CHAPTER

135

Transcranial Direct Current Stimulation (tDCS)

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INTRODUCTION

Since transcranial Direct Current Stimulation (tDCS) is an emerging technology, it is useful to introduce it in the context of other established neuromodulation techniques. Electrotherapy approaches using implanted electrical stimulators, such as Deep Brain Stimulation (DBS) (Aouizerate et al., 2004; Greenberg et al., 2006), and Vagus Nerve Stimulation (VNS) (Rush et al., 2005), are increasingly being used to treat neurological (e.g., refractory movement disorders) and psychiatric disorders (i.e., severe refractory mood and anxiety disorders). However, these approaches inherently require surgery and are thus associated with several manifest limitations related to cost and risk, and do not provide the adaptive flexibility of noninvasive approaches (Bikson et al., 2008). Noninvasive approaches offer the promise of noninvasive and flexible interventions. Among the most established noninvasive electrotherapy approaches, Electroconvulsive Therapy (ECT) and repetitive Transcranial Magnetic Stimulation (rTMS) are US Food and Drug Administration (FDA) approved but

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are associated with costs (e.g., in-office treatments and anesthesia) and side effects (e.g., pain and memory loss). tDCS is an emerging, noninvasive technique that offers the promise of electrotherapy with minimal cost and side effects.

tDCS is a simple and customizable technique that is applied to a wide range of clinical and cognitive neuroscience applications (Brunoni et al., 2012, 2013a). It is a promising tool in cognitive neuroscience and neuropsychiatric therapy with interventions rationalized and based on current to targeted brain regions to modulate excitability (Nitsche and Paulus, 2000; Merton and Morton, 1980) and plasticity (Nitsche and Paulus, 2001).

An ideal electrotherapy treatment would combine ease of administration (ultimately, self-administered at home), effective outcomes through plastic brain changes (not requiring chronic stimulation), low-cost, robust safety (noninvasive, with no major risks), and thus minimal contraindications. From this perspective, tDCS is a highly promising electrotherapy approach (Fregni et al., 2006; Boggio et al., 2008). However, there still remain questions about the clinical efficacy of tDCS.

**Historical Background and Other Transcranial Electrical Stimulation Approaches**

The emergence of tDCS is important to understand in the context of over a century of electrical stimulation history. Such a review also helps to explain and disambiguate terminology used to describe related techniques. Transcranial Electrical Stimulation (tES) encompasses all forms of research and clinical application of noninvasive electrical currents to the brain using electrode(s) (at least one) on the head. The dose of tES is defined by the electrode montage and the stimulation waveform applied to the electrode (Peterchev et al., 2012). There has been a resurgence of interest since 2000, but tES developed incrementally over a century. Historically, there are “streams” of linked categories of tES (Fig. 135.1): (1) Cranial Electrical Stimulation (CES) descended from Electrosleep (ES) through Cranial Electrostimulation Therapy (CET), Transcerebral Electrotherapy (TCET), and Neuroelectric Therapy (NET); (2) Electroanesthesia (EA) went through several periods of waning interest and resurgence when new waveform variations were proposed including Transcutaneous Cranial Electrical Stimulation (TCES), Limoge, and Interferential Stimulation; (3) Polarizing or Direct Current Stimulation includes recent tDCS, Transcranial Micropolarization, High-Definition transcranial Direct Current Stimulation (HD-tDCS) and Galvanic Vestibular Stimulation (GVS); (4) ECT, initially called Electroshock Therapy, evolved in technique and dose, such as Focal Electrically Administered Seizure Therapy (FEAST); and (5) “Contemporary” approaches that have been explored intensely over the last decade, such as transcranial Alternating Current Stimulation (tACS), transcranial Sinusoidal Direct Current Stimulation (tSDCS), and transcranial Random Noise Stimulation (tRNS). Though analogues to these contemporary approaches can be identified in earlier literature, contemporary methods contain dose features that motivate us to consider them novel as a category. Contemporary approaches, along with the rediscovery of tDCS, to some extent, reflect a “reboot” of interest in tES approach with modern technology and clinical research approaches (Paulus, 2011; Güleyupoglu et al., 2013).

Several “streams” of tES began around 1900s (Robinovitch, 1914), and included ES and EA—which are described in the next two sections.

*Developments From ElectroSleep to Cranial Electrotherapy Stimulation*

ES is the name for which the brain was stimulated to induce a sleep-like state in the subject. The first studies on ES were initiated in 1902 (Robinovitch, 1914; Gilula and Kirsch, 2005); however, the first clinical report of ES was published 12 years later by Robinovitch (Robinovitch, 1914; Brown, 1975). New approaches, such as changing electrode position from covering the eyes to locations around the eyes, presumably to “reduce optic nerve irritation” (Brown, 1975; Obrosow, 1959) were developed, mostly in Europe. ES dose waveform was typically pulsed at 30–100 Hz, but at least one (unsuccessful) case of use of DC current was documented (Brown, 1975). In a symposium, it was reasoned that ES does not actually induce sleep, rather it is an indirect side effect of the relaxing effects of stimulation. Therefore, the name of ES was changed to CET (Knutson, 1967). This was the first of several changes of the name of ES over the next few decades, often with notable changes in dose. In 1969, TCET was proposed as another alternative name. However, such devices were renamed as CES (Kirsch, 2010).

A notable device, produced after the name change to CET, was the Neurotone 101, which was based on a Russian ES device brought to the United States. Although the Neurotone 101 is no longer in production, it was the first device to be approved by the FDA as a CES device (Kirsch, 2010) and all subsequent CES devices approved by the FDA, such as the Alpha-Stim, the Oasis Pro, and the Fisher-Wallace Stimulator (Fig. 135.2), were through a 510k process claiming equivalency, either direct or descendant, to the Neurotone 101.

Modern CES is thus a historical descendant of ES, even as dose and indications have continuously evolved. The FDA sanctioned CES in 1978 through a “grandfather clause” and have not, since then, advanced a regulatory consensus, even as more variants were being developed. CES, in this modern form, excludes DC waveforms, so it is distinct from tDCS, but its historical predicates include DC components.
Figure 135.1 A general timeline of Electrical Stimulation (ES)/Electroanaesthesia (EA) noting key points in the history from 1902 until 2011 as well as their relation to Direct Current Stimulation (DCS). Adapted from Corapopoulou, B., Schestatsky, P., Edwards, D., Fregni, F., Bikson, M. (2013). Classification of methods in transcranial electrical stimulation (tES) and evolving strategy from historical approaches to contemporary innovations. J. Neurosci. Methods, 219 (2), 297–311.
Developments From Electroanesthesia to Limoge Current and Other Related Methods

EA, in short, was intended to induce anesthesia in the subject using high frequency stimulation so that chemicals did not have to be used, presurgery. EA studies started in 1903, but were first known as Electronarcosis (EN) (Robinovitch, 1914; Brown, 1975; Limoge et al., 1999). Russian scientists used the term “EA” to describe local anesthesia, while “EN” described general anesthesia (Brown, 1975). However, EA stopped being referred to as local, as applied to the periphery, and began to be known as general anesthesia, as applied to the brain.

