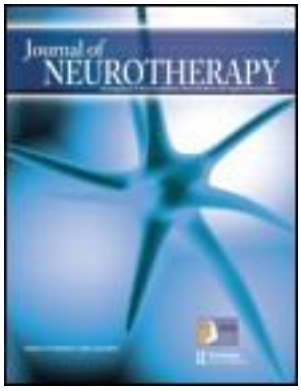

Journal of Neurotherapy: Investigations in Neuromodulation, Neurofeedback and Applied Neuroscience

Transcranial Electrical Stimulation: Methodology and Applications

Efthymios Angelakis [a] & Evangelia Liouta [a]

[a] Department of Neurosurgery , Professor Petros S. Kokkalis Hellenic Center for Neurosurgical Research, National and Kapodistrian University of Athens , Athens, Greece

Published online: 30 Nov 2011.

To cite this article: Efthymios Angelakis & Evangelia Liouta (2011) Transcranial Electrical Stimulation: Methodology and Applications, Journal of Neurotherapy: Investigations in Neuromodulation, Neurofeedback and Applied Neuroscience, 15:4, 337-357, DOI: 10.1080/10874208.2011.623092

To link to this article: http://dx.doi.org/10.1080/10874208.2011.623092

Journal of Neurotherapy, 15:337–357, 2011

ISSN: 1087-4208 print/1530-017X online
DOI: 10.1080/10874208.2011.623092

Routledge
Taylor & Francis Group

TRANSCRANIAL ELECTRICAL STIMULATION: METHODOLOGY AND APPLICATIONS

Efthymios Angelakis, Evangelia Liouta

Department of Neurosurgery, Professor Petros S. Kokkalis Hellenic Center for Neurosurgical Research, National and Kapodistrian University of Athens, Athens, Greece

Low-intensity transcranial current stimulation is a rapidly growing field of research. Transcranial direct current stimulation (tDCS) is the dominant paradigm of this new field, with transcranial alternating current stimulation (tACS) just emerging. Anodal stimulation with tDCS has excitatory effects on the underlying cortex, whereas cathodal stimulation has inhibitory effects. Because both electrodes have significant brain effects when placed at cephalic areas, the term "reference" electrode should be avoided. Most studies have applied tDCS to the motor cortex, the prefrontal cortex, and the occipital cortex. Applications of tDCS include modulation of electrophysiological and hemodynamic brain activity, symptom reduction in neurological and psychiatric pathology, and cognitive improvement in healthy volunteers or clinical populations. There is evidence of motor improvement in patients with stroke, pain reduction in fibromyalgia, improved mood in patients with unipolar or bipolar depression, and reduced craving. Healthy volunteers are shown to improve their verbal fluency, working memory, and implicit learning. Moreover, there are interactions of tDCS with various pharmacological substances. There are no significant side effects, apart from minor skin lesions when tap water is used instead of saline solution in the sponge electrodes. Further research is required to reveal the potential of tACS.

HISTORICAL PERSPECTIVE

Low-intensity transcranial current stimulation is a rapidly growing field of research for the treatment of neurological and psychiatric pathology, as well as for the modulation of cognitive and emotional functions in healthy volunteers. From January to August of 2011 there were more than 100 published peer-reviewed articles on transcranial direct current stimulation (tDCS), more than those published in the 10 years between 1998 and 2008. Therefore, the present review is not comprehensive but rather indicative of the methodologies, the clinical and nonclinical applications, and the brain effects of low-intensity transcranial current stimulation.

Modern application of electrical currents to the human brain for treating neurological or psychiatric illness is dated back to 1938, when Cerletti and Bini initiated Electroconvulsive Therapy (ECT) to treat schizophrenia (Cerletti, 1950). Present applications of electrical brain stimulation include deep brain and scalp-induced currents. The former involves surgical implantation of microelectrodes in deep brain structures, whereas the latter involves placement of electrodes on the scalp, using either strong electric fields in ECT, or weak electric fields in tDCS and transcranial alternating current stimulation (tACS).

Deep brain stimulation (DBS) uses microelectrodes with high frequency alternating

Received 13 August 2011; accepted 31 August 2011.

Preparation of this article was supported by the HIVE project, a Future and Emerging Technologies (FET) programme within the 7th Framework Programme for Research of the European Commission, under FET Open grant number: 222079 (http://hive-eu.org/). We thank Pedro Cavaleiro Miranda from the University of Lisbon for estimating current density distribution.

Address correspondence to Efthymios Angelakis, PhD, Hellenic Center for Neurosurgical Research, 3, Ploutarchou Street, GR 10675, Athens, Greece. E-mail: angelakis@neurosurgery.org.gr

current to stimulate subcortical structures, such as the globus pallidus interna or the subthalamic nucleus of the basal ganglia, as well as the thalamus (Fields & Troster, 2000). It has been used primarily for the improvement of motor function in patients with movement disorders, such as Parkinson's Disease (PD; Breit, Schulz, & Benabid, 2004), and more recently dystonia (Ostrem & Starr, 2008; Sakas et al., 2010), pain (Owen et al., 2007), obsessive-compulsive disorder (Greenberg et al., 2006), epilepsy (Handforth, DeSalles, & Krahl, 2006), depression (Mayberg et al., 2005), and Tourette's syndrome (Neuner et al., 2008). Although the original rationale for DBS was to replace neurosurgical lesions by inducing a reversible functional lesion in overactivated subcortical structures, such as the globus pallidus interna or the subthalamic nucleus, more recent insights hypothesize that the mechanisms of action of DBS are more complex, including depolarization blockade, synaptic inhibition, synaptic depression, and stimulation-induced modulation of pathological network activity (McIntyre, Savasta, Kerkerian-Le Goff, & Vitek, 2004).

Like DBS, ECT was initially introduced as a less invasive alternative to lobotomies in treating mental illness (Pandya, Pozuelo, & Malone, 2007). It involves induction of a seizure via scalp electrodes that apply alternating current electrical charges from 25 to 504 mC and has been applied for the treatment of depression. However, other conditions have also been targeted, either directly or as comorbidities to depression, such as mania, schizophrenia, PD, and other movement disorders, like tardive dystonia, tardive dyskinesia, neuroleptic-induced malignant catatonia, progressive supranuclear palsy, multiple system atrophy, and Wilson's disease (Kennedy, Mittal, & O'Jile, 2003; Rasmussen, Sampson, & Rummans, 2002). ECT is shown to cause side effects on memory, including immediate recognition, long-term storage, delayed verbal recall, and memory for visual designs (Feliu et al., 2008). Unilateral right ECT has been shown to cause fewer cognitive side effects than bilateral ECT (Squire, 1977). Although ECT's exact mechanism of action is not well understood, it seems that antidepressive outcome correlates positively with a paradoxical reduction of cerebral blood flow (Nobler et al., 1994). Moreover, ECT has been shown to increase sensitivity of serotonin (5-HT) receptors 5-HT3 in the hippocampus and to increase the release of noradrenaline and dopamine from the locus coeruleus and the substantia nigra (Ishihara & Sasa, 1999).

PROPERTIES AND METHODOLOGY OF tDCS

Bioelectrical Properties of tDCS

Unlike DBS and ECT, tDCS does not induce neuronal action potentials. Its effects are neuromodulatory only, by affecting sodium and calcium channels (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche et al., 2003), and thus affecting the resting potential of the neuronal membrane (Nitsche et al., 2008). Anodal (positive) tDCS is excitatory, and cathodal (negative) tDCS is inhibitory (Lang, et al., 2005; Nitsche & Paulus, 2000). These effects hold for superficial cortical neurons and are reversed for neurons deep in the sulci. Ten min of cathodal tDCS over the right primary motor cortex is shown to increase power in the delta band of the EEG at that area (C4; Ardolino, Bossi, Barbieri, & Priori, 2005), whereas 20 min of anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC) is shown to reduce the amplitude of the delta band at that area (F3), mostly for the first 5 min (Keeser et al., 2011). Larger current densities will increase the depth of the electrical field relevantly and thus alter excitability of cortical neurons not affected by lower stimulation intensities. However, they may be painful (Wagner, Valero-Cabre, & Pascual-Leone, 2007). Electrode area size is positively related with cortical current density (Wagner et al., 2007).

Primary Effects of tDCS

Effects of tDCS in humans include changes in behavioral measures, like in motor performance (Vines, Cerruti & Schlaug, 2008; Vines, Nair, & Schlaug, 2006) and cognitive performance

(Boggio et al., 2006; Floel, Rosser, Michka, Knecht, & Breitenstein, 2008; Fregni, Boggio, Nitsche, 2005; Iyer et al., 2005; Kincses, Antal, Nitsche, Bártfai, & Paulus, 2004; Monti et al., 2008), and in sensory perception (Antal, Nitsche, & Paulus, 2001); changes in electrophysiological measures, such as motor-evoked potentials (MEPs; Ardolino et al., 2005; Furubayashi et al., 2008; Nitsche & Paulus, 2000; Quartarone et al., 2004) or event-related potentials (Keeser et al., 2011; Nakamura-Palacios et al., 2011), intramuscular coherence (Power et al., 2006), EEG visual-evoked potentials or pain-evoked potentials (Accornero, Li Voti, La Riccia, & Gregori, 2007; Antal, Brepohl, et al., 2008; Terney et al., 2008), and EEG amplitude (Ardolino et al., 2005; Marshall, Moelle, Hallschmid, & Born, 2004), as well as in brain hemodynamic changes measured by functional magnetic resonance imaging (Baudewig, Nitsche, Raulus, & Frahm, 2001; Kwon et al., 2008; Zheng, Alsop, & Schlaug, 2011), or by positron emission tomography (PET; Lang et al., 2005).

Using functional magnetic resonance imaging, Baudewig and colleagues (2001) found decreased regional cerebral blood flow (rCBF) after 5 min of cathodal tDCS at the primary motor cortex, and no changes after anodal tDCS. These changes in rCBF after cathodal stimulation of the primary motor cortex were noted at a nearby area (supplementary motor area). Zheng et al. (2011) replicated these effects and found increased rCBF at the motor cortex *during* anodal tDCS, and a smaller increase in rCBF during cathodal tDCS over that area. When alternating ON/OFF tDCS periods of $3\frac{1}{2}$ min each, anodal stimulation showed constant elevations of rCBF during the ON periods, whereas cathodal tDCS showed decreasing elevations of rCBF during the ON periods. Using proton magnetic resonance spectroscopy, Clark, Coffman, Trumbo, and Gasparovic (2011) found increased concentrations of glutamate and glutamine at the cortical area beneath the anodal electrode (P4), after 30 min of tDCS, with the cathode at the contralateral arm, and no changes at the homologous interhemispheric area.

