

Transcranial Electrical Stimulation: Transcranial Direct Current Stimulation (tDCS), Transcranial Alternating Current Stimulation (tACS), Transcranial Pulsed Current Stimulation (tPCS), and Transcranial Random Noise Stimulation (tRNS)

Ingrid Moreno-Duarte¹, Nigel Gebodh^{1,2}, Pedro Schestatsky^{1,3}, Berkan Guleyupoglu², Davide Reato², Marom Bikson², and Felipe Fregni¹

¹Laboratory of Neuromodulation, Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

²Department of Biomedical Engineering, The City College of the City University of New York, New York, NY, USA

³Programa de Pós-Graduação em Ciências Médicas da Universidade Federal do Rio Grande do Sul, Brasil; Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brazil

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HISTORY OF TRANSCRANIAL ELECTRICAL STIMULATION (tES)

The historical origins of using transcranial electrical stimulation (tES) for therapy follow the history of the discovery of electricity itself. Though with (uncontrolled) dose bearing little resemblance to modern techniques, early attempts utilized electrosensitive animals such as the torpedo fish (*T. torpedo*), and examined the effects of electrical discharge over the scalp on headache pain reduction (Priori, 2003). With the development of man-made electric sources, studies in the 19th and early 20th centuries implemented the use of galvanic currents in the treatment of psychiatric disorders (see also Chapter 1). Electroconvulsive therapy (ECT) emerged in the 1930s (Abrams, 2002; Baghai, Lieb, & Rupprecht, 2012; Gilula & Kirsch, 2005), with the first treatment of a patient occurring in 1939 (Bini, 1995), and was shown to induce epileptogenic activity via the use of strong electrical currents. Variations of the technique continue to be used today with significant effects on psychiatric conditions but with some side effects, in particular memory loss (Gitlin, 2006; Lauber, Nordt, & Rossler, 2005; Lisanby, Kinnunen, & Crupain, 2002; Stagg & Nitsche, 2011; Uk ECT Review Group, 2003; Vitalucci, Coppola, Mirra, Maina, & Bogetto, 2013). In parallel, research

using low-intensity currents continued throughout the 20th century with a recent resurgence in the investigation of weak direct and alternating currents (Nitsche & Paulus, 2000). Four main methods of low-intensity tES have been intensively investigated over the past decade: transcranial direct current stimulation (tDCS), transcranial pulsed current stimulation (tPCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS) (Fig. 2.1). All four techniques are considered well tolerated (where precise established protocols are followed), and operate by influencing spontaneous and sometimes non-spontaneous (if coupled with a cognitive task) neuronal activity, generating gradual changes in neural networks. Here we consider the basis, dose (Peterchev et al., 2012), methods, and applications of each of the approaches.

TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS)

tDCS uses a low-intensity (0.5–2 mA; Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010) constant current (see anodal and cathodal tDCS diagrams in Fig 2.1), which is applied directly to the head, partially penetrates the skull, and enters the brain. This non-invasive method of stimulation has been shown to be a reliable method of modulating cortical excitability (Nitsche & Paulus, 2000), producing changes of up to 40% that can last for between 30 and 120 minutes (Kuo et al., 2013) after the end of stimulation (depending on the parameters used for stimulation). Computer modeling studies have shown that this type of stimulation can induce significant currents in superficial cortical areas (Datta et al., 2009; Miranda, Lomarev, & Hallett, 2006; Wagner, Valero-Cabre, & Pascual-Leone, 2007; see also Chapter 4) and influence neuronal excitability without eliciting action potentials (Bikson et al., 2004). As with other tES approaches, tDCS does pose some limitations, including limits on focality when conventional large electrodes (e.g., 5 × 7 cm) are used. Various methods to shape the outcomes of stimulation using large electrodes have been proposed (Nitsche et al., 2007), as well as approaches to focalize stimulation using smaller (e.g., 1 cm) arrays of high-definition electrodes (HD-tDCS; Bikson et al., 2004; Edwards et al., 2013). Despite the limited focality of conventional montages used in tDCS, global current flow patterns and resulting behavioral and clinical outcomes are montage specific.

Basic Principles

The parameters for dosage in tDCS take into account the amount of current delivered (in mA), the duration of the stimulation (in minutes), and the size and placement of the electrodes (see Fig. 2.1). From the electrode size and applied current, the average current density at the electrode can be

	tDCS	tACS	tPCS	tRNS
Typical electrode size (if present)	Two electrodes, 20–35 cm ² each*	16 cm ² *	16 cm ² *	16 cm ²
Typical type of current delivered	Small direct constant current at 0.5–2 mA	Bidirectional, biphasic current in sinusoidal waves Average intensity, 0.25–1 mA; frequency, 1, 10, 15, 30, and 45 Hz; voltage, 5–15 mV	Unidirectional, monophasic current pulses in typically rectangular waves; can be bidirectional/biphasic Average intensity, 0.6–1 mA; frequency, 1 Hz – 167 kHz	Alternate current along with random amplitude and frequency (between 0.1 and 640 Hz); intensity between –500 and +500 μA with a sampling rate of 1280 samples/s providing a current of 1 mA
Typical time for stimulation	20 min	2 and 5 min	20 min	10 min
NEUROMODEC Classification	tES technique where DC is sustained for greater than 1 minute with amplitude greater than 0.1 mA where current level does not change significantly (>5%)	tES technique where biphasic sinusoidal AC current is sustained for greater than 1 minute with amplitude greater than 0.1 mA peak-to-peak	tES technique in which current with rectangular pulses or trains of pulses, either monophasic or biphasic, is sustained for greater than 1 minute with amplitude greater than 0.1 mA peak-to-peak	tES technique in which AC is sustained for greater than 1 minute with a random and constantly changing amplitude greater than 0.1 mA RMS
Side effects	Tingling, itching, redness	Tingling, itching, redness	Tingling, itching, redness	Tingling, itching
EEG	Increased slow oscillatory activity (3 Hz)	Increased low alpha (8–12 Hz) and high theta (3–8 Hz) activity (Antal, Boros et al., 2008)	Increased slow oscillatory activity (<1 Hz) with 0.75-Hz stimulation (Marshall, Helgadottir, Molle, & Born, 2006)	No change
Cortical excitability	Increased excitability with anodal stimulation (Boros, Poreisz, Munchau, Paulus, & Nitsche, 2008; Nitsche et al., 2003) and decreased excitability with cathodal stimulation (Ardolino, Bossi, Barbieri, & Priori et al., 2005).	No change (Antal, Boros et al., 2008)	No known changes	Apparently enhances corticospinal excitability (Terney, Chaieb, Moliadze, Antal, & Paulus, 2008); although other studies do not support this finding (Fertonani, Pirulli, & Miniussi, 2011), Snowball et al. (2013) suggest modulation of cortical excitability with reduction of regional cerebral blood flow without affecting regional cerebral metabolic rate of oxygen consumption