Research into EA dosage continued and the term TCES was adopted around 1960–63. Even though the term TCES was not adopted until the early 1960s, similar protocols were used, as early as 1902 by Leduc (Limoge et al., 1999). In 1951, Denier proposed that high frequency trains of 90kHz could be used to avoid muscular contraction (Limoge et al., 1999). Three years later, Knutson (1954) claimed that alternating currents (AC) at 700Hz should be applied, but this was abandoned in 1958 due to cardiovascular complications (Limoge et al., 1999). In 1957, investigators in the Soviet Union attempted to add a Direct Current (DC) component to Leduc’s currents but, as claimed by an American scientist, Robert Smith, it resulted in a collection of undesirable side effects (Smith, 1971). In 1964, a study claimed that pulsating currents are more effective than DC for the induction of EA (Brown, 1975). Another study suggested that the use of pure DC for EA required high intensities of approximately 40mA (Brown, 1975). EA, and its derivative technologies, are not explicitly integrated into contemporary neuromodulation research and treatment, but represent important historical precedents that include cases of testing of DC waveforms.

Development of Direct Current Stimulation

DCS has been used intermittently as a component in both ES and EA. In 1957, a DC bias was added to ES,
which is traditionally applied using only AC or Pulse Current (PC). The advent of TCES, around 1960–63, in the third resurgence of EA research, also incorporated a DC bias. In 1969, pure direct current stimulation was investigated for inducing anesthesia (Brown, 1975). However, it was not until 1964 that preliminary studies, heralding modern tDCS, were published (Redfearn et al., 1964).

In 1964, Redfearn and Lippold investigated Polarizing Current for the treatment of neuropsychiatric diseases (Redfearn et al., 1964). Their use of prolonged (minutes) of stimulation was motivated by animal studies showing that prolonged DCs could produce lasting changes in excitability (Bindman et al., 1964). While further open, pilot studies and clinical observations suggested efficacy (Baker, 1970; Nias, 1976; Ramsay and Schlagenhauf, 1966), a following negative, controlled trial (Arfai et al., 1970) seems to have halted investigation (at least as published in Western journals) for several decades.

The neurophysiological basis of neuromodulation using short-duration tDCS was investigated by Priori et al. in 1998. Shortly after, Nitsche and Paulus established that prolonged (minutes) tDCS may produce lasting and polarity-specific changes in cortical excitability (Nitsche and Paulus, 2000). This was followed by pilot clinical studies (Bolognini et al., 2009) for indications spanning depression (Datta et al., 2009), pain (Datta et al., 2008), epilepsy (Datta et al., 2008), and a broad range of neuropsychiatric disorders (Datta et al., 2008). tDCS is further explored for rehabilitation after stroke (Datta et al., 2008). Moreover, due to the perceived safety of tDCS, it was initially validated for neurophysiological changes in healthy subjects and continues to be investigated in healthy individuals for changes in behavior and cognitive performance (Datta et al., 2008).

In 2007, HD-tDCS was proposed as a focalized form of tDCS (Datta et al., 2008, 2009). HD-tDCS electrodes were designed for increased charge-passage capacity through a smaller contact area (Minhas et al., 2010), arranged in arrays that can be optimized per indication (Dmochowski et al., 2011). HD-tDCS montages tested have included the 4×1 configuration (Edwards et al., 2013) as well as individually optimized arrays (Dmochowski et al., 2013). The focalization of current with HD-tDCS is an improvement upon tDCS, where previously a broad area would be stimulated, and now specific targets can be stimulated. Some of the devices that have been used are the Schneider (tDCS), Soterix Medical 1×1 (tDCS), and the Soterix Medical 4×1 (HD-tDCS) (Fig. 135.2).

Transcranial Micropolarization is a technique investigated in Russia which is a modified version of tDCS that uses small electrodes instead of pads and currents up to 1mA, that are claimed to be “weak” (Shelyakin and Preobrazhenskaya, 2009). GVS has been extensively tested for effects on ocular and postural movement (Watson and Colebatch, 1997). Alongside GVS, Caloric Vestibular Stimulation (CVS) is under investigation due to similar areas being targeted by stimulation. However, CVS does not utilize electricity; rather, it uses irrigation of the ear canal using cold or warm water (Miller and Ngo, 2007).

TRANSCRANIAL DIRECT CURRENT STIMULATION CUSTOMIZATION

Transcranial Direct Current Stimulation Terminology

To accurately describe tDCS and, more broadly, tES, electrical therapy “dosage,” it is important to have a basic understanding of the terminology (system of metrics) that is used to define and differentiate the various practical aspects of tES. It is useful to clarify how electrical therapy terms are used (sometimes inconsistently) in the literature.

- Stating that a protocol employs “DC” stimulation indicates that the stimulation remains at peak intensities for the duration of the exposure.
- tDCS/DCS is current controlled, meaning the voltage is varied to maintain a fixed current, typically under 20 V (Domingo et al., 1990), though much of this voltage (especially, any time-dependent component) may reflect the electrode and skin impedance.
- “Monophasic” stimulation indicates that, for the entire exposure, though the intensity may vary, only one polarity is applied (current is passed only in one direction).
- “Biphasic” and “AC” stimulation indicate that, at some point in the course of an exposure, the polarity is reversed, which is not consistent with tDCS.

In the brain, electrical stimulation, anode, and cathode terminology should always be used consistently for indicating the electrode where positive current is entering the body (anode) and the electrode where positive current is exiting the body (cathode) (Merrill et al., 2005). For tDCS/DCS, using two electrodes, there is one fixed anode and one fixed cathode, with the anode at a positive voltage, relative to the cathode. In clinical and animal studies, anodal stimulation or cathodal stimulation would indicate that a cortical region of interest (target) was nearer the anode or the cathode, respectively. It is important to recognize stimulation always includes an anode and cathode.

In classic animal literature, the terms “surface positive” and “surface negative” correspond to an anode or cathode electrode, respectively, placed on the surface of the cortex, with the other electrode often placed on the neck or body. Considering the cortical surface, inward
current and outward current are typically expected under the anode and cathode, respectively (though cortical anatomy may produce deviations). For electric field, the direction also needs to be specified (Bikson et al., 2012b). Datta et al. adopted the convention that an inward current will produce a positive electric field, measured from outside pointed in, while an outward current will produce a negative electric field, measured (Datta et al., 2008); unless otherwise stated, it is implied that the current and electric fields are normal/orthogonal to the cortical surface, rather than tangential/parallel (Bikson et al., 2008). Current density, as used in the literature, indicates the average current density (in ampere per square meter or A/m²) at the electrode, calculated by taking the applied current to a given electrode and dividing by electrode area. Average current density is not necessarily indicative of peak current density at the electrode (which may be concentrated at edges or spots (Kronberg and Bikson, 2012); or in the brain (which depends on many other factors, namely head anatomy; Miranda et al., 2009)). Stimulation charge (in coulombs, C) is determined by multiplying current by duration. Stimulation charge density (A×t/m²=C/m²) is charge divided by electrode area, and is also an average metric. Stimulation power (in W=W×A) is voltage multiplied by current. Stimulation energy (in joules, J=V×A×t) is power multiplied by duration. For any tDCS session, the “summary” metrics are a single number, or a single number per electrode, and determined fully and only by dose (Bikson et al., 2016). Electric field (in V/m) is current density multiplied by local tissue resistivity. The peak current density or electric field represents the maximum value at any point in space, which can be further restricted by head region such as peak current density in the brain or skin. The electric field predicts neuronal activation threshold more meaningfully than current density, but it is very sensitive to assumptions on local tissue resistivity. It is not established whether injury is linked to neuronal activation (e.g., excitotoxic). The tissue properties are not time dependent, but can be combined with time in new metrics (Bikson et al., 2016).