Pharmacological Interactions with tDCS

Regarding the pharmacological interactions with tDCS studies have focused on primary motor cortex stimulation protocols. Various pharmacological substances have been found to either block or prolong the effects of tDCS on the primary motor cortex. A single oral dose of either the Na+-channel-blocking substance carbamazepine (CBZ), or the calcium channel blocker flunarizine, blocked any excitatory effects on MEPs during 4-s/1-mA anodal stimulation or inhibitory effects during similar cathodal stimulation of the primary motor cortex (Nitsche et al., 2003). Moreover, a single oral dose of either CBZ or the N-methyl-D-aspartate-receptor antagonist dextromethorphan, completely blocked any excitatory effects on MEPs after 5-min/1-mA anodal stimulation of the primary motor cortex. Moreover, dextromethorphan—but not CBZ—also completely blocked any inhibitory after-effects of 5-min/1-mA cathodal stimulation on MEPs (Liebetanz et al., 2002). The authors concluded that immediate effects of tDCS are due to modulation of sodium and calcium channels, whereas lasting after effects of tDCS are due to N-methyl-D-aspartate-receptor-dependent neuroplasticity (Nitsche et al., 2003). Similarly, rivastigmine, an acetylcholine agonist, is shown to block any tDCS induced excitatory or inhibitory effects on MEPs after 13-min/1-mA anodal or cathodal stimulation of the primary motor cortex (Kuo, Grosch, Fregni, Paulus, & Nitsche, 2007).

By contrast, a single oral dose of amphetaminil (AMP), a precursor of amphetamine (a dopamine agonist), significantly prolonged the excitatory effects on MEPs after 13-min/1-mA anodal stimulation of the primary motor cortex, whereas it slightly shortened the duration of cathodal tDCS effects. Whereas the excitatory effects of tDCS lasted for about one hour without AMP, they were prolonged until the following morning with AMP (Nitsche et al., 2004). However, levodopa (L-DOPA), a precursor of dopamine, showed opposite effects to AMP. A single oral dose of L-DOPA blocked any tDCS-induced excitatory effects on MEPs after

13-min/1-mA anodal stimulation of the primary motor cortex and prolonged the tDCS induced inhibitory effects on MEPs (Kuo, Paulus, & Nitsche, 2008). Similarly, pergolide, another dopaminergic agonist, was shown to prolong the 15-min/1-mA cathodal tDCS-induced inhibitory aftereffects on laser-evoked potentials from 40 min to 24 hr (Terney et al., 2008). Hence, different dopaminergic agonists have shown opposite effects on tDCS, one prolonging the effects of anodal stimulation but not of cathodal stimulation and the other two blocking the effects of anodal stimulation and/or prolonging the effects of cathodal stimulation. It is possible that these opposing effects are due to the different nature of these dopaminergic agonists, one giving raw material for the production of dopamine (L-DOPA), another making more dopamine available at the synaptic cleft (amphetamine), and yet the third mimicking the effects of dopamine on D2 and D3 receptors (pergolide).

Side Effects of tDCS

Nitsche and colleagues (2008) reported that tDCS protocols (current density up to 0.029 mA/cm^2, stimulation duration up to 13 min) were tested in 2,000–3,000 subjects in laboratories worldwide with no serious side effects. Poreisz and colleagues (2007) analyzed the data from 567 tDCS sessions on 102 participants, including healthy volunteers, and individuals with migraine, tinnitus, and stroke. Stimulation was up to 0.029 mA/cm^2, and lasted from 9 to 15 min. They found side effects to include a mild tingling or itching sensation; moderate fatigue; and seldom-occurring headache, fatigue, and nausea. A mild redness under the electrodes seems to be due to neurally driven vasodilatation. Durand, Fromy, Bouyé, Saumet, & Abraham (2002) delivered transcutaneously 0.1 mA for 1 min to the forearms of healthy volunteers and found a slow progressive vasodilatation, measured by laser Doppler flowmetry. However, repeated daily tDCS with a current density of about 0.06 mA/cm^2 caused clinically significant skin irritation under the electrodes in some patients (Nitsche et al., 2008). Some of the most intense tDCS trials were conducted in the 1960s by Lippold, Redfearn, and Costain (Costain, Redfearn, & Lippold, 1964; Lippold & Redfearn, 1964; Redfearn, Lippold, & Costain, 1964). They delivered up to 0.25 mA/cm2 of anodal and cathodal stimulation to the forehead with the opposite pole to the knee, for consecutive daily 8-hr sessions, to either healthy volunteers or patients with depression.

While delivering current to healthy subjects via bifrontal electrodes with the reference on the leg, Redfearn et al. (1964) encountered one case of respiratory and motor paralysis with cramping of the hands, accompanied by nausea. There was no loss of consciousness, and respiration returned when the current was stopped. The subject was not hospitalized but had impaired fine motor control lasting for 2 days, ultimately returning to normal. There were no other serious adverse events in the study, and apparently this subject received 10 times the intended amperage, probably 3 mA.

In recent studies, skin lesions after long-term treatment with tDCS have been reported. In a pilot study (Palm et al., 2008) on patients with depression, 10 patients underwent 1 mA tDCS and five patients underwent 2 mA tDCS. Each active tDCS was applied for 20 min, 5 days per week, during a 2-week period. For stimulation a CE-certified Eldith DC-stimulator with two water-soaked sponge electrodes (7×5 cm) was used. According to the authors, sponges soaked in tap water instead of saline solution were applied because they cause less uncomfortable itching sensations than saline-soaked sponges and allow EEG recording immediately after tDCS, which was an adjunctive investigation. The anode was placed over the left DLPFC and the cathode over the right supraorbital region. The lesions appeared under the cathode after the fourth or fifth session only in the group receiving 2 mA treatment. The extent of the lesions ranged from 2 to 3 mm up to 2 cm and was proportional to the skin impedance measured while connecting the DC-stimulator. The authors suggested that the occurrence of lesions may depend on the intensity and duration of tDCS, as well as on the impedance between electrode and skin. Also, they hypothesized that

the use of tap water instead of sodium chloride solution may have led to higher impedance and thermal side effects. Similar skin lesions under the anode (right dorsolateral prefrontal cortex) are reported (Frank et al., 2010) in three patients with chronic tinnitus that underwent 1.5 mA tDCS treatment for 30 min, 2 days per week, during a 3-week period, with sponge electrodes soaked in tap water. The authors speculate that accumulation of toxic products from tap water may have accounted for the skin lesions. We also believe that these side effects were due to the use of tap water rather than to the amount of current or the amount of stimulation time, because in our laboratory we have used tDCS in 20-min daily sessions of 0.08 mA/cm^2, via saline-soaked sponge electrodes, 5 days per week, during a 2-week period in healthy volunteers, with no side effects.

Experimental Methodology of tDCS

Reviews examining tDCS methodology used in various studies (Nitsche et al., 2008; Wagner et al., 2007) summarize experimental parameters and make methodological suggestions for future studies:

- Stimulation time duration is positively related to occurrence probability and duration of after-effects.
- tDCS produces stable lasting effects in the human motor cortex for up to an hour if tDCS is applied for 9 to 13 min.
- Current density delivered has varied between 0.029 and 0.08 mA/cm^2 in most published studies.
- Current densities should not exceed 0.029 mA/cm^2 (which refers to 1 mA/35 cm2), above which they could be painful (unpublished observations).
- The application of NaCl solutions between 15 and 140 mM to sponge electrodes is more likely to be perceived as comfortable during tDCS.
- To reduce cutaneous sensation and other transient phenomena at the start and stop of stimulation, current flow should be ramped up and down.
- Ramping for 10 s at the beginning and end of tDCS, combined with a stimulation duration of 30 s in the placebo stimulation condition, made real tDCS (performed more than 20 min) and placebo stimulation indistinguishable.
- If repetitive tDCS is performed to prolong and stabilize long-lasting after-effects, subjects are generally stimulated once a day.

Given the rapidly accumulating research with tDCS, it becomes necessary to know how and why any given study chooses its particular stimulation parameters: stimulation area, opposite pole (''reference'') area, electrode size, current density, stimulation time duration, when to stimulate (e.g., before/during/after a task, during sleep), intermittent or continuous stimulation, control condition, and so on. Understanding the rationale behind these choices may unravel the probable neuronal mechanisms responsible for the effects and, therefore, not only will add face validity to the results but also will help design better future studies.

''Reference'' Electrode is Active. One of the problems with tDCS research design, acknowledged by Nitsche and colleagues in their review (Nitsche et al., 2008), is the confounding effects of the so-called reference electrode. In tDCS there are no inactive electrodes, because one has excitatory effects (anode) and the other has inhibitory effects (cathode) on the underlying cortex. In most of tDCS studies, the ''reference'' electrode has been placed on cephalic areas, right above cortical tissue. These areas include the contralateral orbit for primary motor cortex stimulation (Figure 1) or for DLPFC stimulation, the contralateral DLPFC for DLPFC stimulation, and the vertex for visual cortex stimulation (Nitsche et al., 2008). It has been suggested that enlarging threefold the nontarget (reference) electrode area may reduce this problem, by diffusing and thus minimizing the current density in the underlying brain area (Nitsche et al., 2007).

