Physics of Transcranial Direct Current Stimulation Devices and Their History

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Transcranial direct current stimulation (tDCS) devices apply direct current through electrodes on the scalp with the intention to modulate brain function for experimental or clinical purposes. All tDCS devices include a current controlled stimulator, electrodes that include a disposable electrolyte, and headgear to position the electrodes on the scalp. Transcranial direct current stimulation dose can be defined by the size and position of electrodes and the duration and intensity of current applied across electrodes. Electrode design and preparation are important for reproducibility and tolerability. High-definition tDCS uses smaller electrodes that can be arranged in arrays to optimize brain current flow. When intended to be used at home, tDCS devices require specific device design considerations. Computational models of current flow have been validated and support optimization and hypothesis testing. Consensus on the safety and tolerability of tDCS is protocol specific, but medical-grade tDCS devices minimize risk.

Key Words: brain stimulation, neuromodulation, review, tDCS, tES

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HISTORICAL DEVELOPMENT OF tDCS DEVICES

This history of electrical stimulation dates to the discovery of electrical phenomena, and static voltage sources are among the earliest examples of electrical technology,[1] although with unclear relation to modern transcranial direct current stimulation (tDCS) dose. There have been a continuous history of transcranial electrical stimulation technology development and testing, much of it on non-DC waveforms such as pulsed stimulation.[2–4] Human trial investigated tDCS for neuropsychiatric disorders continued through the middle of the 20th century, typically with current intensities lower and durations longer than modern tDCS.[5] The importance of canonical trials circa 2000 (showing tDCS is a polarity-specific modulator of brain excitability) is evidenced by these trials establishing modern tDCS dose: 1 mA applied over tens of minutes with relatively large electrodes.[6,7] Subsequent pilot trials instituted a 2-mA intensity for therapeutic interventions[8–10] maintained for almost all subsequent clinical evaluation.[11–16] These developments established contemporary tDCS dose and hence the specification of modern tDCS devices (Fig. 1). Iontophoresis devices were adopted for some tDCS trials as an off-label medical device, although they may not provide a steady output.[17,18]

Ongoing refinements in dose (eg, use of 1.5 mA in cognitive neuroscience[19]), electrodes (eg, HD-tDCS[20]), integration with imaging (eg, functional magnetic resonance imaging[21]), and home use (eg, remote supervised[22]) are reflected in specific tDCS device features. Usability device features such as enhanced programming (microcontroller), control systems (eg, response to impedance changes), rechargeable batteries, disposable electrodes, enhanced headgear materials, wireless connectivity, or integration of monitoring technology[23] reflect general progress in available technologies but maintain tDCS dose.

BASICS OF tDCS DEVICES AND POLARITY

All tDCS devices include a battery-powered current-controlled stimulator that generates the stimulation waveform: a sustained direct current of several mA for up to tens of minutes, with a ramp up/down at the beginning/end. This current is applied through wires (leads) to electrodes. All tDCS devices have a minimum of 2 electrodes, with at least 1 electrode placed on the scalp. At an anode electrode, current enters the body, and at a cathode electrode, current exits the body.[24] There must be at least 1 anode and 1 cathode; such tDCS devices with only 2 electrodes have 1 anode and 1 cathode. When there are more than 2 electrodes, the summed current across anode electrodes must equal the summed current across the cathode electrodes[25]; that is because the total current entering the body must equal the total current exiting the body. A majority of tDCS interventions, and thus devices, are limited to 2 mA, which historically is the highest amplitude tested (safety), but protocols, and devices, with higher (3–4 mA) current limits are explored,[26,27] which remain within accepted safety limits.[15,28,29]

The polarity of each electrode can be described by anode or cathode. Because an anode and cathode are always present, the terms anodal or cathodal tDCS refer to a hypothesis that neurophysiological or behavioral changes reflect stimulation of brain regions near the anode or cathode, respectively.[30,31] Similarly, the term reference or return electrode refers to a hypothesis that brain regions near these electrodes are not central in any neurophysiological or behavioral changes.[31,32] However, during tDCS, current passes through all brain regions between electrodes.[20,33,34] "Extracephalic electrode" indicates a position on or below the neck, which does not cancel the effect this electrode can produce (changes in exitability) on the ventral surface of the brain and in deep brain structures.[32,35]

tDCS ELECTRODES

The traditional electrodes used for tDCS are each made from a conductive rubber or metal plate separated from the skin by a saline-soaked sponge or paste.[31] Note that in electrochemistry the conductive rubber or plate would be the electrode, whereas the saline, gel, or paste would be the electrolyte,[24] but in tDCS literature, the entire assembly is called the electrode. Therefore, in tDCS, when electrode size is described (eg, 5×5 cm^2), it is the interface between the skin and the electrolyte. Nonetheless, the configuration of all electrode component dimensions and materials is important to control and document as this affects tolerability.[31,36–39] The thickness of the sponge or paste effectively controls the minimum distance between the conductible rubber or metal and the skin. Contact of conductive rubber or metal with skin during tDCS is avoided as this decreases tolerability and introduces risk of lasting skin irritation.