Transcranial Electrical Stimulation and Transcranial Direct Current Stimulation “Dosage”

tES encompasses all research and clinical technology to modulate brain function by passing current through at least one electrode placed on the scalp. tDCS involves relatively weak (<2 mA) DCS for several minutes. CES encompasses a range of pulsed protocols (>1 Hz) with intensities nominally <5 mA. ECT involves relatively strong (>0.9 A) pulsed waveforms, sufficient to induce electrographic seizures. tDCS and CES are both subconvulsive. The potential range of electrotherapy stimulation paradigms extends well beyond the limited set currently described by tDCS, CES, and ECT. However, clinical treatment with TCS has been generally restricted to this limited set of stimulation protocols, reflecting both safety concerns and restricting innovation and limitations of common clinical stimulation devices. Even within a specific therapy classification (e.g., tDCS), there are “dosage” variables that will fundamentally affect clinical outcome (Bikson et al., 2008).

For any tES, including tDCS research or therapeutic application, the electrotherapy paradigms (“dosage”) will be fully described by the following system of six independent metrics. This system is based on clinical experience with factors found to effect outcome as well as in vivo and in vitro animal and human studies on stimulation mechanisms (Bikson et al., 2004, 2006; Datta et al., 2008; Iyer et al., 2005; Merrill et al., 2005; Miranda et al., 2006; Nitsche and Paulus, 2000, 2001; Nitsche et al., 2003a,b; Rush and Driscoll, 1968). The tES device consists of a programmable stimulator (metrics 1, 4, 5) connected via leads to electrodes placed on the body (metrics 2, 3). In some stimulation paradigms, multiple stimulation devices may be simultaneously activated, in which case, stimulation parameters (metrics 1–6) may be “mirrored” (e.g., same stimulation protocol but opposite hemispheres) or distinct for each device.

1. **Exposure Duration**: A single exposure is defined in the context of the outputs of an electrical stimulator being energized (turned from OFF to ON) and then being turned OFF after a user-determined exposure duration. When the stimulation is OFF no current/voltage is being applied to the electrodes/patient. When stimulation is turned ON it is assumed that the remaining metrics defined in 2–5 of this list are fixed for the duration of any given exposure (e.g., electrodes are not moved during an exposure). If exposure duration is adjusted across patients (metric 7), indicate the range.

2. **Electrode number, connectivity, and position on body**: It is assumed that the default stimulation device has two output wires and each electrode is connected to only one of these two wires. There may be more than two electrodes per stimulation device, such that multiple electrodes are connected to the same output wire. This connectivity and the respective position of every electrode on the surface of the body must be indicated. The position of all scalp electrodes and extracranial electrodes must be accurately reported. It is not sufficient to indicate only the presumed “active” electrodes. In case of tDCS, each electrode can be designated either an “Anode” or a “Cathode,” which indicates connectivity to the respective stimulator, output terminal.
3. Electrode size/shape, electrode material, and contact/skin conditions: The geometry (shape) and size of every electrode can fundamentally impact therapy outcome (Datta et al., 2008). The electrode material should be indicated as well as the use of any specific electrolyte gel and sponge (including salinity/conductivity of sponge fluid; Dundas et al., 2007). The use of conductive solution/gel may change the “effective” area of the electrode. The preparation of the skin should also be described (e.g., no preparation, cleaning skin with alcohol, or abrasive).

4. Stimulation peak intensity (stimulation peak amplitude): Indicate whether the stimulation device is “current controlled” or “voltage controlled.” Indicate the peak intensity of the stimulation as the maximum amplitude of current (for current controlled) or voltage (for voltage controlled), applied to the electrodes during the entire exposure. For the case of tDCS, peak intensity is nominally the intensity of the DCS. If peak intensity is adjusted across patients (metric 7), indicate the range.

5. waveform: The stimulation waveform fully describes the output of the stimulation device during the entire exposure duration (from turning stimulation ON to OFF, including any designed or undesired transients). No aspect of the waveform can be ignored or omitted, including initial transients. The waveform describes how the current (for current controlled) or voltage (for voltage controlled) applied to the electrodes changes over time, never exceeding the peak intensity. Often, the waveform can be described using simple mathematical functions such as ramps, sinuosids, or pulses. It is necessary that in the description of the waveform(s), any change in polarity should be indicated. For the case of tDCS, the waveform does not change polarity (in a given exposure) and remains DC for the majority of the exposure duration; however, the initiation and termination of stimulation may be associated with other waveform components (e.g., on/off ramps).

6. Exposure number and interval: These parameters fully describe the stimulation paradigm (“dose”) used for a single exposure. For multiple exposures, it is also necessary to describe the total number and interval between exposures. For multiple exposures, the stimulation metrics (1–5) for each exposure may change. Since tDCS may have prolonged effects on neuronal excitability (Arfaei et al., 1970) and mood, repeated exposures may interact in a complex fashion. This is of particular clinical significance, as repeated exposure of the same polarity may simplistically lead to cumulative effects, while alternating polarity may potentially interfere with net effects (Bikson et al., 2008).

Each commercial clinical stimulator produces a limited range/comboination of intensities and waveforms, and is often recommended with specific electrode configurations. Theoretically, if the factors are all controlled for, the specific manufacturer/model of stimulation and electrodes will not affect therapy outcome (no more than if two companies produced chemically identical drugs). However, therapeutic devices may not perform ideally (e.g., deliver the peak intensity indicated), in which case, reporting the device used and device settings will allow for post hoc correction of unintended device performance (Bikson et al., 2008).

Just as with pharmaceutical clinical trials, the methodologies and controls used in an electrical therapy trial (including but not limited to dose) will determine how each specific trial is interpreted. Particularly in psychiatric trials, special consideration must be given for potential placebo effects, related to device operation (e.g., beeping) and electricity sensation. As with pharmaceutical trials, a dose-response study may be indicated under certain circumstances; each electrical “dosage” metric (1–6) may be changed independently. However, as in a fixed-dose pharmaceutical study, the “electrotherapy dosage” (metrics 1–6) once standardized, needs to be administered reproducibly for any meaningful conclusions as to efficacy and safety, to be drawn.

There have been considerations in the clinical literature to summarize the dosage of a complete stimulation paradigm, using a single “reduced” metric. Examples of reduced metrics include peak electrode current density (the peak current divided by the area of a selected electrode) or charge-per-phase (the average current in a specific pulse times the duration of the pulse). Working with limited, stimulation, paradigm constraints (e.g., DCS through large scalp electrodes), these single metrics provide general guidelines in normalizing the effects of therapy across subjects and studies (e.g., maintain current density across electrode sizes). However, these reduced metrics do not necessarily serve as absolute normalizing factors for efficacy/safety and simply reporting these metrics does not fully describe the stimulation paradigm; that is, it is not possible to determine/reproduce the stimulation paradigm given only a reduced metric (Bikson et al., 2008).

From the perspective of normalizing stimulation across patients (including efficacy and safety aspects), current-as opposed to voltage-controlled stimulation is preferred. Although voltage-controlled stimulation remains “grandfathered” into some stimulation technologies, with voltage control the electric field induced...
intracranially (which ultimately determines therapy effects) is “not controlled” across patients (Merrill et al., 2005), and will vary in an unpredictable fashion, depending on electrode size and material and skin properties (Bikson et al., 2008). Main features distinguishing modern tDCS from other stimulation techniques are the weak and diffuse electric fields, induced in the brain (Fig. 135.3).

The typical dosage during tDCS (1 mA stimulation intensity) produces ≤0.2 V/m electric field in the brain (Gasca et al., 2010). Animal experiments have shown that such weak fields change the membrane potential by ~0.2 mV (Radman et al., 2009a,b). Neurons, at rest, typically require 15 mV depolarization to reach firing threshold. How can such weak electric fields produce significant changes in brain function?