Because of this fact, it may be argued that the results of many tDCS studies can be reinterpreted as due to the effects of the so-called

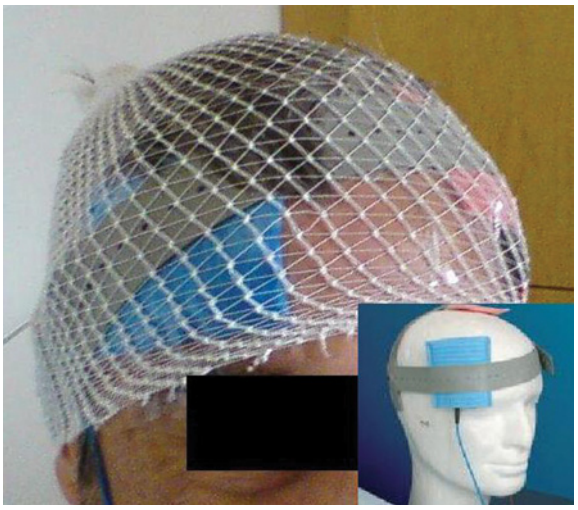

FIGURE 1. Typical arrangement for motor cortex or DLPFC stimulation, with alternative electrode over the contralateral orbit. *Note.* Electrode size 35 cm^2. A net may help the sponge edges to better contact the scalp. (Color figure available online.)

reference electrode. For example, almost all motor cortex tDCS studies have placed the alternative (reference) electrode over the contralateral orbit, that is, the contralateral anterior prefrontal cortex. Thus, increased MEPs thought of as due to anodal stimulation of the primary motor cortex could be reinterpreted as a result of disinhibition due to cathodal (inhibitory) stimulation of the prefrontal cortex. In their pioneering tDCS studies in the 1960s, Lippold and Redfearn (1964) showed that anodal stimulation of bilateral forehead areas produced behavioral excitability (''elevation of mood and an increased involvement in the environment''), whereas cathodal stimulation produced behavioral inhibition (''withdrawal and quietness''). In these experiments, the alternative pole electrode was placed on the leg, so the only brain area directly stimulated should have been the anterior prefrontal cortex. The Lippold and Readfearn results clearly illustrate the significant brain effects of forehead tDCS but do not support the idea of disinhibition for MEPs, because anodal stimulation of the forehead excited and cathodal stimulation inhibited behavior. More evidence against the disinhibition explanation for MEPs includes failure to modify MEPs with electrodes at orbital versus parietal or occipital areas (Furubayashi et al., 2008; Nitsche & Paulus, 2000). Still, failure to show effects on MEPs with alternative pole (reference) electrode at places other than the contralateral orbit (Nitsche & Paulus, 2000) may mean that these effects are due to either (a) a combination of primary motor and prefrontal cortex tDCS, or (b) a unique orientation of the current flow between primary motor and contralateral prefrontal cortex.

Moreover, numerous tDCS studies have shown cognitive effects of anodal stimulation of different areas of the left hemisphere (DLPFC, primary motor area, temporoparietal areas) with the cathodal electrode over the right orbit. For example, working memory (WM) is shown to improve after anodal stimulation of the left DLPFC, with the cathodal electrode over the right orbit in healthy volunteers (Fregni, Boggio, Nitsche, et al., 2005; Ohn et al., 2008), as well as in patients with depression (Fregni, Boggio, Nitsche, et al., 2006), and patients with PD (Boggio et al., 2006). Furthermore, vocabulary learning is shown to improve after anodal stimulation of the left temporoparietal (Wernike's) area, with the cathodal electrode over the right orbit in healthy volunteers (Floel et al., 2008). The role of the right anterior prefrontal cortex is not yet fully understood. It is associated with a variety of cognitive functions, including working memory, episodic memory, semantic monitoring, or motor imagery (McLeod et al., 1998), and it has been hypothesized to play a crucial role in the coordination of multiple cognitive operations (Ramnani & Owen, 2004). Therefore, interpreting the cognitive effects of tDCS as exclusively due to the left hemisphere anode, when the cathode is over the right orbit, is incomplete and may neglect important brain mechanisms.

Attempting to measure the effects of tDCS in neuronal activity, Lang and associates (2005) measured rCBF with PET, immediately after 10 min of 1 mA stimulation via 35 cm^2 electrodes over the hand area of the left primary motor cortex and the right orbit. Comparing anodal versus cathodal stimulation, they found that, when the anode was over the left primary motor cortex, rCBF increased at many brain

areas, including bilateral prefrontal, premotor, primary motor, and temporal cortex, as well as the right thalamus, cerebellum, and cingulate sulcus, and the left occipital sulcus. Anodal stimulation of the right orbit, instead, showed rCBF increases in very few areas, including the right temporal cortex and insula, the left posterior cingulated gyrus, and the right occipital cortex. Moreover, anodal stimulation of the right orbit showed rCBF decreases in many more areas than anodal stimulation of the left primary motor cortex. The authors interpreted these results as the effects of anodal versus cathodal stimulation of the left primary motor cortex. However, it is obvious that this represents only half of the effects, because the alternative electrode was over the right anterior prefrontal cortex. Hence, these rCBF changes can also be interpreted as due to activation (via anode) of either the left primary motor cortex or the right anterior prefrontal cortex. Even better, these results should be interpreted as the combined excitation/inhibition of these two brain areas or of adjacent areas that are in the path of the current flow.

It is quite reasonable to see the right orbital area as an active participant in this process, not only because it has been shown to affect behavior when stimulated with tDCS (Lippold & Redfearn, 1964) but also because it is adjacent to other significant areas, like the right inferior frontal gyrus (Broadmann's area 47) and the anterior part of the left superior frontal sulcus (Broadmann's area 10) that are particularly involved in behavioral and cognitive inhibition (Aron, Robbins, & Poldrack, 2004; Asahi, Okamoto, Okada, Yamawaki, & Yokota, 2004; Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Konishi, Chikazoe, Jimura, Asari, & Miyashita, 2005). Using a numerical method to implement a standard spherical head model (Miranda, Lomarev, & Hallett, 2006), assuming tDCS electrodes of 25 cm^2 over the left primary motor cortex and the right orbit, we have estimated that right inferior frontal gyrus and anterior part of the left superior frontal sulcus receive more than 75% of the current density received by the targeted brain areas, that is, by those right under the electrodes (Figure 2; P. C. Miranda, personal communication, 2009). Therefore, it is possible that the current flow between anode in the right orbit and cathode in the left primary motor cortex, reported in the PET study by Lang and associates (2005), activates the right inferior frontal gyrus or/and the anterior part of the left superior frontal sulcus and therefore show few rCBF increases and many rCBF decreases due to the inhibitory function of these brain areas.

In conclusion, electrodes over the right orbit thought of as inactive ''reference'' may induce significant effects in cognitive and behavioral measures, due to activation or inhibition of the right anterior prefrontal cortex, or of the adjacent areas, such as the right inferior frontal gyrus and the anterior part of the left superior frontal sulcus.

Anodal Stimulation. Most tDCS studies found significant results in either symptom improvement in patient samples, or improved cognitive or motor performance in healthy volunteers via anodal stimulation, which has excitatory effects on the underlying cortex. These include improvement of depression symptoms (Boggio, Rigonatti, et al., 2008; Costain et al., 1964; Rigonatti et al., 2008), decreased craving for smoking (Fregni, Liguori, et al., 2008), alcohol (Boggio, Rigonatti, et al., 2008), and foods (Fregni, Orsati, et al., 2008),

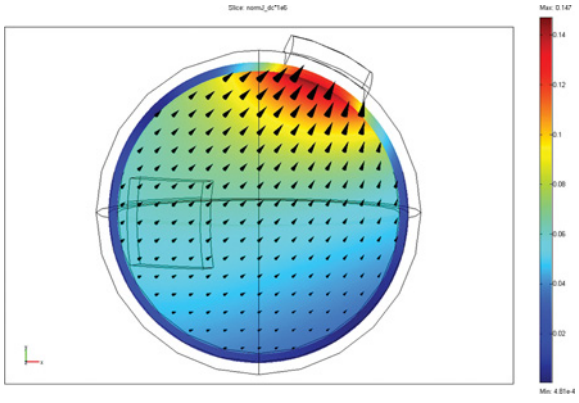

FIGURE 2. Standard spherical head model illustration of current density spread. *Note*. Anodal electrode over left primary motor cortex and cathodal electrode over the right orbit. Arrows show the direction and the magnitude of the current density (A/m^2). (Color figure available online.)

improved motor performance in patients with stroke or PD (Boggio et al., 2006; Boggio, Nunes, et al., 2007; Hummel et al., 2005; Hummel et al., 2006), improved WM in patients with PD (Boggio et al., 2006), improved word recognition in patients with AD (Ferrucci et al., 2008), improvement in fibromyalgia symptoms (Fregni, Gimenes, et al., 2006), pain improvement in patients with central pain due to traumatic spinal cord injury (Fregni, Boggio, Lima, et al., 2006), increased pain threshold in healthy volunteers (Boggio, Sultani, et al., 2008), enhanced language learning and picture naming in healthy volunteers (Floel et al., 2008), and enhanced verbal fluency in healthy volunteers (Iyer et al., 2005).

Cathodal Stimulation. On the contrary, much fewer tDCS studies found significant results with cathodal stimulation. These include improved naming in stroke patients with chronic nonfluent aphasia (Monti et al., 2008), improved motor function in patients with stroke (Boggio, Nunes, et al., 2007; Fregni, Boggio, Mansur, et al., 2005), diminished pain perception in healthy volunteers (Antal, Brepohl, et al., 2008), decreased craving for alcohol (Boggio, Rigonatti, et al., 2008) and foods (Fregni, Orsati, et al., 2008), suppressed motor excitability in control subjects, but no effects in patients with focal dystonia (Lang, Nitsche, Paulus, Rothwell, & Lemon, 2004; Nitsche & Paulus, 2000; Quartarone et al., 2005).

Brain Areas of Stimulation with tDCS. One methodological question with tDCS research is *where* to stimulate. There are many different combinations of electrode placement from which to choose for any particular application: cephalic stimulation with noncephalic opposite pole (reference), left versus right hemisphere versus bilateral, anterior prefrontal versus dorsolateral prefrontal, and so on. Existing studies seem to have based their electrode placement rationales according to known functional compartmentalization of the cortex, but poor understanding of the current distribution and current direction relative to the cortical columns makes such rationales simplistic.

APPLICATIONS OF tDCS

The Primary Motor Cortex

Nonclinical Volunteers. One of the most studied applications of tDCS in the motor cortex is its effects on hand-recorded MEPs induced by transcranial magnetic stimulation. It has been shown that anodal tDCS of the hand area of the primary motor cortex increases the excitability of this cortical area, that is, increases the hand MEPs, whereas cathodal tDCS has the opposite effect, that is, decreases the hand MEPs (Ardolino et al., 2005; Furubayashi et al., 2008; Nitsche & Paulus, 2000; Quartarone et al., 2004). These effects have been achieved by 5 to 10 min of 1 to 1.5 mA tDCS through 35 cm2 square saline-soaked sponge electrodes. Moreover, these effects were possible only with one pole over the hand area of the motor cortex and the other pole over the contralateral orbit, whereas no other combination (e.g., left vs. right motor cortex, occipital vs. orbit) modulated the MEPs (Furubayashi et al., 2008; Nitsche & Paulus, 2000). Jeffery and associates (2007) were able to establish increased leg MEPs with 10 min of 2 mA of anodal tDCS via a 35 cm2 electrode over the leg area of the motor cortex but failed to show decreased leg MEPs with cathodal stimulation.