Neurotransmitters

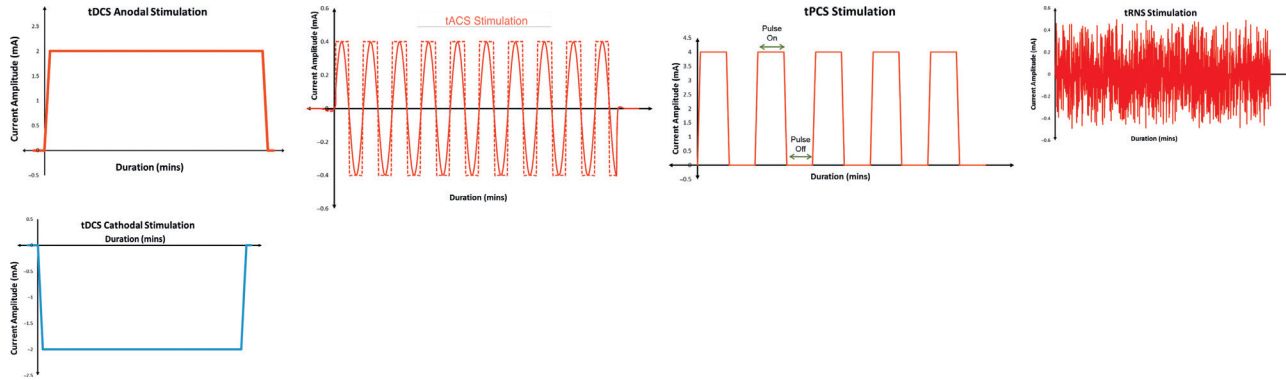
Increased brain-derived neurotrophic factor (BDNF) (Fritsch et al., 2010) and extrasynaptic GABA (Stagg et al., 2011), and decreased interaction of glutamate with its receptor (Fritsch et al., 2010)

No known changes

No known changes

Possibly activation of glutamate-mediated synapses (Terney et al., 2008)

Waveform



Multi-electrode montages are possible; however, effects have not been fully explored.

FIGURE 2.1 Summary of non-invasive brain stimulation techniques: tDCS, tACS, tPCS, and tRNS.

calculated (the current delivered divided by the size of the electrode). The most commonly used equipment for tDCS involves two saline-soaked sponges, electrodes (typically conductive rubber), non-conductive elastic straps, cables, and a battery powered tDCS current stimulating device (DaSilva, Volz, Bikson, & Fregni, 2011). The two saline-soaked sponges are usually 20–35 cm² in area and contain slits into which electrodes (an anode and cathode) are placed, creating an electrode–sponge unit (Fig. 2.2).

The shape and size of the sponges is designed so that they promote a uniform distribution of current over the stimulation area, reducing the risk of skin burns caused by electricity concentrations (or “hot spots”) in areas of the sponge/skin interface (Furubayashi et al., 2008; Kronberg & Bikson, 2012). These electrodes are concurrently attached to a battery-operated tDCS current stimulating device, which delivers a constant flow of weak current (up to 2 mA depending on the device) to the electrode–sponge units for a desired amount of time (Fig. 2.3).

The electrode placement on the scalp is usually derived from the International EEG 10–20 System. At least one of the electrode–sponge units is placed on the scalp, whereas the second can be placed at another cephalic location (known as a bipolar or bicephalic montage) or extracephalic location (known as a unipolar or monocephalic montage), usually the shoulder or upper arm (Datta, Baker, Bikson, & Fridriksson, 2011). The electrode–sponge units, which are secured by non-conducting rubber elastic straps, can also be placed in configurations where the reference electrode is placed over the forehead (above the supraorbital ridge) and the active electrode is placed over the contralateral hemisphere, commonly over the motor cortex (M1) or the dorsolateral prefrontal cortex (DLPFC), depending on the design (Fig. 2.4; Nitsche & Paulus, 2000).

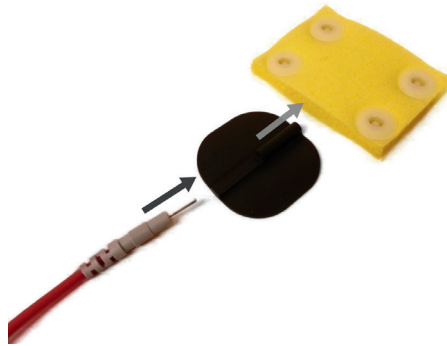


FIGURE 2.2 Electrode–sponge unit setup in tDCS. The metallic end of the cable is plugged into the carbon rubber electrode, which is then placed between the slits of the saline soaked sponge.