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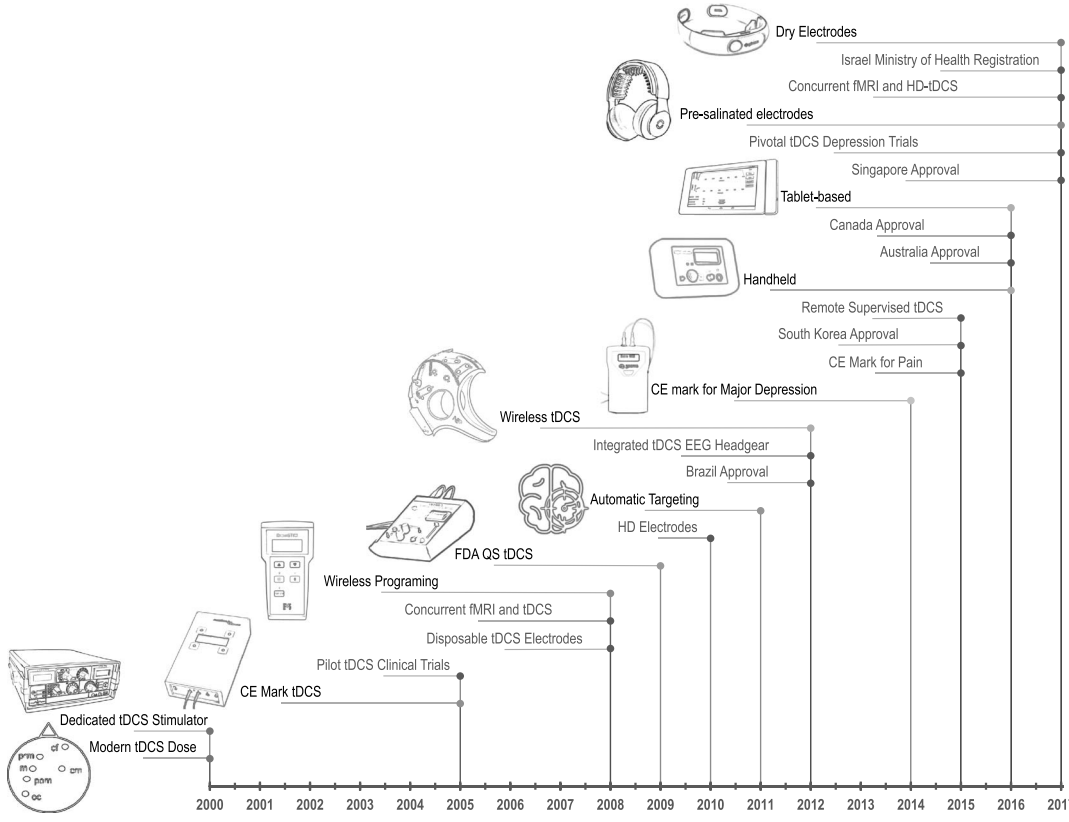

FIGURE 1. Timeline of tDCS innovations: technology and regulatory milestones. CE mark indicates Conformité Européene Marking; FDA QS, Food and Drug Administration Quality Systems; fMRI, functional magnetic resonance imaging; HD, high definition/density.

Single-use electrodes are advantageous. In any case, the electrolyte is not reused (as it dehydrates, its properties will change). Electrodes typically positioned based on the electroencephalography (EEG) 10/10 system (eg, anode of F3) through customized placement based on neuronavigated,[40–43] functional,[44] nonneuronavigated,[45] or image-based approaches (eg, EEG reciprocity[23,46–48]) have been developed. Either the headgear is designed to support the determination electrodes positions (eg, a cap or marked straps[49,50]), or the headgear is generic (eg, rubber bands[51]), and independent measurement is used to position the electrodes.