Other studies have shown changes in motor performance after tDCS of the primary motor cortex. Vines et al. (2006) showed that anodal stimulation of the left primary motor cortex improved right-hand finger sequence performance, whereas cathodal stimulation of the same area improved performance of the left hand. Moreover, Vines, Cerruti, and Schlaug (2008) showed that concurrent cathodal stimulation of the left primary motor cortex and anodal stimulation of the right primary motor cortex improved motor performance of the left hand compared to anodal stimulation of the right primary motor cortex alone. Stimulation was 1 mA for 20 min, via 16.3 cm^2 electrodes.

Finally, tDCS has been shown to affect intermuscular coherence. Power et al. (2006) found that anodal tDCS caused an increase in MEP size that was accompanied by an increase in β-band intermuscular coherence. In addition,

the reduction in MEP size produced by cathodal tDCS was accompanied by a reduction in β-band intermuscular coherence, whereas sham stimulation did not result in any change in either MEP amplitude or β-band intermuscular coherence. According to the authors these changes suggest that at least some of the action of tDCS is on cortical networks and that combined tDCS and intermuscular coherence analysis may be useful in the diagnosis of pathologies affecting motor cortical excitability.

Stroke. Several controlled studies have shown that tDCS may be very useful in the rehabilitation of patients with stroke. Kumar and colleagues (2011) found significant improvement in dysphagia symptoms, in a sham-controlled study of anodal tDCS to the sensorimotor cortical representation of swallowing in the unaffected hemisphere, in patients with stroke. Hummel and colleagues (Hummel et al., 2005, Hummel et al., 2006) found shortened reaction times, improved pinch force, and improved functional hand motor skills in the paretic hand of patients with a history of ischemic cerebral infarct (1 year poststroke), after 20 min of 1 mA anodal stimulation over the hand area of the affected hemisphere's primary motor cortex, via a 25 cm^2 electrode, with the cathode over the contralateral orbit. Boggio, Nunes, and associates (2007) found improved functional hand motor skills in patients with chronic, subcortical stroke, after 20 min of 1 mA anodal stimulation over the hand area of the affected hemisphere's primary motor cortex, or with cathodal stimulation over the hand area of the unaffected hemisphere's primary motor cortex, with the alternative pole over the contralateral supraorbital area, via 35 cm^2 electrodes. Moreover, these researchers found accumulative effects after 5 consecutive days of cathodal stimulation over the hand area of the unaffected hemisphere's primary motor cortex.

There is more evidence to suggest that, in treating patients with stroke, it may be as meaningful to inhibit the unaffected hemisphere with cathodal tDCS, as to excite the affected hemisphere with anodal tDCS. In patients with subacute stroke, Kim and colleagues (2010) found that cathodal tDCS of the unaffected motor cortex—but not anodal tDCS of the affected motor cortex—showed grater improvement of the affected upper limb function, compared to sham tDCS at 6-month follow-up. In a double-blind, sham-controlled study, Bolognini and associates (2011) tried simultaneous tDCS of both affected and unaffected motor cortices, with anodal stimulation to the former, and cathodal stimulation to the latter, in patients with chronic stroke. They found that tDCS enhanced the effects of constraint-induced movement therapy and that only the real tDCS group showed neurophysiological evidence of reduced interhemispheric inhibition from the unaffected to the affected motor cortex.

Pain. Anodal stimulation of the primary motor cortex is associated with pain reduction in healthy volunteers and in patients with fibromyalgia. Boggio, Zaghi, Lopes, and Fregni (2008c) found that 5 min of 2 mA anodal stimulation with a 35 cm^2 sponge electrode over the left primary motor cortex (C3), and the cathode over the right orbit, increased thresholds for pain and perception of peripheral electrical stimulation of the right index finger in healthy volunteers. Fregni, Roizenblatt and colleagues (Fregni, Gimenes, et al., 2006; Roizenblatt et al., 2007) found that, after 5 days of 20-min/2-mA anodal stimulation of the left primary motor cortex, there was increased sleep efficiency associated with an improvement in fibromyalgia symptoms. Using the same stimulation paradigm (5 days of 20-min/2-mA anodal stimulation of the primary motor cortex), Fregni, Boggio, Lima, and colleagues (2006) found pain reduction in patients with central pain due to traumatic spinal cord injury. Contrary to these findings, Antal, Brepohl, and associates (2008) found no tDCS effects in right-hand laser-induced pain thresholds after 15 min of 1 mA anodal stimulation with a 35 cm2 sponge electrode over the left somatosensory cortex and the cathode over the right orbit. Instead, these researchers found pain threshold elevations after cathodal stimulation of the left somatosensory cortex. Given the insignificant topographical distance between primary motor and primary somatosensory cortices relative to the electrode sizes used in

these studies, the only basic differences between these studies are duration and intensity of stimulation (5-min/2-mA vs. 15-min/1-mA), and the means to induce pain (electrical vs. laser).

The Dorsolateral Prefrontal Cortex

Anodal stimulation of the left DLPFC has been shown to improve cognitive functions, including verbal fluency, WM, response inhibition, and verbal and implicit learning in healthy volunteers, as well as in different patient samples.

Nonclinical Volunteers. Iyer and associates (2005) found improved verbal fluency in healthy volunteers after 20 min with 2 mA (0.08 mA/cm^2) of anodal stimulation of the left DLPFC and the alternative electrode over the right orbit, no effects after 1 mA, and decreased verbal fluency after cathodal stimulation of the same area. Cattaneo, Pisoni, and Papagno (2011) replicated the improvement in verbal fluency, both for semantic and phonemic, after 2 mA anodal stimulation of the left DLPFC, with no effects after anodal stimulation of the right DLPFC.

Fregni, Boggio, Nitsche, and associates (2005) found improved performance in a 3-back working memory task after 10 min with 1 mA (0.029 mA/cm^2) of anodal stimulation of the left DLPFC and the alternative electrode over the right orbit, and Mulquiney, Hoy, Daskalakis, and Fitzgerald (2011) replicated these findings, whereas Ohn and colleagues (2008) showed that this effect increases with increasing stimulation time (20 and 30 min with 1 mA, 0.04 mA/cm^2). Andrews, Hoy, Enticott, Daskalakis, and Fitzgerald (2011) found greater improvement in performance during a WM task (Digit Span Forward) with preceding anodal stimulation of the left DLPFC during a WM task (n-back) than with preceding anodal stimulation during rest.

Kincses and colleagues (2004) found improved implicit learning in a probabilistic classification task, during the second 5-min half of 10 min with 1 mA (0.029 mA/cm^2) of anodal stimulation of the left DLPFC (Fp3) and the alternative electrode over the vertex (Cz). Reversed polarity of the same montage, or anodal stimulation over the occipital cortex (Oz) with the alternative electrode over the vertex, had no effect. Fertonani and colleagues (2009) reported anodal tDCS of the left DLPFC to improve naming performance and speeding up verbal reaction times after the end of the stimulation, whereas cathodal stimulation had no effect. The authors hypothesized that the cerebral network dedicated to lexical retrieval processing is facilitated by anodal tDCS of the left DLPFC.

Fecteau and colleagues explored the effects of DLPFC stimulation on risk-taking behavior in two parallel studies (Fecteau, Knoch, et al. 2007; Fecteau, Pascual-Leone, 2007). In both studies, they recruited healthy volunteers and stimulated their left and right DLPFC with left-anodal/right cathodal tDCS, and vice versa arrangement. The only difference between the two studies was that they used different (even though very similar) risk-taking tasks, both of which involved some kind of gambling with monetary reward. Surprisingly, the two studies gave different results, that is, one found that lateralization of polarity did not affect risk taking, whereas the other found that only right-anodal/left-cathodal stimulation reduced risk, compared to sham stimulation. The authors were not able to explain this controversy, and they hypothesized that it might be due to the nature of the two tasks—one involving risk and the other ambiguity.

These results may be explained by a model proposed by Davidson (2003) that suggests that the left prefrontal cortex is responsible for an ''approach system'' where positive emotions are combined with goal-directed behaviors, whereas the right prefrontal cortex is responsible for a ''withdrawal system'' where negative emotions are combined with behavioral inhibition. Some studies with tDCS further support this model, by showing that lateralization of stimulation of the frontal cortex is responsible for selective recall for pleasant or unpleasant stimuli, increased impulsive aggression, and improved response inhibition. Penolazzi and associates (2010) found improved recall both for pleasant images after anodal stimulation of the left and cathodal stimulation of the right

fronto-temporal cortex and for unpleasant images after stimulation with the reverse arrangement (left cathodal, right anodal). Hortensius, Schutter, and Harmon-Jones (2011) found increased aggressive behavior in healthy volunteers with anodal stimulation of the left frontal cortex and no effect with anodal stimulation of the right frontal cortex. Jacobson, Javitt, and Lavidor (2011) found improved response inhibition measured by a stop signal task after anodal stimulation of the right DLPFC but not after anodal stimulation of the right parietal cortex. However, Hsu and associates (2011) found similar results after anodal stimulation over the prefrontal midline (electrode Fz) and opposite effects (worsened response inhibition) after cathodal stimulation over the same area, showing that cortical representation of response inhibition may not be completely lateralized.

Cognitive Effects in Clinical Studies. Similar effects have been noted in clinical samples. Monti and associates (2008) found improved picture naming in patients with chronic nonfluent aphasia after 10 min with 2 mA (0.057 mA/cm^2) of anodal stimulation of an area slightly posterior to the left DLPFC. Boggio and associates (2006) found improved WM in patients with PD after 20 min with 2 mA (0.057 mA/cm^2) of anodal stimulation of the left DLPFC. Fregni, Boggio, Nitsche, and colleagues (2006) found similar results in patients with depression after five daily 20-min sessions with 1 mA (0.029 mA/cm^2), whereas Boggio, Bermpohl, et al. (2007) reported improved performance in a go/no-go task in patients with depression after a single 20-min session with 2 mA (0.057 mA/cm^2) of anodal stimulation of the left DLPFC.

Depression. Anodal stimulation of the left DLPFC has effects on mood as well. Based on neuroimaging results, indicating focal frontal dysfunction in depressed patients and, more specifically, left DLPFC hypo-activity (Arul-Anandam & Loo, 2009), tDCS studies have focused on the left DLPFC as the target for possible antidepressant effects. A randomized, controlled, double-blind trial (Fregni, Boggio, Nitsche, et al., 2006) investigated the effects of 5 days of anodal stimulation of the left DLPFC in 10 patients with major depression. The anode electrode was placed over F3 (10–20 International EEG system) and the cathode over the contralateral supraorbital area, and a constant current of 1 mA was applied for 20 min/day. Active stimulation led to a significant decrease in the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory scores compared with baseline, something not observed when patients received sham stimulation.