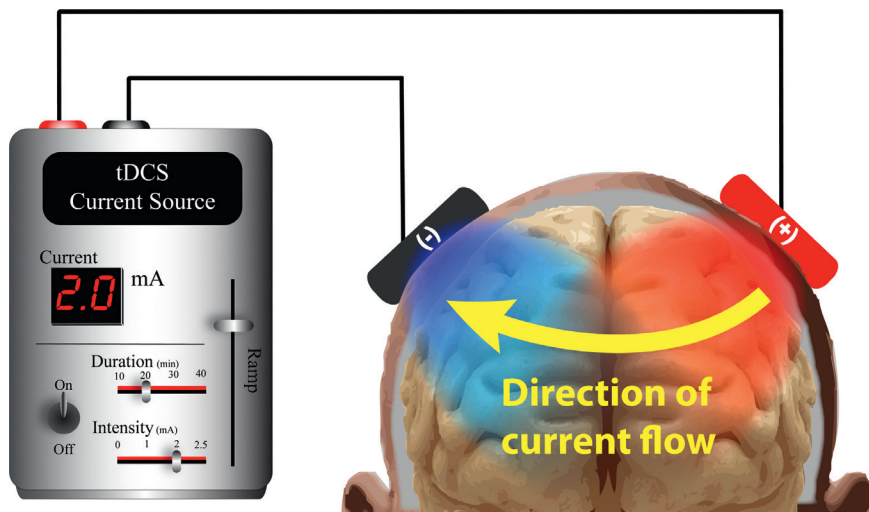


FIGURE 2.3 Parameters of current intensity (mA), duration (min) and direction of current flow in tDCS. The current delivered by the tDCS current stimulating device, enters the brain through the anode (+), passes through cortical and subcortical regions then leaves through the cathode (-).

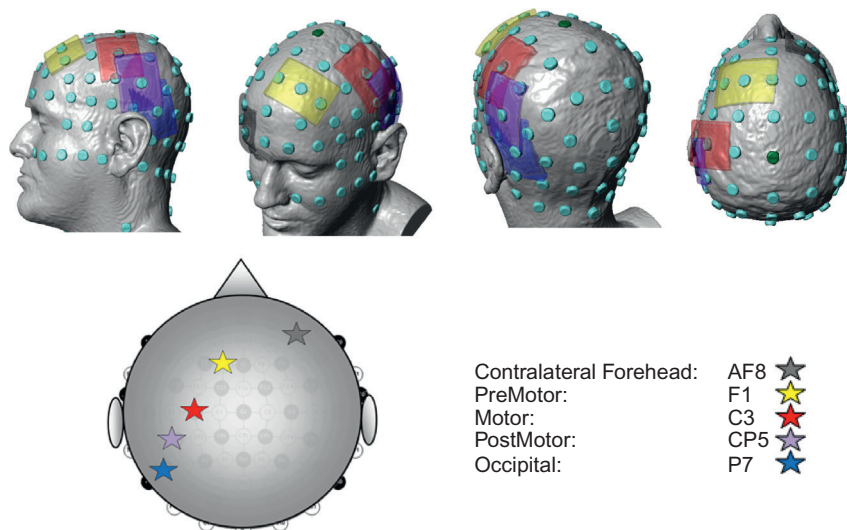


FIGURE 2.4 Common electrode placement for tDCS based on the International EEG10–20 system. The reference electrode is placed over the contralateral forehead (AF8), whereas the active electrode can be placed over the premotor (F1), motor (C3), postmotor (CP5), or occipital (P7) area.

The duration of the stimulation most often ranges between 20 and 40 minutes (Brunoni et al., 2012; Paulus, 2011).

Although some parameters of stimulation may vary, the outcomes have been strongly associated with the current density, duration of stimulation, polarity, and location of stimulation (Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010). In particular, electrode polarity will influence the effects on cortical excitability. For example, for currents up to 1 mA and duration less than 20 minutes, anodal stimulation over the motor cortex increases the motor evoked potential (MEP) and results in an opposite effect when the polarity is changed to cathodal stimulation (Paulus, 2011). Importantly, changing stimulation dose, including increasing duration and/or intensity, or alterations in ongoing brain activity, can change and even invert the direction of excitability modulation (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013). The amount of current that reaches neuronal tissue, though, is dependent on several uncontrollable factors, including the resistance of several cephalic structures such as skin, skull, blood vessels, and brain tissue (Brunoni et al., 2012).

Neurophysiological Mechanisms of tDCS

While the use of surface electrodes results in some shunting of current at the scalp as well as cerebrospinal fluid (CSF), a portion of current will penetrate to the brain, producing a peak electric field of approximately 0.3 V/m per 1 mA applied. While the resulting electric fields are low intensity (for comparison, TMS produces an almost 100-V/m electric field), the sustained electric field produced during tDCS will modify the transmembrane neuronal potential and can influence the level of excitability and the responsiveness to synaptic input (Rahman et al., 2013), and modulate the firing rate of individual neurons (Miranda et al., 2006; Wagner et al., 2007). tDCS-induced neuroplastic changes may be associated with modulation of neuronal ionic channels, specifically the L-type voltage gated calcium channel (L-VGCC), and N-methyl-D-aspartate (NMDA) receptors (Paulus, 2011). Mechanisms analogous to long-term potentiation (LTP) or long-term depression (LTD) have been attributed to tDCS effects on plasticity (see Chapter 5).