In addition to being weak, the induced electric field in the brain is highly diffuse when using conventional (non-HD) tDCS montages (Datta et al., 2009). Current flows from the anode to cathode, while generating equivalent electric field magnitudes in both the target brain region and adjacent brain regions (Fig. 135.4). These areas may be part of the functional network that is being targeted. Additionally, brain regions that are not being targeted are also exposed to the electric field. This raises a question of the specificity of electrical stimulation. How can a diffuse electric field, which simultaneously polarizes neurons across the brain, have precise effects on brain functions?

**Origins of Specificity During Transcranial Direct Current Stimulation: Anatomical, Activity-Selective, and Input-Bias Mechanisms**

tDCS is investigated for a broad range of neuropsychiatric indications, used for various rehabilitation
applications, and used to modulate cognitive performance in diverse tasks. Specificity of tDCS refers broadly to the ability of tDCS to produce precise, as opposed to diffuse, changes in brain function. Practically, specificity of tDCS implies application-specific customization of protocols to maximize desired outcomes and minimize undesired effects. Especially given the simplicity of tDCS and the complexity of brain function, understanding the mechanisms leading to specificity is fundamental to the rational advancement of tDCS.

Bikson et al. grouped the origins of specificity based on anatomical and functional factors (Bikson et al., 2013). Anatomical specificity derives from guiding current to targeted brain structures. Functional specificity may derive from active, neuronal networks that are preferentially modulated by tDCS. Rational advancement of tDCS may require leveraging all forms of specificity.

**Anatomical Transcranial Direct Current Stimulation Specificity and the “Sliding-Scale” Model**

Anatomical specificity refers to the preferential neuromodulation of targeted brain regions by delivering stimulation current to the targeted area. The number, location, and size of anatomical targets are application specific. For example, the targeted, brain region may be a specific cortical area, implicated in a task or pathology. Anatomical specificity is achieved only through the control of tDCS electrode dose (defined as electrode montage and current) to guide current to specific brain regions (Peterchev et al., 2012). However, applied without consideration for functional specificity, anatomical specificity is technically and conceptually limited.

Both computational models of current flow in the brain and imaging studies indicate that conventional tDCS methodology using two large sponge pads (5 × 5 cm) produce dispersed current through much of the cortex (Datta et al., 2009; Faria et al., 2011; Antal et al., 2014; Neuling et al., 2012) and even deep brain structures (Dasilva et al., 2012). It is important to distinguish between well conducted studies that demonstrate dose-specific (e.g., electrode position) outcomes (Fiori et al., 2013; Hauser et al., 2013; Penolazzi et al., 2013), from implications that current flow is limited to one brain target. These studies also typically leverage other forms of functional targeting.

Technology for HD-tDCS using arrays of electrodes allows categorical increases in anatomical targeting by increasing the focus of current flow (Datta et al., 2009; Dmochowski et al., 2011), but even so, any brain region is evidently involved in multiple tasks. Which presents the inherent conceptual challenge when relying exclusively on anatomical specificity: How can passing DC current through a multitasking, complex, brain region produce specific functional changes?

In the absence of further sophistication, the goals of tDCS are often described as increasing excitability (near the anode) or decreasing excitability (near the cathode) of the target brain region, with brain function and disease thus reduced to a “sliding-scale” of excitability, to be adjusted by stimulation (cf., Rahman et al., 2013). For example, under the sliding-scale concept “anodal tDCS” can enhance the performance of a cognitive task by exciting an implicated brain region. Similarly, anodal tDCS is intended to increase left, prefrontal cortex activity in depression and enhance rehabilitation around lesions, after stroke. Following early evaluations of transcranial/transcortical polarization in humans and animal models (Bindman et al., 1962; Redfearn et al., 1964; Elbert et al., 1981), influential neurophysiological studies of tDCS (Nitsche and Paulus, 2000) established modulation of experimental, evoked potentials (e.g., motor evoked potential responses to Transcranial Magnetic Stimulation (TMS)). There is significant extrapolation from these experimental findings to behavior and cognition (TMS evoked responses may provide poor evidence for effects on behavior Ridding and Rothwell, 2007). Moreover, even the direction of this basic modulation of experimentally evoked potentials is highly sensitive to both tDCS dose intensity (Matsunaga et al., 2004; Dieckhöfer et al., 2006; Batsikadze et al., 2013), direction (Chan and Nicholson, 1986; Bikson et al., 2004; Rahman et al., 2013), and dependent on brain state (Frohlich and McCormick, 2010; Reato et al., 2010). Animal studies that show anodal/cathodal DCS producing somatic depolarization/hyperpolarization (Radman et al., 2009a,b), and increase/decrease in firing rate (Purpura and McMurtry, 1965; Reato et al., 2010), are cited to support a sliding-scale concept; however, global changes in firing rate across a brain region implies a nonspecific effect (Reato et al., 2013). In summary, it is reasonable to conclude from neurophysiologic studies that tDCS can produce dose-specific changes in brain functions (Nitsche and Paulus, 2000) that can, with careful extrapolation, serve as a basis for behavioral interventions (Kuo et al., 2013, 2014). However, relying solely on anatomical specificity by guiding current to specific brain regions (and so the “sliding-scale” rationale) remains limited by the complex and divergent functions of any brain region.

Further sophistication in anatomical targeting follows from considering tangential as well as radial inward/outward currents (Dmochowski et al., 2012). Indeed, the assumption of inward (“excitatory”) and outward (“inhibitory”) current under the anode and cathode, respectively, may be a further oversimplification. Electrophysiological studies, in animal models of DCS, suggest differential processing of afferent information (Rahman et al., 2013) and that polarity-specific effects invert due to neuronal morphology (Bikson et al., 2004; Kabakov et al., 2012).
Activity-Selectivity and Task-Specific Modulation

Activity-selectivity refers to tDCS preferentially modulating a neuronal network that is already activated, while not modulating separate, neuronal networks that are inactive. The active, neuronal network may be activated for a host of reasons described. The active and inactive networks can in fact overlap in space (e.g., in the same cortical column) such that activity-selectivity does not require physical separation, in contrast to anatomical specificity. Therefore, we refer to activity-selectivity as a form of functional specificity. The active network may represent a subset of neurons and/or a subset of connections (synapses). Because tDCS produces low-intensity, electric fields in the brain, “subthreshold” neuromodulation may reflect changes in ongoing processes, in contrast to suprathreshold driven firing by TMS. Activity-selectivity thus assumes there is some feature of the active network that makes it preferentially sensitive to modulation by tDCS when compared to other inactive networks. We consider two neurophysiological substrates for this preferred sensitivity: ongoing activity-selectivity and input-selectivity.

Activity-selectivity is based on the assumption that tDCS will preferentially modulate specific forms of ongoing activity. For example, at a cellular level, DCS may enhance plasticity in a given synaptic pathway while stimulated at a preferential frequency (0.1 Hz in (Fritsch et al., 2010)) or consolidate a specific pattern of activity, presented during DCS (Morrell, 1961). DCS may preferentially modulate the level of potentiation in the activated pathway (Ranieri et al., 2012). It may facilitate long-term potentiation through membrane polarization and removal of Mg+ block (Stagg and Nitsche, 2011), but only those pathways activated during DCS (by a task or experimental stimulation) would benefit from this facilitation. It may be too weak and/or unspecific in isolation to enhance synaptic efficacy, but may boost ongoing (e.g., Hebbian) plasticity, activated by task performance (i.e., modulation of input specific plasticity along an activated synaptic pathway while sparcily activated synapses). In humans, TES may also preferentially modulate networks with heightened oscillatory activity (Reato et al., 2010) or preferentially change the progression of an active network during memory consolidation or synaptic downscaling (Reato et al., 2013).