The specificity of the left DLPFC for the treatment of depression was addressed by a tDCS double-blind clinical trial with 40 patients with major depression (Boggio, Rigonatti, et al., 2008). In this study, medication-free patients were allocated randomly into three groups of treatment: anodal tDCS of the left DLPFC (active group), anodal tDCS of the occipital cortex (active control group), and sham tDCS (placebo control group). For the active conditions, patients received 2 mA tDCS for 20 min for 10 days. These parameters of stimulation were chosen based on recent studies showing that 2 mA of stimulation induces a larger behavioral effect compared to 1 mA (Boggio et al., 2006; Iyer et al., 2005). Results showed significantly larger reductions in depression scores after DLPFC tDCS (HDRS reduction of 40.4%) compared to occipital (HDRS reduction of 21.3%) and sham tDCS (HDRS reduction of 10.4%), with the beneficial effects of tDCS in the DLPFC group to last for 1 month after the end of treatment.

In another study, anodal tDCS over F3 (2 mA of intensity for 20 min for 10 days) was found to be as effective as a 6-weeks course of fluoxetine treatment, at a relatively small dose of 20 mg/day, in a sample of 42 patients with unipolar major depression (Rigonatti et al., 2008). In an open label pilot study, Martin and associates (2011) found significant antidepressant effects of anodal tDCS over the left DLPFC, with a noncephalic cathode (right upper arm). The stimulation protocol included 20-min daily sessions of 2 mA during working days for 4 weeks, with no reported side effects. Recent studies have shown antidepressant

effects of anodal tDCS over the left DLPFC in patients with major depression as well as in patients with bipolar disorder (Brunoni et al., 2011; Dell'osso et al., 2011).

However, others (Loo et al., 2010; Palm et al., 2008) have failed to replicate the efficacy of tDCS over placebo in treating depression, even though they found significant reduction in depressive symptoms in both experimental and control groups, even in patients not responding to drug therapy. Because one of those studies (Loo et al., 2010) failed to differentiate treatment effects after five tDCS sessions and found improvement in depressive symptoms after 10 real sessions in both groups, further research with more sessions for each group is required.

Tinnitus. A somewhat reverse tDCS protocol to that for depression has shown symptom reduction in some patients with tinnitus. Applying anodal stimulation over the right DLPFC and concurrent cathodal stimulation over the left DLPFC, some investigators have found primary symptom reduction in a subgroup of patients (Vanneste & De Ridder, 2011), or secondary symptom reduction with no primary symptom reduction (Frank et al., 2011). Vanneste, Focquaert, Van de Heyning, and De Ridder (2011) found that responders to tDCS had elevated amplitude in the gamma frequency of the EEG in the right primary and secondary auditory cortex, as well as in the right parahippocampal area. Others (Garin et al., 2011) have found a reduction in tinnitus symptoms with anodal (but not cathodal) stimulation of the left temporo-parietal area.

Craving. Stimulating either left or right side of the DLPFC with one pole and the other side with the other pole (anode/cathode) seems to reduce craving and consumption. Boggio, Sultani, and colleagues (2008) found decreased craving for alcohol after 20 min with 2 mA (0.057 mA/cm^2) of either anodal left/cathodal right or anodal right/cathodal left stimulation of the DLPFC. Similarly, Fregni, Liguori, and colleagues (2008) found decreased craving for smoking after 20 min with 2 mA (0.057 mA/cm^2) of either anodal left/cathodal right or anodal right/cathodal left stimulation of the DLPFC. Moreover, Fregni, Orsati, and colleagues (2008) found decreased craving for foods after 20 min with 2 mA (0.057 mA/cm^2) of anodal right/cathodal left stimulation of the DLPFC, as well as reduced food consumption after either anodal left/cathodal right or anodal right/cathodal left stimulation.

Other Clinical Cases. Schneider and Hopp (2011) found improved language (syntax) acquisition in a group of children with autism after a single 30-min tDCS session, with anodal stimulation over the left DLPFC. Vercammen et al. (2011) found increased variability in performance on a probabilistic association learning task, after 20 min of anodal stimulation of the left DLPFC, in a group of patients with schizophrenia and suggested that this may imply beneficial effects in a subgroup of these patients.

Bilateral Stimulation of the DLPFC. The first to use bilateral tDCS of the prefrontal cortex were Lippold, Redfearn, and Costain. These pioneers of tDCS found significant behavioral effects of anodal tDCS, including mood elevation after 3 hr of anodal stimulation and withdrawal after cathodal stimulation (Lippold & Redfearn, 1964), as well as improvement of depression symptoms after 12 daily 8-hr sessions of anodal stimulation with 0.260 mA (Costain et al., 1964).

Marshall and colleagues (2004) applied 30 min of intermittent (15 s on, 15 s off) 0.26 mA/cm^2 bilateral anodal tDCS at the DLPFC (with the opposite pole at the mastoids) of healthy volunteers during slow-wave sleep and found post-sleep improved performance in verbal memory for material learned before stimulation but no effect on procedural learning. Of interest, similar stimulation during wakefulness did not produce learning effects, something attributed by the authors to the consolidation properties of slow-wave sleep. The rationale for bilateral stimulation seems to be an attempt to potentiate the nonlateralized frontal endogenous direct current (DC) potentials seen in slow-wave sleep. The authors did not clarify the reasons why intermittent (rather than continuous) tDCS was selected, and whether this by itself might be an experimental variable.

In a different study, Marshall, Moelle, Siebner, and Born (2005) used the same

paradigm of intermittent tDCS of bilateral DLPFC during performance of a WM task. They found that either anodal or cathodal stimulation of bilateral DLPFC increased reaction time in the WM task. Similarly, Priori and associates (2008) found increased reaction time when participants had to deny seeing stimuli they had actually seen (experimental manipulation of a lie), after 10 min with 1.5 mA (0.03 C/cm^2) of continuous anodal stimulation of bilateral DLPFC.

The Occipital Cortex

Visual cortex tDCS shows the well-established excitation with anodal stimulation and inhibition with cathodal stimulation, but, contrary to tDCS in other brain areas, it seems that cathodal stimulation shows the strongest effects. Cathodal stimulation of the Oz and the alternative pole over the Cz at 1 mA for 7 min decreased visual contrast sensitivity, whereas anodal stimulation had no effect (Antal et al., 2001). A similar arrangement showed lowered threshold for transcranial magnetic stimulation–induced light sensations called phosphenes after 10 min of anodal stimulation of the occipital cortex, and increased threshold after cathodal stimulation (Antal, Kincses, Nitsche, & Paulus, 2003a; 2003b; Lang et al., 2007). This arrangement also showed increased amplitude for the N70 component of the visual evoked potential (VEP) 10 min after 15-min 1 mA anodal stimulation of the occipital cortex and decreased amplitude immediately after cathodal stimulation (Antal, Kincses, Nitsche, Bartfai, & Paulus, 2004). Opposite effects have been found for a different component of the VEP, the P100, where cathodal stimulation increased VEP amplitude and vice versa, and this effect is stronger with the alternative electrode at the neck (Accornero et al., 2007; Antal et al., 2004).

TRANSCRANIAL ALTERNATING CURRENT STIMULATION

In comparison to tDCS, very little is reported on the effects of tACS. The latter is using the same equipment and methodology as tDCS but with alternating current. Frequency-dependent effects of tACS have been shown on the motor cortex. Although Antal, Boros, et al. (2008) failed to show effects on cortical excitability after 5 min of 0.025 mA/cm^2 tACS at different frequencies (1, 10, 15, 30, and 45 Hz), Zaghi and associates (2010) have shown that stronger current and longer stimulation period (20 min of 0.08 mA/cm2 tACS at 15 Hz), bilaterally over the motor cortex, has inhibitory effects as shown by decreased MEPs. Schutter and Hortensius (2011) found increased cortical excitability (measured by MEPs) after either 5 Hz or 20 Hz tACS, whereas Chaieb, Antal, and Paulus (2011) reported similar effects after 1–5 kHz tACS. Kanai, Chaie, Antal, Walsh, and Paulus (2008) suggested frequency-dependent effects of tACS on the visual cortex, due to the occurrence of phosphenes (visual perceptions of flickering light). The fact that phosphenes were mostly perceived with stimulation at 10 and 12 Hz when the participants were in a dark room, and with 16 and 18 Hz when participants were in an illuminated room, was interpreted by the authors as due to interaction with the ongoing EEG alpha and beta rhythms, respectively. However, others have suggested that tACS-induced phosphenes may well be due to retinal stimulation (Schutter & Hortensius, 2010), and therefore it is not clear whether they are a direct effect of stimulating the visual cortex (Schwiedrzik, 2009). Frequency-dependent effects of tACS on the visual cortex have also been suggested by Zaehle, Rach, and Herrmann (2010), who in a placebo-controlled experiment found that tACS at each participant's own individual alpha frequency (as measured by EEG), bilaterally over the occipital cortex, enhanced EEG alpha power. As with tDCS, there are no significant side effects reported in tACS experiments. In our lab, we have tested several volunteers and patients with movement disorders, with daily consecutive 20-min sessions of 2 mA tACS at 15 Hz over the motor cortex, for at least 2 weeks ($5 + 5$ sessions) with no side effects. However, we have noticed frequency-dependent improvement or worsening of symptoms in some of our patients.

CONCLUSIONS

Low-intensity tDCS is a well-established experimental paradigm that shows stimulation-specific effects in a variety of neurobehavioral measures and in relation to different brain areas. There are effects on motor performance, cognitive performance, perception, emotion, electrophysiology, and brain metabolism, both in healthy volunteers and in groups with various neurological and psychiatric pathologies, including stroke, PD, depression, fibromyalgia, aphasia, tinnitus, and addiction. These effects are shown to have practical significance by improving healthy functions or reducing clinical symptoms. Application of tDCS in most studies includes large (>25 cm^2) saline-soaked sponge electrodes, currents of up to 2 mA, for durations from 5 to 30 min. For such stimulation parameters there are no significant side effects reported when saline solution is used in the sponge electrodes. Effects of tDCS are dependent on area of stimulation for both anodal and cathodal electrodes, stimulation polarity, stimulation duration, and current density. In contrast, tACS is still under explored, with very few studies reported.