Importantly, since the current used in tDCS is subthreshold, it does not induce action potentials (Bikson et al., 2004); instead it modulates spontaneous neuronal activity (evoked, ongoing/endogenous activity) in a polarity-dependent fashion (Fig. 2.5). Surface anodal stimulation will typically produce inward current flow at the cortex, which is expected due to somatic depolarization of pyramidal cortical neurons and apical dendrite hyperpolarization, while surface cathodal stimulation will typically produce outward current flow at the cortex and is expected to result in somatic hyperpolarization of pyramidal cortical neurons and apical

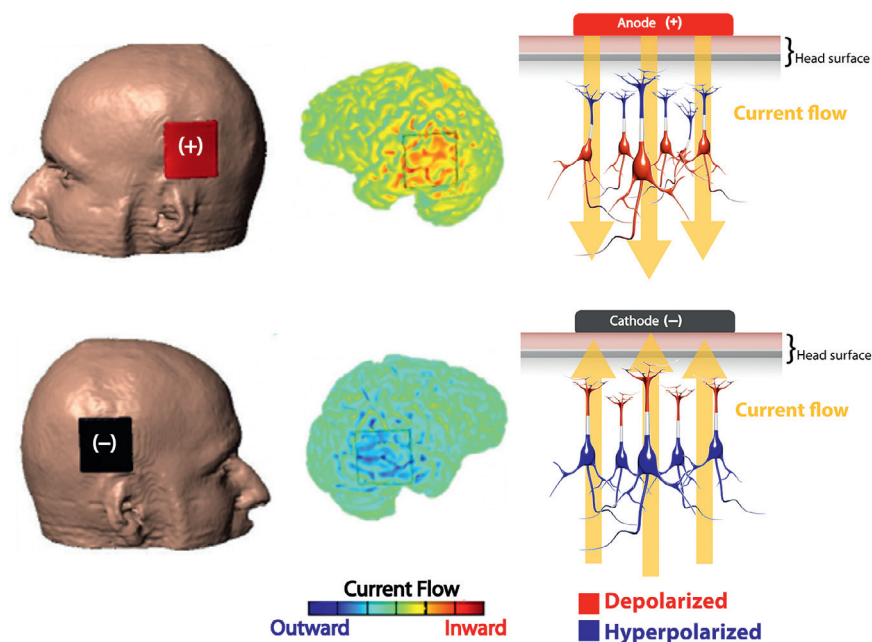


FIGURE 2.5 With tDCS, electrode polarity determines current direction of flow in the brain. The polarity also influences the cortical and subcortical regions that are activated by the stimulation. *Upper right:* Direction of current flow through the anode (+) in tDCS. The current passes through structures, including the scalp and bone, before reaching cortical and subcortical regions. In the pyramidal cortical neurons under the anode, apical dendritic regions of the neuron become hyperpolarized (blue) whereas the somatic regions become depolarized (red). *Lower right:* Direction of current flow through the cathode (–) in tDCS. The current passes through cortical and subcortical structures, then through the bone and scalp, before reaching the cathode. In the pyramidal cortical neurons under the cathode, apical dendritic regions of the neuron become depolarized (red) whereas the somatic regions become hyperpolarized (blue).

dendrite depolarization (Radman, Ramos, Brumberg, & Bikson, 2009; Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010).

Changes in brain excitability are assumed to track somatic polarization, at least at moderate stimulation intensities and durations. For example, 1-mA, 20-minute anodal tDCS applied over the motor cortex increases, whereas cathodal tDCS at the same intensities decreases, the excitability of the said region (Nitsche & Paulus, 2000; Wassermann & Grafman, 2005).

While the nominal targets of tDCS are often under the electrodes, the current flow produced using conventional tDCS spans all cortical regions between and around the electrodes and is thus not restricted to the area under the electrodes (Nitsche et al., 2004). It is therefore important to take care to distinguish between stimulating with an electrode “over” a region and specifically targeting that region. Moreover, current flow with conventional montages is expected to reach deep structures and, with

extracephalic electrodes, the midbrain and spinal cord (Bikson, Datta, Rahman, & Scaturro, 2010; Brunoni et al., 2012; DaSilva et al., 2012; Keeser et al., 2011; Miranda et al., 2006; Salvador, Mekonnen, Ruffini, & Miranda, 2010; Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010). This far-reaching activation is thought to be due to the stimulation of regions on alternate neural networks (Nitsche et al., 2005). In fact, tDCS has been found to modulate resting-state functional connectivity after prefrontal stimulation (Keeser et al., 2011). However, as noted above, the diffuse nature of current flow does not mean that (even small) changes in montage can change the *pattern* of current flow leading to significant changes in specific outcome measures (Nitsche & Paulus, 2000; Mendonca et al., 2011). In addition, tDCS may be “functionally” focalized by timing stimulation with specific tasks (Cano, Morales-Quezada, Bikson, & Fregni, 2013; Cohen Kadosh, Soscic, Iuculano, Kanai, & Walsh, 2010).