At a behavioral level, specific brain activity is often targeted by training, in conjunction with tDCS, with the goal that this select activity be sensitized to tDCS neuromodulation (and so, it implies that other brain functions, not active in training, may be less so). For example, use-dependent modulation and learning of motor skills is mediated by tDCS (Reis and Fritsch, 2011; Madhavan and Shah, 2012). Clinically, tDCS is often applied to enhance the efficacy of rehabilitation or cognitive training (Edwards et al., 2009; Kuo and Nitsche, 2012; Gomez Palacio Schjetnan et al., 2013; Leśniak et al., 2014; Ochi et al., 2013), which may further confer functional specificity through activity-selectivity. Clinically, when tDCS is applied to subjects at rest, we can speculate that any functional specificity results from increased sensitivity of pathological network activity to tDCS (e.g., dysfunctional pain or mood regulating networks). It has been speculated that altered network function, associated with brain injury (stroke), may alter the susceptibility to tDCS (Olma et al., 2013). Generally, any interaction between brain activity and the efficacy of tDCS modulation (Kim and Ko, 2013; Pirulli et al., 2013) suggests that “tDCS can be highly focal when guided by a behavioral task” (Lapenta et al., 2013).

Although the mechanisms may vary, in any case, functional specificity through activity-selectivity presumes that the enhanced activity of the network makes it preferentially sensitive to modulation by tDCS. Thus, activity-selectivity necessitates an ongoing network process becoming preferentially tuned to influence by DCS when compared to the myriad of other ongoing (background) brain functions.

Input-Selectivity and Bias

A third form of specificity is input-selectivity, which assumes a neuronal network that is predisposed to serve at least two functions or operate in at least two states, such that tDCS can switch the network from one function/state to another (for example, attentional bias in the prefrontal cortex (Eldar et al., 2013)). tDCS would change the state of the system toward a different input bias and thus enhance information processing of a specific stream of information. Input-selectivity may activate endogenous “gating” systems (e.g., gate theory of pain) or bistable, neuronal states, where a nonspecific DC signal is able to “switch” a system between complex functions or modes. In contrast to a sliding-scale hypothesis for a stimulated brain region or activity-selectivity affecting a specific ongoing process, input-selectivity implies that a regional process is enhanced, at the cost of another process, and not that input-selectivity results in a zero-sum effect in regard to lasting cognition or behavior outcomes. However, input-selectivity does emphasize the “cost” of acute stimulation. Input-selectivity is also considered a form of functional specificity since it does not require gross anatomical targeting of current flow. Input-selectivity thus differs conceptually from functional-selectivity, in that it does not presuppose coactivation (e.g., by training), and moreover implies that one process may be enhanced at the cost of enhancing another.

Animal studies that have investigated the modulation of information processing, for example, through synaptie efficacy (as opposed to simply membrane polarization and excitability (Chan and Nicholson, 1986; Radman et al., 2007)), have observed that DCS will differentially
modulate incoming inputs. We initially showed in hippocampal slice that DCS enhances some and inhibits other afferent inputs (Bikson et al., 2004), a finding verified (Kabakov et al., 2012) and extended to the cortex (Rahman et al., 2013). The cellular origins of bias in favor of selective inputs are two-fold. First, although anodal and cathodal TDCS are mistakenly referred to as depolarizing and hyperpolarizing, it is more accurate to describe TDCS as redistributing polarization across the cellular axis (for example, one dendritic branch vs. another (Fritsch et al., 2010; Rahman et al., 2013)). This change in “weights” across the dendrite may provide a cellular substrate to influence the input bias of a network. Second, polarization of afferent axons, itself, appears to exert pathway specific modulation (Arlotti et al., 2012; Kabakov et al., 2012; Rahman et al., 2013; Bikson et al., 2013).

PREPARATION FOR TRANSCRANIAL DIRECT CURRENT STIMULATION STIMULATION

The purpose of electrodes in tDCS is to facilitate delivery of current from the stimulation device to the scalp. Referring to the comprehensive paper by A.J. Woods et al., it is important to prepare electrodes and contact medium, to optimize electrode placement, to adhere to established tDCS protocols, to train the operator, and to use certified devices to prevent tDCS sessions without skin injury (Brunoni et al., 2011a,b, 2013b; Kalu et al., 2012; Loo et al., 2012; Fertonani et al., 2015).

Selecting and Preparing Electrodes and Contact Medium

The electrode assembly most commonly used for tDCS comprises (1) a metal or conductive rubber electrode, (2) an electrode sponge, and (3) an electrolyte-based contact medium (e.g., saline, gel, or conductive cream) to facilitate delivery of current to the scalp, as well as (4) any materials used to shape these components or otherwise direct current flow (plastic casing, rivets). During tDCS, the metal or conductive rubber electrode is the site of electrochemical reactions (Merrill et al., 2005) and should not directly contact the skin. Rather, an electrolyte is used as a buffer between the electrode and the skin with sufficient electrolyte volume preventing chemicals formed at the electrode from reaching the skin (Minhas et al., 2010; Palm et al., 2014). The electrolyte can be placed in a sponge encasing the electrode (i.e., saline) or, in the case of electrode cream, placed directly on the electrode surface. However, in the case of saline, oversaturation of the electrode sponge significantly undermines the reproducibility of tDCS application and effects. When sponges are oversaturated, saline is evacuated from the sponge and covers an area of the scalp outside of the surface area, electrode sponge. Rather than delivering current through a specified surface area on the scalp under the electrode (e.g., 5 × 5 cm), the electrode surface area and area of current delivery now encompasses the entire area of the scalp that is covered in saline. This creates an amorphous area of current delivery that is not reproducible within or between subjects. It is important to obtain good contact under, and only under, the electrode with the electrode sufficiently, but not overly saturated. Methods, allowing quantification of saline (e.g., syringes), can assist in achieving a consistent and appropriate amount of contact medium. Whereas, traditional tDCS preparation techniques involves assembly of the electrode components for each session and manual saturation (Fig. 135.5, A1), updated methods use presaturated, assembled sponges with a snap connector. The sponge is saturated and designed for optimal contact.

Consistent with issues introduced by oversaturation of sponges, the shape/size of electrodes/sponges significantly alter the distribution of current that is delivered to the scalp and the brain (Minhas et al., 2011; Kronberg and Bikson, 2012). At a constant, current intensity level (e.g., 1 mA), increases in electrode size or differences in electrode assembly shape result in differences in the distribution of the current across the surface area of the scalp, resulting in differences in the distribution of current throughout the brain (Minhas et al., 2011; Kronberg and Bikson, 2012). Thus, it is critical for investigators to consistently report, not only the current intensity applied and the amount of contact medium used, but also the shape and size of the electrode assembly.

Selecting and Preparing Electrode Placement

A critical consideration for tDCS is determining where to place electrodes on the head. Studies monitoring physiological changes following TDCS and computational modeling studies of predicted, current flow demonstrate that the relative location of electrodes results in significant differences in where and how much current is delivered to the brain (Minhas et al., 2012; Kessler et al., 2013; Woods et al., 2015). For example, Nitsche and Paulus (2000) demonstrated that relative differences in electrode locations altered whether or not tDCS impacted TMS generated motor-evoked potentials (MEPs). Numerous, modeling studies have demonstrated significant differences between relative locations of electrodes, with results varying from stimulation of the whole brain to more selective stimulation of particular lobes of the brain (Minhas et al., 2012; Kessler et al., 2013; Woods et al., 2015). Woods et al. (2015) further demonstrated that as little as 1 cm
of movement in electrode position significantly altered the distribution of predicted current flow in the brain, as well as the intensity of stimulation in specific brain regions. Computational modeling can be a useful tool for the a priori design of tDCS electrode positions, for a given study (Woods et al., 2016).