There are several parameters in this field that need better focus, or redefinition. First, there should be no more reference to ''reference'' electrodes, because both electrodes in tDCS are active on the brain, unless they are placed on noncephalic areas. Anodal electrodes excite and cathodal electrodes inhibit the underlying cortical tissue, and in almost all studies, both electrodes have been placed over cortical tissue. Therefore, future studies should design their electrode placement considering the effects of both electrodes and interpret their findings accordingly. Second, not only may each electrode separately affect the underlying cortex, but also the orientation of the two electrodes may have effects specific to the current flow direction, as was very well shown in motor cortex stimulation studies (Nitsche & Paulus, 2000). This will also depend on the orientation of the cortical columns, which will vary by the position of the targeted areas being either on the gyri or deep in the sulci. Third, the spread of the current flow must always be calculated. We have estimated that cortical areas neighboring to the ones targeted by several centimeters may also receive significant amounts of current density. Fourth, interhemispheric inhibition must be accounted for, especially in motor cortex stimulation, where any motor effect on one side of the body will be followed by the opposite effect on the other side of the body (Vines et al., 2006). Fifth, when experimenting with patient groups, medication must be carefully considered, because it has been shown that different substances may significantly alter the effects of tDCS (Kuo et al., 2007; Kuo et al., 2008; Nitsche et al., 2003; Nitsche et al., 2004; Terney et al., 2008).

Future research with tDCS should address the previously mentioned factors as closely as possible and justify the rationale for the selection of the particular stimulation parameters, including stimulation area for each electrode, electrode size, current density, stimulation time duration, when to stimulate (e.g., before/during/after a task, during sleep), intermittent or continuous stimulation, and the selection of the control condition. Regarding the latter, opposite polarity stimulation will provide more understanding of the observed neural effects than sham stimulation. In addition, future research should investigate the long-term effects of tDCS, with appropriate follow-up. Moreover, we believe there is potential of tACS research in both healthy cognitive and emotional functions and in clinical entities. Future research should thoroughly investigate the brain correlates of alternating current stimulation at different frequencies, based on the current knowledge of brain EEG rhythms and their behavioral correlates. In general, future studies will advance the understanding of the underlying neural phenomena if they develop concrete and complex neuroanatomical models upon which to base the selection of the stimulation parameters.

REFERENCES

Accornero, N., Li Voti, P., La Riccia, M., & Gregori, B. (2007). Visual evoked potentials modulation during direct current cortical

polarization. *Experimental Brain Research*, *178*, 261–266.

Andrews, S. C., Hoy, K. E., Enticott, P. G., Daskalakis, Z. J., & Fitzgerald, P. B. (2011). Improving working memory: The effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. *Brain Stimulation*, *4*(2), 84–89.

Antal, A., Boros, K., Poreisz, C., Chaieb, L., Terney, D., & Paulus, W. (2008). Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. *Brain Stimulation*, *1*, 97–105.

Antal, A., Brepohl, N., Poreisz, C., Boros, K., Csifcsak, G., & Paulus, W. (2008). Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. *The Clinical Journal of Pain*, *24*, 56–63.

Antal, A., Kincses, T. Z., Nitsche, M. A., Bartfai, O., & Paulus, W. (2004). Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: Direct electrophysiological evidence. *Invest Ophthalmol Vis Sci*, *45*, 702–707.

Antal, A., Kincses, T. Z., Nitsche, M. A., & Paulus, W. (2003a). Manipulation of phosphene thresholds by transcranial direct current stimulation in man. *Experimental Brain Research*, *150*, 375–378.

Antal, A., Kincses, T. Z., Nitsche, M. A., & Paulus, W. (2003b). Modulation of moving phosphene thresholds by transcranial direct current stimulation of V1 in human. *Neuropsychologia*, *41*, 1802–1807.

Antal, A., Nitsche, M. A., & Paulus, W. (2001). External modulation of visual perception in humans. *Neuroreport*, *12*, 3553–3555.

Ardolino, G., Bossi, B., Barbieri, S., & Priori, A. (2005). Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. *Journal of Physiology*, *568*, 653–663.

Aron, A. R., Robbins, T. W., & Poldrack, R. A. (2004). Inhibition and the right inferior frontal cortex. *Trends in Cognitive Science*, *8*, 170–177.

Arul-Anandam, A. P., & Loo, C. (2009). Transcranial direct current stimulation: A new tool for the treatment of depression? *Journal of Affective Disorders*, *117*, 137–145.

Asahi, S., Okamoto, Y., Okada, G., Yamawaki, S., & Yokota, N. (2004). Negative correlation between right prefrontal activity during response inhibition and impulsiveness: An fMRI study. *European Archives of Psychiatry and Clinical Neuroscience*, *254*, 245–251.

Baudewig, J., Nitsche, M. A., Paulus, W., & Frahm, J. (2001). Regional modulation of BOLD MRI responses to human sensorimotor activation by transcranial direct current stimulation. *Magnetic Resonance in Medicine*, *45*, 196–201.

Boggio, P. S., Bermpohl, F., Vergara, A. O., Muniz, A. L., Nahas, F. H., Leme, P. B., . . . Fregni, F. (2007). Go–no-go task performance improvement after anodal transcranial DC stimulation of the left dorsolateral prefrontal cortex in major depression. *Journal of Affective Disorders*, *101*, 91–98.

Boggio, P. S., Ferrucci, R., Rigonatti, S. P., Covre, P., Nitsche, M., Pascual-Leone, A., & Fregni, F. (2006). Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. *Journal of the Neurological Sciences*, *249*, 31–38.

Boggio, P. S., Nunes, A., Rigonatti, S. P., Nitsche, M. A., Pascual-Leone, A., & Fregni, F. (2007). Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. *Restorative Neurology and Neuroscience*, *25*, 123–129.

Boggio, P. S., Rigonatti, S. P., Ribeiro, R. B., Myczkowski, M. L., Nitsche, M. A., Pascual-Leone, A., & Fregni, F. (2008). A randomized, doubleblind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *International Journal of Neuropsychopharmacology*, *11*, 249–254.

Boggio, P. S., Sultani, N., Fecteau, S., Merabet, L., Mecca, T., Pascual-Leone, A., . . . Fregni, F. (2008). Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: A double-blind, sham-controlled

study. *Drug and Alcohol Dependence*, *92*, 55–60.

Boggio, P. S., Zaghi, S., Lopes, M., & Fregni, F. (2008). Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. *European Journal of Neurology*, *15*, 1124–1130.

Bolognini, N., Vallar, G., Casati, C., Abdul Latif, L., El-Nazer, R., Williams, J., ... Fregni, F. (2011). Neurophysiological and behavioral effects of tDCS combined with constraint-induced movement therapy in poststroke patients. *Neurorehabilitation and Neural Repair*. Advance online publication. doi:10.1177/1545968311411056

Breit, S., Schulz, J. B., & Benabid, A. L. (2004). Deep brain stimulation. *Cell Tissue Research*, *318*, 275–288.

Brunoni, A. R., Ferrucci, R., Bortolomasi, M., Vergari, M., Tadini, L., Boggio, P. S., ... Priori, A. (2011). Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder. *Progress in Neuropsychopharmacol & Biological Psychiatry*, *35*(1), 96–101.

Bunge, S. A., Dudukovic, N. M., Thomason, M. E., Vaidya, C. J., & Gabrieli, J. D. (2002). Immature frontal lobe contributions to cognitive control in children: Evidence from fMRI. *Neuron*, *33*, 301–311.

Cattaneo, Z., Pisoni, A., & Papagno, C. (2011). Transcranial direct current stimulation over Broca's region improves phonemic and semantic fluency in healthy individuals. *Neuroscience*, *183*, 64–70.

Cerletti, U. (1950). Old and new information about electroshock. *American Journal of Psychiatry*, *107*, 87–94.

Chaieb, L., Antal, A., & Paulus, W. (2011). Transcranial alternating current stimulation in the low kHz range increases motor cortex excitability. *Restorative Neurology and Neuroscience*, *29*, 167–175.

Clark, V. P., Coffman, B. A., Trumbo, M. C., & Gasparovic, C. (2011). Transcranial direct current stimulation (tDCS) produces localized and specific alterations in neurochemistry: A (1)H magnetic resonance spectroscopy study. *Neuroscience Letters*, *500*(1), 67–71.

Costain, R., Redfearn, J. W. T., & Lippold, C. J. (1964). A Controlled trial of the therapeutic effects of polarization of the brain in depressive illness. *British Journal of Psychiatry*, *110*, 786–799.

Davidson, R. (2003). Affective neuroscience and psychophysiology: Toward a synthesis. *Psychophysiology*, *40*, 655–665.

Dell'osso, B., Zanoni, S., Ferrucci, R., Vergari, M., Castellano, F., D'Urso, N., ... Altamura, A. C. (2011). Transcranial direct current stimulation for the outpatient treatment of poor-responder depressed patients. *European Psychiatry*. Advance online publication. doi:10.1016/j.eurpsy.2011.02.008

Durand, S., Fromy, B., Bouyé, P., Saumet, J. L., & Abraham, P. (2002). Vasodilatation in response to repeated anodal current application in the human skin relies on aspirin-sensitive mechanisms. *Journal of Physiology*, *540*, 261–269.

Fecteau, S., Knoch, D., Fregni, F., Sultani, N., Boggio, P., & Pascual-Leone, A. (2007). Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: A direct current stimulation study. *Journal of Neuroscience*, *27*, 12500–12505.

Fecteau, S., Pascual-Leone, A., Zald, D. H., Liguori, P., Théoret, H., Boggio, P. S., & Fregni, F. (2007). Activation of prefrontal cortex by transcranial direct current stimulation reduces appetite for risk during ambiguous decision making. *Journal of Neuroscience*, *27*, 6212–6218.

Feliu, M., Edwards, C. L., Sudhakar, S., McDougald, C., Raynor, R., Johnson, S., ... Logue, P. E. (2008). Neuropsychological effects and attitudes in patients following electroconvulsive therapy. *Neuropsychiatric Disease and Treatment*, *4*, 613–617.

Ferrucci, R., Mameli, F., Guidi, I., Mrakic-Sposta, S., Vergari, M., Marceglia, S., ... Priori, A. (2008). Transcranial direct current stimulation improves recognition memory in Alzheimer disease. *Neurology*, *71*, 493–498.

Fertonani, A., Rosini, S., Cotelli, M., Rossini, P. M., & Miniussi, C. (2010). Naming facilitation induced by transcranial direct current stimulation. *Behav Brain Res*, *208*(2), 311–318.