Clinical Applications of tDCS

Due to the pronounced neuromodulatory effects of tDCS, specifically its effects on modulating rate of learning, tDCS has been tested with several neuropsychiatric disorders (see Table 2.1). For instance, tDCS has been used for motor learning enhancement in stroke rehabilitation (Schlaug, Renga, & Nair, 2008), for behavioral performance enhancement with Alzheimer’s patients (Boggio, Khoury et al., 2009; Ferrucci et al., 2008; see also Chapter 13), for modulation of emotional affective neural circuits in depression patients (Boggio, Zaghi, & Fregni, 2009; Bueno et al., 2011; Kalu, Sexton, Loo, & Ebmeier, 2012; Loo et al., 2012; see also Chapter 14), and for patients with chronic pain (Boggio, Zaghi, Lopes, & Fregni, 2008; Fenton, Palmieri, Boggio, Fanning, & Fregni, 2009; Fregni, Marcondes, Boggio, Marcolin, Rigonatti et al., 2006; Gabis et al., 2009; Zaghi, Thiele, Pimentel, Pimentel, & Fregni, 2011). In stroke neurorehabilitation, tDCS has shown benefits when used together with other interventions such as rehabilitatory training, in primates (Plautz et al., 2003; see Chapter 12) or occupational therapy in humans (Nair, Renga, Lindenberg, Zhu, & Schlaug, 2011). In terms of pain, tDCS has been applied to cases of chronic pain refractory to pharmacologic interventions (Lefaucheur et al., 2008; Nizard, Lefaucheur, Helbert, de Chauvigny, & Nguyen, 2012) and for a number of different pain conditions such as fibromyalgia, pelvic pain, and neuropathic pain (DaSilva et al., 2012; Fenton et al., 2009; Fregni, Boggio, Santos, Lima, Vieira et al., 2006). Some studies have also examined the effects of anodal tDCS on learning in healthy subjects, showing improvement in implicit learning (Kincses, Antal, Nitsche, Bartfai, & Paulus, 2004), motor memory (Galea & Celnik, 2009), working memory (Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011; Ohn et al.,

TABLE 2.1 Examples of tDCS Electrode Montages in Different Clinical Conditions

Disease	Authors	Anode	Cathode
Depression	Boggio, Berman et al., 2007; Boggio, Rigonatti et al., 2008; Loo et al., 2012	DLPFC	Supraorbital
Stroke	Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010	M1	Contralateral M1
	Boggio, Nunes et al., 2007	M1 (affected side)	Supraorbital
		Supraorbital	M1 (non-affected side)
Tinnitus	Fregni, Gimenes, Valle, Ferreira, Rocha et al., 2006	LTA	Supraorbital
Parkinson	Benninger et al., 2010	M1/DLPFC	Mastoid
	Fregni, Boggio, Nitsche, Marcolin, Rigonatti et al., 2006; Fregni, Boggio, Nitsche, Rigonatti, & Pascual-Leone, 2006; Fregni, Boggio, Santos, Lima, Vieira et al., 2006; Boggio et al., 2006	M1	Supraorbital
Migraine	Antal, Kincses, Nitsche, & Paulus, 2003; Antal, Lang et al., 2008; Antal, Kriener, Lang, Boros, & Paulus, 2011; Chadaide et al., 2007; Antal et al., 2011	V1	Oz
Alcohol abuse	Boggio, Sultani et al., 2008	R/L – DLPFC	L/R – DLPFC

LTA, left temporoparietal area; V1, visual cortex; DLPFC, dorsolateral prefrontal cortex; M1, motor cortex; R, right; L, left; Oz, occipital lobe at midline (EEG 10/20 system).

2008), and memory retrieval (Boggio, Nunes et al., 2007; Boggio, Fregni et al., 2009; Chi, Fregni, & Snyder, 2010; see also Chapter 9).

Although the majority of the preliminary clinical results show positive outcomes, it should be noted that in most cases stimulation parameters were varied across clinical studies. It should also be noted that these studies contained small sample sizes with relatively homogeneous populations, and used mostly surrogate outcomes.

The field of tDCS is, however, ever advancing, with a new method of tDCS having been recently developed. This method, known as “high definition” tDCS (HD-tDCS), utilizes an array of smaller electrodes (Fig. 2.6). The position and current at each electrode can be optimized for intensity or targeting (Dmochowski, Datta, Bikson, Su, & Parra, 2011). One HD-tDCS, the “4 × 1 ring” electrode montage, has been shown to be a more focused method of stimulation compared to conventional tDCS (Fig. 2.7; Datta et al., 2009; Edwards et al., 2013). Though relatively few

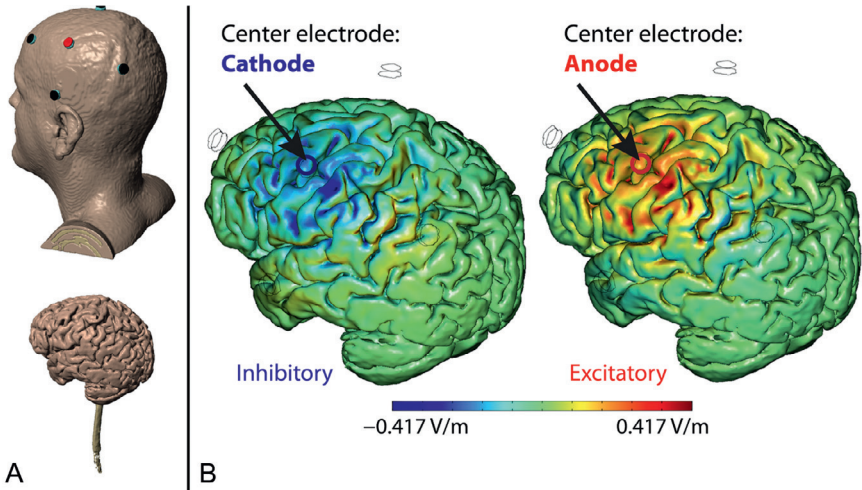
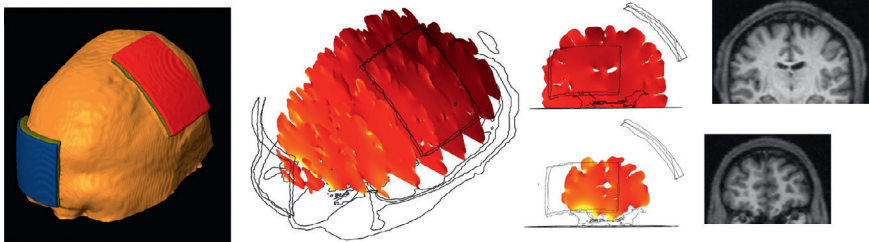


FIGURE 2.6 HD-tDCS setup and current penetration. (A) One center electrode (red) is placed over the area of stimulation and four return electrodes (black) are placed around it. The radius of the ring around the center electrode determines the modulation of the area of interest. (B) An inhibitory effect is achieved with the center electrode as a cathode, whereas an excitatory effect is achieved with the center electrode as an anode.