Once desired locations are identified, the electrode assembly must be affixed to the head for delivery of current. Nonconductive headgear, used to position the electrodes on the body or scalp (e.g., elastic straps), are not included in the electrode assembly, but are critical for appropriate electrode placement (Woods et al., 2015).
tDCS, using sponge-covered electrodes, elastic straps are traditionally used headgear for electrode placement. They require manual measurement of each electrode position, at each session (Fig. 135.5,A2) and are typically adjusted on the head in an ad hoc manner (Fig. 135.5,A3). If these straps are not properly set-up, electrodes may move over the course of a tDCS session. Thus, the distribution of current delivery changes over the duration of a tDCS session (Woods et al., 2015), which undermines tDCS tolerability and replicability (Woods et al., 2016). Moreover, if electrode straps are overtightened, there is an increase in the probability of evacuation of saline from the electrode sponges. For this reason, poorly designed head ear (such as neoprene caps) are not recommended for sponge-based tDCS, where fluid may run under the cap, leading to current flow distortion. Updated tDCS approaches can use headgear where the locations of the electrodes are preset (in this case each montage will have an associated headgear (Fig. 135.5,B2)). This type of headgear then simply slides onto the subject’s head, which also simplifies setup and increases consistency (Fig. 135.5,B3).

**Computational Models of Transcranial Direct Current Stimulation for Electrode Placement**

tDCS is a single, programmable, electrotherapy device that can be simply configured to provide a diversity of dosages. Though this flexibility underpins the utility of neuromodulation, the myriad of potential dosages (e.g., stimulator settings and combinations of electrode placements) can lead to a great number of possibilities, thus making the optimal choice very difficult to readily ascertain. The essential issue in dose design is to relate each externally, controlled dose with the associated, brain regions targeted (and spared) by the resulting current flow and hence, the desired clinical outcome. Computational forward models aim to represent a critical tool in the rational design, interpretation, and optimization of neuromodulation (Bikson et al., 2012a).

**Common Montages**

Primary motor cortex (M1) (Anode)-Supraorbital (SO) (Cathode): this is the most common tDCS montage. M1 is a target that modulates the sensory and motor, subthalamic activity, associated with chronic pain. It has been shown that the cortical excitability can be changed up to 40% (Nitsche and Paulus, 2000). The polarity (anode/cathode) of the electrode refers to the M1 electrode. Anodal stimulation results in neuronal, soma depolarization and increasing neuronal excitability, while cathodal stimulation has opposite results (Nitsche and Paulus, 2000). Only one motor cortex is stimulated, so that bilateral montages are an alternative for bilateral pain syndromes (DaSilva et al., 2011). Potential confounding effects of the supraorbital electrode needs to be considered.

Dorsolateral Prefrontal Cortex (DLPFC) (Anode)-SO (Cathode): is commonly tested for the treatment of depression (Boggio et al., 2008) and chronic pain (Fregni et al., 2007). This montage has yielded encouraging results (Boggio et al., 2008; Fregni et al., 2007). Typical montages are bilateral DLPFC stimulation with the anode over the left DLPFC, but unilateral montages are possible (DaSilva et al., 2015).

4 × 1 High-Definition (HD)-tDCS: Experimental results demonstrate the neurophysiological efficacy of HD-tDCS on motor cortex plasticity. 4 × 1 HD-tDCS, as well as other HD deployments, may offer the opportunity to induce plasticity more focally than conventional tDCS protocols (Kuo et al., 2013, 2014). Most published studies on 4 × 1 HD-tDCS have targeted the primary motor cortex (M1), particularly for pain-related outcomes (Villamar et al., 2013). However, there is a study that DLPFC was targeted also (Brunyé et al., 2014).

**Methods for the Generation and Use of Computational Forward Models of Transcranial Direct Current Stimulation**

Computational models of tDCS range in complexity from concentric, sphere models to high-resolution models, based on an individual’s MRI. The appropriate level of modeling detail depends on the clinical question, being asked (as well as the available computational resources). Whereas simple geometries (e.g., spheres) may be solved analytically, realistic geometries employ specialized software, as described later, that include numerical solvers (namely finite element methods [FEM]). Regardless of complexity, all forward models share the primary outcome of correctly predicting brain-current flow during transcranial stimulation to guide clinical, therapeutic delivery.

For clinicians interested in using computational forward models to inform study design or interpretation, several options are available: (1) a collaboration with a modeling group or a company can allow for customized exploration of montage options (2) referencing existing published reports or databases for comparable montages (3) by utilizing a recently developed process, where a desired brain target can be selected and the optimized stimulation electrode montage is proposed within seconds (Datta et al., 2008). If tDCS continues to emerge as an effective tool in clinical treatment and cognitive neuroscience, and concurrent modeling studies emphasize the need for rational (and in cases of patient-specific) dose decisions, then it will become incumbent for clinical research teams to understand the applications (and limitations) of computational forward models (Bikson et al., 2012a,b).

While the specific software applications used can vary across modeling groups, in general, the approach and work-flow for model generation follows a similar
pattern. The steps for generating high-resolution (anatomically specific) forward models of noninvasive neuromodulation are adapted from extensive, prior work on computational modeling. These involve various steps:

Step 1, demarcation of individual, tissue types (masks) from high-resolution, anatomical data, using a combination of automated and manual segmentation tools. It is worth noting that the respective contribution of the automated/manual interventions depends on (a) sophistication of the particular automated algorithm employed, since they are usually not optimized for forward, transcranial modeling (Datta et al., 2011) and (b) the need for identification of anomalies, in suspect populations like skull defects, lesions, shunts, and so on. Consequently, as emphasized later in this section, the number and precision of the individual masks obtained is pivotal for the generation of accurate, three-dimensional (3D) models to capture critical, anatomical details that may influence current flow.

Step 2, modeling of the exact, physical properties of the electrodes (e.g., shape and size) and precise placement within the segmented image data (i.e., along the skin mask outer surface).

Step 3, generation of accurate meshes (with high-quality factor) from the tissue/electrode masks, while preserving resolution of subject and anatomical data.

Step 4, resulting volumetric meshes are then imported into a commercial, finite element solver.

Step 5, at this step, resistivity is assigned to each mask and the boundary conditions are imposed. The standard Laplacian equation is solved using appropriate numerical solver and tolerance settings (Datta et al., 2008; Wagner et al., 2007a,b; Miranda et al., 2006).

Step 6, data are plotted as induced, cortical electric fields or current density maps.

As head size and shape vary from person to person, it is important to use a method for common localization of electrode position. There are several methods for addressing this issue:

1. international 10–20 (or 10–5) electrode placement system (Klem et al., 1999; Oostenveld and Praamstra, 2001), or another, gross anatomical, coordinate system (Seibt et al., 2015),
2. neuronavigation systems (e.g., MRI guided; Feurra et al., 2011a,b, 2013; Santaronecchi et al., 2014), or
3. physiology-based placement (e.g., TMS generated MEPs). At present, physiology-based placement can only be performed for motor and other primary cortices (e.g., sensory). However, further options may become available in the future (e.g., Transcranial magnetic stimulation (TMS)-electroencephalogram (EEG) methods). Regardless, these methods can be used to reproducibly center each electrode on the head, accommodating varied head shape or size (Woods et al., 2016).