Fields, J. A., & Troster, A. I. (2000). Cognitive outcomes after deep brain stimulation for Parkinson's Disease: A review of initial studies and recommendations for future research. *Brain and Cognition*, *42*, 268–293.

Floel, A., Rosser, N., Michka, O., Knecht, S., & Breitenstein, C. (2008). Noninvasive brain stimulation improves language learning. *Journal of Cognitive Neuroscience*, *20*, 1415–1422.

Frank, E., Schecklmann, M., Landgrebe, M., Burger, J., Kreuzer, P., Poeppl, T. B., ... Langguth, B. (2011). Treatment of chronic tinnitus with repeated sessions of prefrontal transcranial direct current stimulation: Outcomes from an open-label pilot study. *Journal of Neurology* Advance online publication. doi:10.1007/s00415-011-6189-4

Frank, E., Wilfurth, S., Landgrebe, M., Eichhammer, P., Hajak, G., & Langguth, B. (2010). Anodal skin lesions after treatment with transcranial direct current stimulation. *Brain Stimulation*, *3*, 58–59.

Fregni, F., Boggio, P. S., Lima, M. C., Ferreira, M. J., Wagner, T., Rigonatti, S. P., ... Pascual-Leone, A. (2006). A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain*, *122*, 197–209.

Fregni, F., Boggio, P. S., Mansur, C. G., Wagner, T., Ferreira, M. J., Lima, M. C., ... Pascual-Leone, A. (2005). Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. *Neuroreport*, *16*, 1551–1555.

Fregni, F., Boggio, P. S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., ... Pascual-Leone, A. (2005). Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. *Experimental Brain Research*, *166*, 23–30.

Fregni, F., Boggio, P. S., Nitsche, M. A., Rigonatti, S. P., & Pascual-Leone, A. (2006). Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. *Depression and Anxiety*, *23*, 482–484.

Fregni, F., Gimenes, R., Valle, A. C., Ferreira, M. J., Rocha, R. R., Natalle, L., ... Boggio, P. S. (2006). A randomized, sham controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. *Arthritis and Rheumatism*, *54*, 3988–3998.

Fregni, F., Liguori, P., Fecteau, S., Nitsche, M. A., Pascual-Leone, A., & Boggio, P. S. (2008). Cortical stimulation of the prefrontal cortex with transcranial direct current stimulation reduces cue-provoked smoking craving: a randomized, sham-controlled study. *Journal of Clinical Psychiatry*, *69*, 32–40.

Fregni, F., Orsati, F., Pedrosa, W., Fecteau, S., Tome, F. A., Nitsche, M. A., ... Boggio, P. S. (2008). Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. *Appetite*, *51*, 34–41.

Furubayashi, T., Terao, Y., Arai, N., Okabe, S., Mochizuki, H., Hanajima, R., ... Ugawa, Y. (2008). Short and long duration transcranial direct current stimulation (tDCS) over the human hand motor area. *Experimental Brain Research*, *185*, 279–286.

Garin, P., Gilain, C., Van Damme, J. P., de Fays, K., Jamart, J., Ossemann, M., & Vandermeeren, Y. (2011). Short- and long-lasting tinnitus relief induced by transcranial direct current stimulation. *Journal of Neurology*. Advance online publication. doi:10.1007/s00415–011-6037–6

Greenberg, B. D., Malone, D. A., Friehs, G. M., Rezai, A. R., Kubu, C. S., Malloy, P. F., ... Rasmussen, S. A. (2006). Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. *Neuropsychopharmacology*, *31*, 2384–2393.

Handforth, A., DeSalles, A. A., & Krahl, S. E. (2006). Deep brain stimulation of the subthalamic nucleus as adjunct treatment for refractory epilepsy. *Epilepsia*, *47*, 1239–1241.

Hortensius, R., Schutter, D. J., & Harmon-Jones, E. (2011). When anger leads to aggression: Induction of relative left frontal cortical activity with transcranial direct current stimulation increases the anger-aggression relationship. *Social Cognitive and Affective Neuroscience*, Advance online publication. doi:10.1093/scan/nsr012

Hsu, T. Y., Tseng, L. Y., Yu, J. X., Kuo, W. J., Hung, D. L., Tzeng, O. J., ... Juan, C. H.

(2011). Modulating inhibitory control with direct current stimulation of the superior medial frontal cortex. *Neuroimage*, *56*, 2249–2257.

Hummel, F., Celnik, P., Giraux, P., Floel, A., Wu, W. H., Gerloff, C., & Cohen, L. G. (2005). Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain*, *128*, 490–499.

Hummel, F. C., Voller, B., Celnik, P., Floel, A., Giraux, P., Gerloff, C., & Cohen, L. G. (2006). Effects of brain polarization on reaction times and pinch force in chronic stroke. *BMC Neuroscience*, *7*, 73.

Ishihara, K., & Sasa, M. (1999). Mechanism underlying the therapeutic effects of electroconvulsive therapy (ECT) on depression. *Japanese Journal of Pharmacology*, *80*, 185–189.

Iyer, M. B., Mattu, U., Grafman, J., Lomarev, M., Sato, S., & Wassermann, E. M. (2005). Safety and cognitive effect of frontal DC brain polarization in healthy individuals. *Neurology*, *64*, 872–875.

Jacobson, L., Javitt, D. C., & Lavidor, M. (2011). Activation of inhibition: Diminishing Impulsive behavior by direct current stimulation over the inferior frontal gyrus. *Journal of Cognitive Neuroscience*, Advance online publication. doi:10.1162/jocn_a_00020

Jeffery, D. T., Norton, J. A., Roy, F. D., & Gorassini, M. A. (2007). Effects of transcranial direct current stimulation on the excitability of the leg motor cortex. *Experimental Brain Research*, *182*, 281–287.

Kanai, R., Chaie, L., Antal, A., Walsh, V., & Paulus, W. (2008). Frequency-dependent electrical stimulation of the visual cortex. *Current Biology*, *18*, 1839–1843.

Keeser, D., Padberg, F., Reisinger, E., Pogarell, O., Kirsch, V., Palm, U., … Mullert, C. (2011). Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: A standardized low resolution tomography (sLORETA) study. *Neuroimage*, *55*, 644–657.

Kennedy, R., Mittal, D., & O'Jile, J. (2003). Electroconvulsive therapy in movement disorders: An update. *Journal of Neuropsychiatry and Clinical Neurosciences*, *15*, 407–421.

Kim, D. Y., Lim, J. Y., Kang, E. K., You, D. S., Oh, M. K., Oh, B. M., & Paik, N. J. (2010). Effect of transcranial direct current stimulation on motor recovery in patients with subacute stroke. *American Journal of Physical Medicine and Rehabilitation*, *89*, 879–886.

Kincses, T. Z., Antal, A., Nitsche, M. A., Bártfai, O., & Paulus, W. (2004). Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. *Neuropsychologia*, *42*, 113–117.

Konishi, S., Chikazoe, J., Jimura, K., Asari, T., & Miyashita, Y. (2005). Neural mechanism in anterior prefrontal cortex for inhibition of prolonged set interference. *Proceedings of the National Academy of Sciences U S A*, *102*, 12584–12588.

Kumar, S., Wagner, C. W., Frayne, C., Zhu, L., Selim, M., Feng, W., & Schlaug, G. (2011). Noninvasive brain stimulation may improve stroke-related dysphagia: A pilot study. *Stroke*, *42*, 1035–1040.

Kuo, M. F., Grosch, J., Fregni, F., Paulus, W., & Nitsche, M. A. (2007). Focusing effect of acetylcholine on neuroplasticity in the human motor cortex. *Journal of Neuroscience*, *27*, 1442–1447.

Kuo, M. F., Paulus, W., & Nitsche, M. A. (2008). Boosting focally-induced brain plasticity by dopamine. *Cereb Cortex*, *18*, 648–651.

Kwon, Y. H., Ko, M. H., Ahn, S. H., Kim, Y. H., Song, J. C., Lee, C. H., … Jang, S. H. (2008). Primary motor cortex activation by transcranial direct current stimulation in the human brain. *Neuroscience Letters*, *435*(1), 56–59.

Lang, N., Nitsche, M. A., Paulus, W., Rothwell, J. C., & Lemon, R. N. (2004). Effects of transcranial direct current stimulation over the human motor cortex on corticospinal and transcallosal excitability. *Experimental Brain Research*, *156*, 439–443.

Lang, N., Siebner, H. R., Chadaide, Z., Boros, K., Nitsche, M. A., Rothwell, J. C., … Antal, A. (2007). Bidirectional modulation of primary visual cortex excitability: A combined tDCS and rTMS study. *Investigative Ophthalmology & Visual Science*, *48*, 5782–5787.

Lang, N., Siebner, H. R., Ward, N. S., Lee, L., Nitsche, M. A., Paulus, W., … Frackowiak,

R. S. (2005). How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *European Journal of Neuroscience*, *22*, 495–504.

Liebetanz, D., Nitsche, M. A., Tergau, F., & Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced aftereffects of human motor cortex excitability. *Brain*, *125*, 2238–2247.

Lippold, O. J. C., & Redfearn, J. W. T. (1964). Mental changes resulting from the passage of small direct currents through the human brain. *British Journal of Psychiatry*, *110*, 768–772.

Loo, C. K., Sachdev, P., Martin, D., Pigot, M., Alonzo, A., Malhi, G. S., . . . Mitchell, P. (2010). A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. *International Journal of Neuropsychopharmacology*, *13*(1), 61–69.

MacLeod, A. K., Buckner, R. L., Miezin, F. M., Petersen, S. E., & Raichle, M. E. (1998). Right anterior prefrontal cortex activation during semantic monitoring and working memory. *Neuroimage*, *7*(1), 41–48.

Marshall, L., Moelle, M., Hallschmid, M., & Born, J. (2004). Transcranial direct current stimulation during sleep improves declarative memory. *Journal of Neuroscience*, *24*, 9985–9992.

Marshall, L., Moelle, M., Siebner, H. R., & Born, J. (2005). Bifrontal transcranial direct current stimulation slows reaction time in a working memory task. *BMC Neuroscience*, *6*, 23.

Martin, D. M., Alonzo, A., Mitchell, P. B., Sachdev, P., Gálvez, V., & Loo, C. K. (2011). Fronto-extracephalic transcranial direct current stimulation as a treatment for major depression: An open-label pilot study. *Journal of Affective Disorders* Advance online publication. doi:10.1016/j.jad.2011.05.018

Mayberg, H. S., Lozano, A. M., Voon, V., McNeely, H. E., Seminowicz, D., Hamani, C., . . . Kennedy, S. H. (2005). Deep brain stimulation for treatment-resistant depression. *Neuron*, *45*, 651–660.

