**225–232.
28. Carney MWP: **Brain negative polarization in the treatment of manic states.** *Ir J Med Sci* 1969, **2:**133–135.
29. Nias DKB, Shapiro MB: **The effects of small electrical currents upon depressive symptoms.** *Br J Psychiatry* 1974, **125:**414–415.