**SAFETY CONSIDERATIONS FOR TRANSCRANIAL DIRECT CURRENT STIMULATION**

The application of tDCS presents with minimal risk in numerous studies, when it has been applied in research or clinical studies, within standard parameters. Minimal risk means there have been no serious adverse events (SAEs), and that reasonable efforts at assessment have determined there is no evidence of brain damage. Common, adverse events (AEs), such as reddening of the skin are mild and short-lived. Standard parameters to date mean that (1) the current is less than 2.5 mA, (2) it is applied through electrodes that are known to minimize skin burns at the specific current level, (3) the current application duration is less than 20–60 min per session, and (4) that sessions are not more frequent than twice per day. This does not imply that exceeding these stimulation parameters will result in substantial risk, but that experience with these stimulation parameters is limited, and thus definite statements are not possible to date (Fregni et al., 2015).

The human trials with tDCS, with “conventional” protocols (e.g., waveform intensities and durations), have specific limitations, due to safety. Conventional current intensities span 0.1 mA (used occasionally as a sham) to 4.0 mA, with the majority of studies applying 1.0 mA and 2.0 mA. Conventional durations span from 4 s (used only for transient changes (Nitsche and Paulus, 2000); to 40 min (>10 min of stimulation are commonly used to elicit durable changes)). Conventional charge (reflecting duration and intensity) is limited to 7.2 C (e.g., 40 min, 3 mA). Skin preparation does not typically include significant abrasion (intended to remove epidermis; Shiozawa et al., 2013), though cleaning of the skin/hair with saline or alcohol is sometimes used (DaSilva et al., 2011). The details of electrode assembly design are considered important for tolerability and skin safety. For example, it is important to maintain a minimal distance between the electrode and skin, as well as the area of the electrode, when compared to the electrolyte-skin area (Kronberg and Bikson, 2012). Pad electrodes, by virtue of size and materials, are typically limited in number to a maximum of 3–4. HD electrodes are circular <1 cm diameter with a sintered, Ag/AgCl electrode and conductive gel or paste (Minhas et al., 2010). A higher number and density of HD electrodes may be used (Dmochowski et al., 2012, 2013). When one or more HD electrodes are
used, tDCS is called HD-tDCS, regardless of the number of electrodes or if stimulation is optimized for focality or intensity (Dmochowski et al., 2011).

Human subject protection protocols often adopt pre-determined and measurable stopping criteria to manage AEs. Specific rules for subject withdrawal or trial cessation are designed to minimize risk in a real-time manner, which is distinct from a trial designed to establish safety. For example, in a trial of tDCS for epilepsy, stop criteria may include: (1) discontinuation of the session if the frequency of interictal discharges or seizures increases by 50% above baseline, in the 1 h after stimulation or (2) cessation of the study if over 50% of subjects in a stimulation study have a 50% increase of seizure frequency in the first 24 h after tDCS. Such rules provide greater objectivity for an investigator when deciding whether a given event was serious enough to potentially cause harm to the patient, regardless of causality, and thus erring on the side of safety. Then, in later analysis and discussion, a determination of probable causality can be decided (Bikson et al., 2016).

If tDCS is applied with the intention to produce an abnormal brain state, for example, to interrupt normal brain processing, then the abnormal brain state would be expected and appropriate, safety measures would be in place, if needed (e.g., hospitalization). Nonetheless, sham-controlled trials are the best way to empirically assess AEs, including SAEs; and this review addresses the scale of data collected to date (Bikson et al., 2016).

Transcranial Direct Current Stimulation Safety Data From Human Trials and Models

There is direct support for the safety of tDCS, as applied thus far in controlled human trials (previously reviewed in Brunoni et al., 2011a,b, 2012, 2013a). Mild skin erythema is common during tDCS, resolves after stimulation, and is not inherently hazardous (Guarenti et al., 2015). tDCS was not found to produce edema or injurious alterations of the blood-brain barrier or cerebral tissue detectable by MRI (Nitsche et al., 2004), though noninjurious, reversible changes in brain perfusion, as a result of direct action on endothelial cells or indirectly via modulation of neuronal (metabolic) activity, are plausible (Mielke et al., 2013; Wachter et al., 2011).

During tDCS, the ratio of current density in the skin to the brain is predicted to exceed 10:1 (Minhas et al., 2011). If one assumes comparable sensitivity to injury of skin and brain, then the tolerability to tDCS, evidenced by lack of skin lesions, provides indirect support for safety, with respect to the brain. For example, tDCS produces negligible temperature changes in the skin (Minhas et al., 2010), making direct injury from brain heating improbable. Poor electrode skin contact (dry sponges) will lead to skin irritation (e.g., by dramatically reducing the stimulation area). In rare cases, poorly designed or prepared electrodes produced skin lesions (Frank et al., 2010; Palm et al., 2014; Rodriguez et al., 2014; Wang et al., 2015). If these are attributed to electrochemical reactions produced locally at the electrode (Bikson et al., 2009; Minhas et al., 2010), it would not be relevant for brain injury since chemical products, above the skin surface, are not expected to diffuse to the brain. Important factors in electrode design and preparation have been reviewed (Woods et al., 2016).

For a given applied current, the maximum current density generated in the brain will vary according to montage and head anatomy; the resulting current density can be quantified using computational models and demonstrated experimentally (Edwards et al., 2013). In susceptible populations, such as stroke or poststroke encephalomalacia (Datta et al., 2011) or patients with postsurgical or trauma induced skull defects (Datta et al., 2010), current flow to the head may be further altered by pathological changes in the cranium or brain tissue. Further divergence from expected current flow may be attributable to the immature brain anatomy in children (Gillick et al., 2014; Kessler et al., 2013). Across heads and montages, the maximum predicted brain current density (0.23 A/m^2 for a small adult head and 0.32 A/m^2 for pediatric head) remains substantially below injury threshold levels in animals (6.3–17 A/m^2, described in detail in this chapter). Peak current densities, in the modeling literature (spanning heads, model parameterization and tDCS dose), range from 0.0828 to 0.211 A/m^2 (Laakso and Hirata, 2013; Mekonnen et al., 2012; Rampersad et al., 2014; Sadleir et al., 2010).

Controlled human studies involving the general population, susceptible subjects (e.g., children), and potentially susceptible (e.g., subject with altered neuroanatomy or neurophysiology) populations support safety (Grecco et al., 2014a,b; Mattai et al., 2011; Vestito et al., 2014). There is no direct evidence from human trials involving tDCS that suggests tissue damage, nor is there evidence of behavioral changes that suggest irreversible brain injury. Though methodology and rigor for reporting AEs, or SAEs for that matter, in tDCS are inconsistent across studies (Brunoni et al., 2011a,b; Kessler et al., 2012; Morales-Quezada et al., 2014; Nitsche et al., 2003a; Poreisz et al., 2007; Raimundo et al., 2012; McIntire et al., 2014; Russo et al., 2013; Tadini et al., 2011), human trials (per institutional review board (IRB) guidance) should have specifically, designed, safety monitoring and reporting.

The acceleration in the number of publications regarding tDCS are not associated with a general increase in trial size (number of subjects) or duration (number of sessions per trial). This is consistent with tDCS being adopted by increasingly more independent groups as well as increased activity within these groups, and so there are more investigators in general. Demographics of these studies suggest that a majority of sessions were
applied to healthy subjects. This is consistent with the use of tDCS to study normal brain function under the assumption that tDCS is associated with minimal risk. tDCS has been used to explore treatment for a broad range of indications. Distribution of sessions by medical indications often reflects the size of trials rather than the number of publications (e.g., tinnitus). The distribution and diversity of clinical trials with tDCS support the generalization of overall safety findings (Bikson et al., 2016).