McIntyre, C. C., Savasta, M., Kerkerian-Le Goff, L., & Vitek, J. L. (2004). Uncovering the mechanism(s) of action of deep brain stimulation: Activation, inhibition, or both. *Clinical Neurophysiology*, *115*, 1239–1248.

Miranda, P. C., Lomarev, M., & Hallett, M. (2006). Modeling the current distribution during transcranial direct current stimulation. *Clinical Neurophysiology*, *117*, 1623–1629.

Monti, A., Cogiamanian, F., Marceglia, S., Ferrucci, R., Mameli, F., Mrakic-Sposta, S., . . . Priori, A. (2008). Improved naming after transcranial direct current stimulation in aphasia. *Journal of Neurology, Neurosurgery, and Psychiatry*, *79*, 451–453.

Mulquiney, P. G., Hoy, K. E., Daskalakis, Z. J., & Fitzgerald, P. B. (2011). Improving working memory: Exploring the effect of transcranial random noise stimulation and transcranial direct current stimulation on the dorsolateral prefrontal cortex. *Clinical Neurophysiology* Advance online publication. doi:10.1016/j.clinph.2011.05.009

Nakamura-Palacios, E. M., de Almeida Benevides, M. C., da Penha Zago-Gomes, M., de Oliveira, R. W., de Vasconcellos, V. F., de Castro, L. N., . . . Fregni, F. (2011). Auditory event-related potentials (P3) and cognitive changes induced by frontal direct current stimulation in alcoholics according to Lesch alcoholism typology. *International Journal of Neuropsychopharmacology*. Advance online publication. doi:10.1017/S1461145711001040

Neuner, I., Podoll, K., Janouschek, H., Michel, T. M., Sheldrick, A. J., & Schneider, F. (2008). From psychosurgery to neuromodulation: Deep brain stimulation for intractable Tourette syndrome. *World Journal of Biological Psychiatry*, *13*, 1–11.

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., . . . Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation*, *1*, 206–223.

Nitsche, M. A., Doemkes, S., Karakose, T., Antal, A., Liebetanz, D., Lang, N., . . . Paulus, W. (2007). Shaping the effects of transcranial

direct current stimulation of the human motor cortex. *Journal of Neurophysiology*, *97*, 3109–3117.

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., ... Paulus, W. (2003). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *Journal of Physiology*, *553*, 293–301.

Nitsche, M. A., Grundey, J., Liebetanz, D., Lang, N., Tergau, F., & Paulus, W. (2004). Catecholaminergic consolidation of motor cortical neuroplasticity in humans. *Cerebral Cortex*, *14*, 1240–1245.

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *Journal of Physiology*, *527*, 633–639.

Nobler, M. S., Sackeim, H. A., Prohovnik, I., Moeller, J. R., Mukherjee, S., Schnur, D. B., ... Devanand, D. P. (1994). Regional cerebral blood flow in mood disorders, III: Treatment and clinical response. *Archives of General Psychiatry*, *51*, 884–897.

Ohn, S. H., Park, C. I., Yoo, W. K., Ko, M. H., Choi, K. P., Kim, G. M., ... Kim, Y. H. (2008). Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. *Neuroreport*, *19*, 43–47.

Owen, S. L., Green, A. L., Nandi, D. D., Bittar, R. G., Wang, S., & Aziz, T. Z. (2007). Deep brain stimulation for neuropathic pain. *Acta Neurochirurgica Supplement*, *97*(Pt. 2), 111–116.

Ostrem, J. L., & Starr, F. A. (2008). Treatment of dystonia with deep brain stimulation. *NeuroTherapeutics*, *5*, 320–330.

Palm, U., Keeser, D., Schiller, C., Fintescu, Z., Reisinger, E., Mulert, C., ... Padberg, F. (2008). Transcranial direct current stimulation in therapy-resistant depression: Preliminary results from a double-blind, placebo-controlled study. *Brain Stimulation*, *1*, 241–242.

Pandya, M., Pozuelo, L., & Malone, D. (2007). Electroconvulsive therapy: What the internist needs to know. *Cleveland Clinic Journal of Medicine*, *74*, 679–685.

Penolazzi, B., Di Domenico, A., Marzoli, D., Mammarella, N., Fairfield, B., & Franciotti, R. (2010). Effects of transcranial direct current stimulation on episodic memory related to emotional visual stimuli. *PLoS One*, *5*(5), e10623.

Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Res Bull*, *72*, 208–214.

Power, H. A., Norton, J. A., Porter, C. L., Doyle, Z., Hui, I., & Chan, K. M. (2006). Transcranial direct current stimulation of the primary motor cortex affects cortical drive to human musculature as assessed by intermuscular coherence. *J Physiol*, *577*, 795–803.

Priori, A., Mameli, F., Cogiamanian, F., Marceglia, S., Tiriticco, M., Mrakic-Sposta, S., ... Sartori, G. (2008). Lie-specific involvement of dorsolateral prefrontal cortex in deception. *Cerebral Cortex*, *18*, 451–455.

Quartarone, A., Morgante, F., Bagnato, S., Rizzo, V., Sant'Angelo, A., Aiello, E., ... Girlanda, P. (2004). Long lasting effects of transcranial direct current stimulation on motor imagery. *Neuroreport*, *15*, 1287–1291.

Quartarone, A., Rizzo, V., Bagnato, S., Morgante, F., Sant'Angelo, A., Romano, M., ... Siebner, H. R. (2005). Homeostatic-like plasticity of the primary motor hand area is impaired in focal hand dystonia. *Brain*, *128*, 1943–1950.

Ramnani, N., & Owen, A. M. (2004). Anterior prefrontal cortex: Insights into function from anatomy and neuroimaging. *Nature Reviews Neuroscience*, *5*, 184–194.

Rasmussen, K. G., Sampson, S. M., & Rummans, T. A. (2002). Electroconvulsive therapy and newer modalities for the treatment of medication-refractory mental illness. *Mayo Clinic Proceedings*, *77*, 552–556.

Redfearn, J. W., Lippold, O. C., & Costain, R. (1964). A preliminary account of the clinical effects of polarizing the brain in certain psychiatric disorders. *Br J Psychiatry*, *110*, 773–785.

Rigonatti, S. P., Boggio, P. S., Myczkowski, M. L., Otta, E., Fiquer, J. T., Ribeiro, R. B., ... Fregni, F. (2008). Transcranial direct stimulation and fluoxetine for the treatment of depression. *European Psychiatry*, *23*, 74–76.

Roizenblatt, S., Fregni, F., Gimenez, R., Wetzel, T., Rigonatti, S. P., Tufik, S., ... Valle, A. C. (2007). Site-specific effects of transcranial direct current stimulation on sleep and pain in fibromyalgia: A randomized, sham-controlled study. *Pain Practice*, *7*, 297–306.

Sakas, D. E., Panourias, I. G., Stavrinou, L. C., Boviatsis, E. J., Themistocleous, M., Stathis, P., ... Gatzonis, S. (2010). Restoration of erect posture in idiopathic camptocormia by electrical stimulation of the globus pallidus internus. *Journal of Neurosurgery*, *113*, 1246–1250.

Schneider, H. D., & Hopp, J. P. (2011). The use of the Bilingual Aphasia Test for assessment and transcranial direct current stimulation to modulate language acquisition in minimally verbal children with autism. *Clinical Linguistics & Phonetics*, *25*, 640–654.

Schutter, D. J., & Hortensius, R. (2010). Retinal origin of phosphenes to transcranial alternating current stimulation. *Clinical Neurophysiology*, *121*, 1080–1084.

Schutter, D. J., & Hortensius, R. (2011). Brain oscillations and frequency-dependent modulation of cortical excitability. *Brain Stimulation*, *4*, 97–103.

Schwiedrzik, C. M. (2009). Retina or visual cortex? The site of phosphene induction by transcranial alternating current stimulation. *Frontiers in Integrative Neuroscience*, *3*, 6.

Squire, L. R. (1977). ECT and memory loss. *American Journal of Psychiatry*, *134*, 997–1001.

Terney, D., Bergmann, I., Poreisz, C., Chaieb, L., Boros, K., Nitsche, M. A., ... Antal, A. (2008). Pergolide increases the efficacy of cathodal direct current stimulation to reduce the amplitude of laser-evoked potentials in humans. *Journal of Pain and Symptom Management*, *36*, 79–91.

Vanneste, S., & De Ridder, D. (2011). Bifrontal transcranial direct current stimulation modulates tinnitus intensity and tinnitus-distress-related brain activity. *European Journal of Neuroscience*, *34*, 605–614.

Vanneste, S., Focquaert, F., Van de Heyning, P., & De Ridder, D. (2011). Different resting state brain activity and functional connectivity in patients who respond and not respond to bifrontal tDCS for tinnitus suppression. *Experimental Brain Research*, *210*, 217–227.

Vercammen, A., Rushby, J. A., Loo, C., Short, B., Weickert, C. S., & Weickert, T. W. (2011). Transcranial direct current stimulation influences probabilistic association learning in schizophrenia. *Schizophrenia Research*, *131*(1–3), 198–205.

Vines, B. W., Cerruti, C., & Schlaug, G. (2008). Dual-hemisphere tDCS facilitates greater improvements for healthy subjects' non-dominant hand compared to uni-hemisphere stimulation. *BMC Neuroscience*, *9*, 103.

Vines, B. W., Nair, D. G., & Schlaug, G. (2006). Contralateral and ipsilateral motor effects after transcranial direct current stimulation. *Neuroreport*, *17*, 671–674.

Wagner, T., Valero-Cabre, A., & Pascual-Leone, A. (2007). Noninvasive human brain stimulation. *Annual Review of Biomedical Engineering*, *9*, 527–565.

Zaehle, T., Rach, S., & Herrmann, C. S. (2010). Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS One*, *5*(11), e13766.

Zaghi, S., de Freitas Rezende, L., de Oliveira, L. M., El-Nazer, R., Menning, S., Tadini, L., & Fregni, F. (2010). Inhibition of motor cortex excitability with 15 Hz transcranial alternating current stimulation (tACS). *Neuroscience Letters*, *479*, 211–214.

Zheng, X., Alsop, D. C, & Schlaug, G. (2011). Effects of transcranial direct current stimulation (tDCS) on human regional cerebral blood flow. *Neuroimage*, *58*(1), 26–33.