Conventional tDCS bipolar large electrodes



High Definition tDCS 4x1 configuration

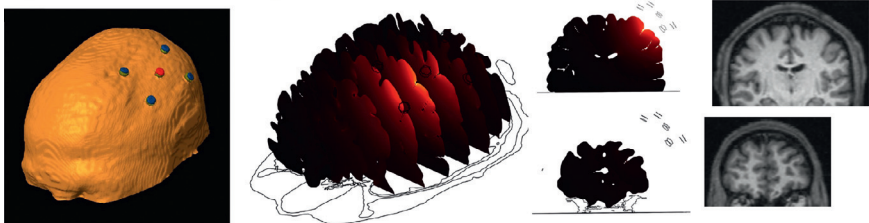


FIGURE 2.7 Comparison between tDCS and HD-tDCS in terms of set-up, focality, and depth of current penetration. tDCS is shown to activate the region of interest as well as other cortical and subcortical areas, whereas HD-tDCS focuses the stimulation to the cortical region of the area of stimulation.

HD-tDCS studies have been published as of yet, 4×1 HD-tDCS has been shown to be a reliable method of targeting specific cortical areas, can produce plasticity changes that may outlast conventional tDCS (Kuo et al., 2013), and has even been shown to reduce the perception on pain in fibromyalgia patients (Villamar, Volz et al., 2013; Villamar, Wivatvongvana et al., 2013) and in experimental pain (Borckardt et al., 2012). In the coming decades we can expect the field of tDCS to see advancements in areas like methods of deeper current penetration, more specific cortical targeting, more specific patient dosage parameters, and a larger shift of the use of tDCS in clinical environments.

TRANSCRANIAL ALTERNATING CURRENT STIMULATION (tACS)

Basic Principles

Broadly, alternating current (AC) stimulation is a method of delivering a non-constant current to the brain. This method of stimulation is accomplished by using pulses of current in either rectangular waves (the intensity reaches a certain amplitude, is held at that amplitude for a short duration of time, is then interrupted by zero current, the polarity of the current changes, and the process repeats) or sinusoidal waves (Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010). For a recent review of the cellular mechanisms of tACS, see Reato, Rahman, Bikson, and Parra (2013). Briefly, as for DC (Bikson et al., 2004), AC stimulation alters the transmembrane potential of single neurons, with maximal effects when currents are directed along the somatodendritic axis. The polarization profile tracks the applied current – so, for example, sinusoidal stimulation leads to a sinusoidal fluctuation of the membrane potential. The polarization is linearly proportional to the current applied but is also frequency-dependent (Deans et al., 2007; Reato, Rahman, Bikson, & Parra, 2010). Therefore, AC stimulation at low frequencies induces bigger polarizations than stimulation at high frequencies.

Stimulation with alternating current is used in deep brain stimulation, motor cortex stimulation, spinal cord stimulation, transcutaneous nerve stimulation, vagal nerve stimulation, transcranial magnetic stimulation, and electroconvulsive therapy. Among the variety of methods of low-intensity non-invasive AC stimulation in this chapter we will focus on tACS, which typically consists of biphasic sine waves (Fig. 2.1), albeit other methods with established clinical effects, including cranial electrotherapy stimulation (CES), transcutaneous electrical stimulation (TCES) with Limoge's current, and transcranial electrical stimulation (tES) with Lebedev's current, exist.

Transcranial Alternating Current Stimulation (tACS)

Low-intensity AC methods use different electrode montages and current characteristics. The use of alternating currents with a similar montage as that used in tDCS is known as transcranial alternating current stimulation (tACS; [Antal, Boros et al., 2008](#)) (see tACS diagram in [Fig. 2.1](#)). [Antal, Boros et al. \(2008\)](#) applied tACS for 2 and 5 minutes, with a current intensity of 0.25–0.40 mA using a 16-cm² electrode (current density = 25 $\mu\text{A}/\text{cm}^2$) at several frequencies (1, 10, 15, 30, and 45 Hz). The study claimed not to have an effect on cortical excitability, as assessed by MEPs and electroencephalogram power; however, it did show that 5 minutes of tACS at 10 Hz applied at the motor cortex was related to improvement in implicit motor learning while other studies have claimed effects on cortical excitability, as mentioned in the next section, using higher frequencies. Moreover, [Kanai, Chaieb, Antal, Walsh, and Paulus \(2008\)](#) applied tACS to the visual cortex at 5–30 Hz and 250 μA to 1000 μA to assess the visual phosphene threshold. The study showed the influence of tACS on inducing phosphenes at 20 Hz (beta frequency range) when applied in an illuminated room, and 10 Hz (alpha frequency range) in darkness. These studies suggest that the effects seen as a result of this type of stimulation are dependent on the intensity of the current, and the frequencies and duration of the stimulation. However, the direction of the effect (either increasing or decreasing cortical excitability) is not clear yet. Note, however, that a later study has attributed Kanai et al.'s results to retinal rather than cortical effects ([Schutter & Hortensius, 2010](#)). Recent studies also extended the usage of tACS to the high-level cognitive domain (e.g., [Santarnecchi et al., 2013](#); see also [Chapter 11](#)).