There are also data on individual patients who have received over 100 treatment sessions of tDCS without any indication of AEs arising from cumulative exposure. These include a patient with schizophrenia who received maintenance tDCS once to twice daily on a domiciliary basis, over a three-year period (i.e., >1000 sessions) (Andrade, 2013) and patients with depression who received multiple courses of tDCS (>100 sessions, in total) safely, assessed with structured questionnaires of side effects and formal, neuropsychological testing (Tadini et al., 2011). Furthermore, 33 healthy volunteers received up to 30 sessions (6 weeks) of tDCS (2 mA, 20 min, high-performance, adhesive electrodes) without an SAE (Bikson et al., 2016).

According to Bikson et al., the FDA considers trials of tDCS as nonsignificant risk. The FDA requires reporting of “unanticipated” AEs. As of this date, the FDA “MedWatch” database search returns no reports of SAEs for “tDCS” or “transcranial Direct Current Stimulation.” A similar research status approval is in place from Health Canada and internationally (Fregni et al., 2015; Bikson et al., 2016).

EFFICACY

A fundamental effect of tDCS is to modulate cortical excitability (Nitsche and Paulus, 2000; Fregni et al., 2005; Dieckhöfer et al., 2006; Nitsche et al., 2007; Wagner et al., 2007b); therefore, tDCS has been examined as a potential therapeutic intervention in multiple, clinical disorders that include depression, chronic pain, stroke, Alzheimer’s disease, and Parkinson’s disease (Boggio et al., 2011, 2012; Loo et al., 2012; Hansen et al., 2011; Lindenberg et al., 2010; Antal and Paulus, 2011; Borckardt et al., 2011; Riberto et al., 2011; Dasilva et al., 2012; Knottkova et al., 2012; Kumru et al., 2013; Borckardt et al., 2012).

One of the main clinical applications being tested with tDCS is stroke. Daily sessions of tDCS improve upper limb function in stroke patients (Butler et al., 2013) and increases scores of activities of daily living (ADLs). These findings have been confirmed by meta-analysis that has demonstrated that various montages of tDCS treatment—with or without adjunct physical therapy—improve motor function in patients with mild to moderate stroke (Butler et al., 2013).

Besides motor function in stroke, language recovery has also been explored with tDCS. Anodal tDCS, over perilesional areas, improves language function, but this effect was found to persist over time, only when tDCS was coupled with language training (Monti et al., 2013; Marangolo and Caltagirone, 2014). More research is required to evaluate the effectiveness of tDCS for practical language rehabilitation (anodal/cathodal/dual), primarily through examining the stability of the improvement, over clinically significant intervals of time (Elser et al., 2013). For example, using cathodal stimulation over the injured cortex, Monti et al. (2013) showed that, although the tDCS treatment in aphasia induced a gain in speech performance of approximately ~25%, this effect was transient.

There has been considerable interest in treating depression with tDCS, applied asymmetrically to the frontal lobes (typically with anodal electrode over left dorsolateral prefrontal cortex and cathode over right supraorbital cortex). The most recent meta-analysis, incorporating all randomized controlled trials (RCTs), to date, found that active tDCS was more effective than a sham, stimulation comparator (Shiozawa et al., 2014). However, given the limited number of RCTs available (n = 7), evidence for the antidepressant efficacy of tDCS cannot be considered conclusive, and further trials are required. Earlier meta-analyses reported mixed findings, likely because of heterogeneity in the evidence base (Berlim et al., 2013; Kalu et al., 2012). An important consideration may be concurrent antidepressant drug treatment. When tDCS was used as monotherapy, a 63% response rate was observed, with more than doubling of the remission rates, over sham control (Berlim et al., 2013). In other reviews of tDCS and depression, the odds ratio (OR) for favorable symptom response was 1.63; and the OR for remission was 2.50 (Shiozawa et al., 2014). When an acute course of tDCS was followed by weekly to fortnightly maintenance, tDCS sessions, the cumulative probability of avoiding relapse was 83.7% at three months, and 51.1% at six months (Martin et al., 2013). When Major Depressive Disorder (MDD) and Bipolar Depressive Disorder (BDD) were examined separately, five sessions of anodal stimulation induces a beneficial effect that persists at one week and one month, in both groups (Brunoni et al., 2011a,b).

In patients with schizophrenia that were refractory to medication, cathodal tDCS over the left, temporoparietal junction (TPJ), coupled with anodal tDCS over the left, DLPFC reduces auditory, verbal hallucinations by 31%, lasting for up to three months. Also, general, severity of illness improves on the Positive and Negative Syndrome Scale (Brunelin et al., 2012).
In studies of tDCS effects on pain sensitivity in healthy subjects, anodal stimulation leads to an increment in pain threshold and better tolerance when compared to sham stimulation (Zandieh et al., 2013). Cathodal stimulation reduces the sensitivity to Aδ-fiber-mediated cold sensation and C-fiber-mediated warm sensation as compared to baseline, whereas Aβ-fiber-mediated somatosensory inputs were less affected (Grundmann et al., 2011). In patients undergoing total knee arthroplasty, tDCS reduces opioid consumption and pain level (Borckardt et al., 2013). Although a prespecified, subgroup analysis in meta-analysis with distinct types of chronic pain indicated that tDCS was superior to sham (O’Connell et al., 2011), a further meta-analysis failed to detect a superiority of tDCS over sham for reducing pain (O’Connell et al., 2014), possibly due to heterogeneity of the cohort. When tDCS is combined with the technique of visual illusion, there is a better analgesic effect in all pain subtypes, while tDCS alone improves only continuous and paroxysmal pain (Soler et al., 2010). Also, tDCS, when combined with visual illusion, improves neuropathic pain in spinal cord injury, with a 50% mean decrease of symptoms (Soler et al., 2010). In episodic migraine without aura, anodal tDCS, preventive treatment reduces migraine attack frequency, the number of migraine days, attack duration, and acute medication intake. This benefit persists on the average of 4.8 weeks, after the end of treatment (Viganò et al., 2013). In chronic migraine, the anodal effect, applied on a primary motor cortex, induces a delayed response (Dasilva et al., 2012). Evidence also points to the potential of tDCS for the treatment of phantom limb pain (Bolognini et al., 2013a,b).

Although the findings on treating pain with tDCS have thus been varied, the effects of tDCS on chronic pain are promising and may justify the use of tDCS to treat pain in selected patient populations. For the most part, the studies of anodal stimulation have demonstrated at least a moderate size effect. Two excitability-enhancing (anodal) tDCS montages have resulted in analgesic effects, one montage with the anode over the primary motor cortex and another montage with the anode over the DLPFC (Vasheghi et al., 2014). Typically, the analgesic effects of tDCS have been shown to be cumulative, with the majority of clinical trials providing stimulation on five consecutive days (with some extending over 10 days). The problems with this aforementioned research are (a) the heterogeneity or lack of homogeneity of pain types in the studies make specific comparisons difficult, (b) the lack of systematic, intention-to-treat designs, and (c) the high dropout rates of patients from the studies. Finally, new, placebo-controlled studies of tDCS for the treatment of pain are required that they include a systematic follow-up according to the recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (Dworkin et al., 2005).

tDCS has also been used to decrease the cravings that are associated with food, smoking, cocaine, and alcohol. A recent meta-analysis examined the use of frontal lobe tDCS or rTMS to reduce craving, considering both craving in substance dependence and craving for high palatable food (Jansen et al., 2013). Both rTMS and tDCS over the DLPFC revealed no significant difference between the treatments. In its application to manage tinnitus, anodal tDCS reduces the intensity of these symptoms (Song et al., 2012). Finally, anodal tDCS, over the pre-motor areas, also improves sleep and fatigue symptoms in patients with postpolio syndrome (Acler et al., 2013; Fregni et al., 2015).

References


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REFERENCES


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