Proposed Mechanisms of Action in AC Stimulation with Weak Electric Current

Changes in Cortical Excitability

Several studies performed with tACS have used a variety of current intensities and frequencies, showing contradictory results on cortical excitability. Using a current density of 25 $\mu\text{A}/\text{cm}^2$ at 1, 10, 15, 30, and 45 Hz for 5 minutes, [Antal, Boros et al. \(2008\)](#) showed that AC stimulation did not result in significant changes to cortical excitability as measured by TMS evoked motor potentials. Another study, by [Zaghi, de Freitas Rezende et al. \(2010\)](#), showed differing results. The latter authors tested tACS with a lower current density (0.08 $\mu\text{A}/\text{cm}^2$) at a frequency of 15 Hz and for a longer duration (20 minutes) than previously used (i.e., around 0.16–0.25 mA/m² for current and 2–5 minutes for timing) ([Antal, Boros et al., 2008](#)). With the aforementioned parameters of stimulation, Zaghi et al.

found a decrease in MEPs and intracortical facilitation, reflecting a change in the cortical excitability. Alternatively, [Chaieb, Antal, and Paulus \(2011\)](#) used high frequencies (1, 2, and 5 kHz) for 10 minutes at 1 mA (current density $20.8 \mu\text{A}/\text{cm}^2$) and found increased amplitude in the MEPs at all frequencies compared to baseline, suggesting that high frequencies might be associated with increased excitability of the motor cortex. Regarding the intensity of the current, [Moliadze, Atalay, Antal, and Paulus \(2012\)](#) showed that 1 mA is associated with increased cortical excitability, while lower intensities close to 0.4 mA promote a switch to inhibition. All these studies found different results, suggesting that changes in the cortical excitability due to AC stimulation are frequency and intensity specific.

Changes in Brain Electrical Activity

Electroencephalography (EEG) changes during cranial stimulation with low-intensity AC have been seen. An early EEG study found that one 30-minute session of cranial AC stimulation daily for 5 days increased the amplitude of slower EEG frequencies with increased alpha wave (8–12 Hz) activity ([McKenzie, Rosenthal, & Driessner, 1971](#)). In contrast, [Schroeder and Barr \(2001\)](#) compared EEG activity in sham and active CES (at frequencies of 0.5 and 100 Hz), showing a decrease of the alpha band median frequency and beta band power fraction in the active group. As for tACS, [Zaehle, Rach, and Herrmann \(2010\)](#) performed a study investigating tACS over the occipital cortex while measuring alpha activity on EEG. They found that tACS increased alpha activity, which could be potentially useful for treating patients with cognitive dysfunction due to the modulatory effects of tACS seen in this and previous studies. The effects observed in the EEG recordings provide initial mechanistic data to explain tACS results, in particular presenting additional evidence of the frequency and intensity-specific effect of this technique; however, further studies are needed to clarify the cellular mechanisms of this intervention.

Biochemical Changes

There is evidence that AC stimulation is associated with changes in neurotransmitters such as urinary free catecholamines, 17-ketosteroids ([Briones & Rosenthal, 1973](#)), and endorphin release. A study by [Kirsch and Smith \(2004\)](#), analyzed presynaptic membranes before, during, and after cranial AC stimulation in monkeys. They showed a reduction in the number of vesicles at the beginning of stimulation, then an increase after 5 minutes, and finally a regression to normal shortly after the end of stimulation. These changes were believed to be related to serotonin-releasing raphe nuclei, norepinephrine-releasing locus ceruleus, or the cholinergic laterodorsal tegmental and pediculo-pontine nuclei of the brainstem ([Giordano, 2006](#); [Kirsch, 2002](#)). Plasmatic and CSF levels of endorphins have been found to increase during cranial AC stimulation

(Limoge, Robert, & Stanley, 1999). In fact, there are reports on naloxone antagonizing the analgesic effects of stimulation, which might account for its effects on endorphins (Limoge et al., 1999). Although some controversy exists regarding the findings of such studies, they do suggest that there might be an association between cranial AC stimulation and neurotransmitter release (Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010).

Basic Principles

Pulsed current stimulation is a non-invasive brain stimulation technique that uses repeated bursts or pulses of current to induce changes over cortical and subcortical brain structures (see tPCS diagram in Fig. 2.1; Datta, Dmochowski, Guleyupoglu, Bikson, & Fregni, 2012). Much like tDCS, it is possible to use many different electrode placements on the head as well as high-definition electrodes to make it more focal. The introduction of pulses, rather than sine waves as traditionally used in tACS, in stimulation allows for different waveforms to be used for optimized dosage considerations. CES is the most common form of modern pulsed current stimulation, and involves the application of current to infra- or supra-auricular structures such as the ear lobes, mastoid processes, zygomatic arches, or maxillo-occipital junction (Ferdjallah, Bostick, & Barr, 1996). Current is usually applied through saline-soaked clips or pads.

Modeling studies predict that, for common CES montages, intensities between 0.2–0.6 V/m are produced in cortical and subcortical structures (Datta et al., 2012; Guleyupoglu, Schestatsky, Edwards, Fregni, & Bikson, 2013). These intensities are near the limit of those established to modulate the waveform of active neuronal networks (Deans, Powell, & Jefferys, 2007; Francis, Gluckman, & Schiff, 2003; Reato, Gasca et al., 2013). As such, the term CES (with “transcranial”) may suggest the possibility of actions through stimulation of peripheral nerves (Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010). Thus, CES can also be considered a form of peripheral nerve stimulation due to the electrode locations. Studies with CES have used variable parameters of stimulation, including duration, current density, intensity, and electrode size for the treatment of anxiety, depression, stress, and insomnia (Kirsch & Smith, 2004; Smith, 2007). These studies have shown differing results that could be due to variation in the parameters of stimulation, which include frequency ranges of 0.5–167 kHz, intensities of 0.1–4 mA, and durations ranging from 5 minutes to 6 consecutive days.

Other Methods of Pulsed Current Stimulation

Limoge’s current (or “transcutaneous electrical stimulation,” TCES; Guleyupoglu et al., 2013) applies a current transmitted over three cutaneous electrodes: one negative (cathode), which is placed between the

eyebrows, and two positive (anodes), which are placed in the mastoid regions. Stimulation carries a voltage ranging from 30 to 35 V, an average intensity of 2 mA, and a frequency of 166 kHz with 4 ms ON and 8 ms OFF (Guleyupoglu et al., 2013; Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010). The waveform of this type of stimulation includes trains of successive impulse waves of a particular shape: one positive impulse (S1) of high intensity and short duration, followed by a negative impulse (S2) of weak intensity and long duration (Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010). This form of transcranial stimulation has been suggested to decrease the amount of narcotics required to maintain anesthesia during surgical procedures (Limoge, 1999).

Lebedev used Limoge's electrode positions, but combined AC and DC current at a 2:1 ratio. First, a pulse train of AC is delivered at a frequency of 77.5 Hz for 3.5–4.0 ms and then is separated from the next train by 8 ms. Two trains of AC stimulation are then followed by 4 ms of constant DC (Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010). Lebedev's current has been suggested to be effective for the treatment of stress and affective disturbances (Lebedev et al., 2002).

TRANSCRANIAL RANDOM NOISE STIMULATION (tRNS)

Transcranial random noise stimulation (tRNS) has not been extensively investigated, but preliminary results are encouraging. Terney et al. (2008) were among the first to recently revisit the use of this technique. They showed that by using an alternate current along with random amplitude and frequency (between 0.1 and 640 Hz; see tRNS diagram in Fig. 2.1) on healthy subjects, the motor cortex excitability increased significantly, but this effect was limited to high frequencies. The effects lasted for approximately 60 minutes after 10 minutes of stimulation. The physiological mechanisms underlying the effects of tRNS are not well known, but it is suspected that they may be due to the repeated opening of sodium channels (Paulus, 2011) or to the increased sensitivity of neuronal networks to modulation (Francis et al., 2003). The technique includes all the frequencies up to half of the sampling rate (1280 samples/s) – i.e., 640 Hz (Moliadze, Antal, & Paulus, 2010). Compared to tDCS it has the advantage of being more comfortable (Moliadze et al., 2010), which makes it potentially advantageous for setting and blinding studies (Ambrus, Paulus, & Antal, 2010). Studies with fMRI have shown a reduction of the blood oxygen level dependence (BOLD) after the use of tRNS, relating the change in blood flow to the energy used by brain cells (Chaieb et al., 2009). The same authors also studied the effect of tRNS at frequencies of 100–640 Hz and with decreasing duration of the stimulation (4, 5, and 6 minutes) on motor cortical excitability (Chaieb, Paulus, & Antal, 2011). They found significant increased facilitation at 5 and 6 minutes

and none at 4 minutes, suggesting that a minimal duration of 5 minutes is necessary to observe an effect. [Mulquiney et al. \(2011\)](#) used tRNS in the dorsolateral prefrontal cortex to assess its effects on working memory. They used a randomly alternating level of current of between -500 and $+500$ μA with a sampling rate of 1280 samples/s and high range frequencies (101–640 Hz), providing a current of 1 mA. This study did not find any significant changes in working memory with the use of tRNS. [Fertonani et al. \(2011\)](#) tested the role of high- and low-frequency tRNS on perceptual learning compared to anodal and cathodal tDCS. The parameters used for tRNS were a duration of approximately 4 minutes in five experimental blocks (22 minutes total), with a current of 1.5 mA and frequencies in the low (0.1–100 Hz) and high range (100–640 Hz). The study concluded that high-frequency tRNS subjects showed better accuracy on the perceptual task compared with the other groups. Low-frequency tRNS subjects did not show any difference compared to sham or high-frequency tRNS, which supports the consideration that this stimulation might be useful in the high-frequency range. However, the optimal parameters of stimulation for tRNS as well as the potential clinical effects of this technique remain unclear. tRNS has been coupled with near-infrared spectroscopy to evaluate the hemodynamic changes in the prefrontal cortex. [Snowball et al. \(2013\)](#) reported an improvement on calculation- and memory-recall based arithmetic learning with tRNS that was associated with hemodynamic responses suggesting an efficient neurovascular coupling on the dorsolateral prefrontal cortex. These changes were maintained up to 6 months after the stimulation, implying that the neuromodulatory effects are seen over the long-term.

CONCLUSION

Interest in neuromodulatory interventions has increased in recent decades, as it is considered a promising tool for the management of numerous conditions that range from psychiatric diseases to chronic pain. Studies on non-invasive brain stimulation with weak electrical currents have shown potential benefits by the induction of changes in cortical excitability and, consequently, in neuroplasticity. The effects catalyzed by these techniques seem to depend on the parameters of the stimulation, including intensity, duration, and frequency, which explains the variability of the results. While there is an increased understanding of the mechanisms of tDCS, the mechanisms that underline other methods described here are poorly understood. Therefore, more research is needed, which will lead to a better understanding of the neurophysiological effects and mechanisms of transcranial stimulation (see also [Chapters 4–6](#)), and the suitability of each method to enhance the human brain, as indicated by the various chapters in this book.

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