HD-tDCS ELECTRODES AND MONTAGES

In transcranial electrical stimulation, smaller electrodes are called high-definition (HD) electrodes[52] and typically are made from small circular Ag/AgCl electrode separated from the skin by a gel contained in a plastic cylinder.[53] The plastic cylinder controls the distance between the electrode and the skin. Because they are smaller, use of HD electrodes for tDCS allows more precision in electrode position[54] and the option to use more electrodes.[25,55–57]

The 4 × 1 HD-tDCS montage uses 1 center electrode surrounded by 4 electrodes (Fig. 2) of the opposite polarity, with the intention to target cortical regions.[20,58–63] Bipolar HD-tDCS montages (1 anode and 1 cathode) when electrodes are positioned closely can be used to probe the role of current direction across the cortex[54] and when electrodes are positioned across the head to maximize brain current flow.[25] Increasing the number of HD electrodes can support multifocal stimulation.[56,57,64–67]

tDCS DOSE AND CURRENT FLOW MODELING

Electrode size and position on the scalp along with the current applied to each electrode conventionally define tDCS dose.[68] Transcranial direct current stimulation dose, along with head anatomy, determines the resulting current flow (intensity and pattern) in the brain and in turn affects resulting neurophysiological and behavioral changes.[69] Indeed, the canonical studies establishing the neuromodulation actions of tDCS did so by showing dose (electrode montage)–specific effects.[6] Yet, systematic ongoing studies have characterized additional factors beyond electrode montage such as brain state,[70,71] interindividual differences,[72–74,74,75] and nonmonotonic (eg, "more is not always better"[76–78]) dose response. This complexity of tDCS dose-response is in line with other forms of brain stimulation,[79–81] whereas the sensitivity to brain state is consistent with hypothesized mechanisms of actions.[82] Notably, in contrast to other common forms of clinical brain stimulation (repetitive transcranial magnetic stimulation, electroconvulsive therapy, deep brain stimulation, etc), tDCS is not typically titrated on subject-specific basis; ongoing research on methods to individualize tDCS dose is warranted.[46,83–85]

For a given dose and anatomy, computational models predict the resulting current flow (electric field distribution) in the brain (Fig. 2). Computational models have been developed[20,25,34,57,86–89] and repeatedly validated[33,90–93] over a decade. It is important not to conflate established montage-specific effects (eg, "shaping" the outcomes of stimulation[94]) with demonstration of focality (eg, current delivery to 1 region of interest). Rather, models of conventional tDCS and HD-tDCS support testing hypothesis linking brain regions to neurophysiologic or behavioral changes.[95] This includes registering results from current flow models with imaging data.[96]

tDCS BIOPHYSICS

Although there are open questions about the mechanisms and efficacy of tDCS for varied indications and the biophysics

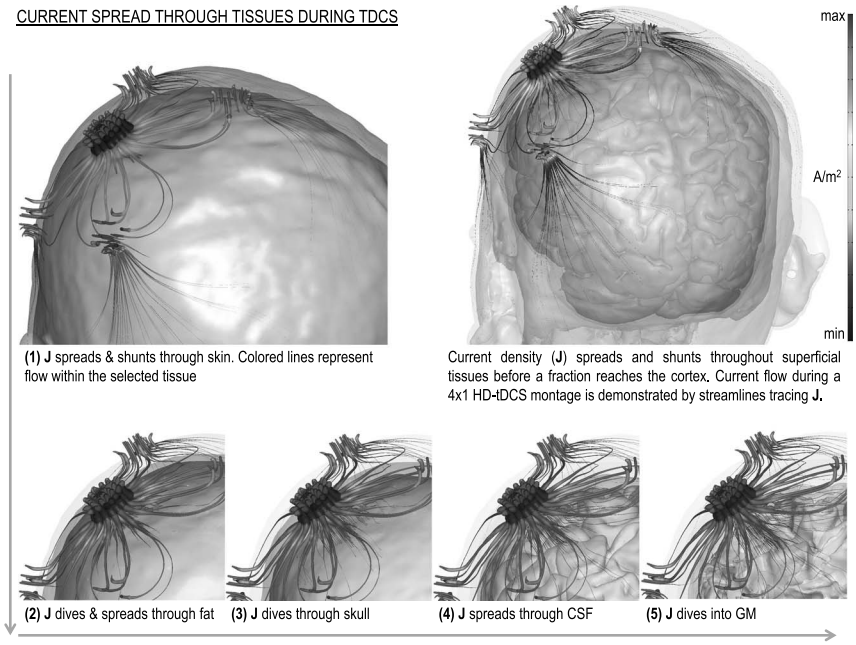

FIGURE 2. Illustration of current spreading and shunting through superficial tissues. Streamlines seeded under the electrodes trace current density as it loops from anode to cathode. Line diameter is logarithmic with intensity. Insets (1) through (5) isolate and desaturate current outside the tissue of interest. Only a fraction of the current delivered during tDCS reaches the cortex. In the 4 × 1 HD-tDCS example, the center anode and surround cathodes (or vice versa) are in close proximity on the scalp surface. Much of the current shunts through skin but a fraction of the current spreads into deeper tissues and eventually into the cortex.

of tDCS related to current delivery to the brain, the resulting polarization of neuronal membranes is well established.[97,98] Current that is passed through tDCS electrodes takes a path through the head determined by the head anatomy and the resistivity of each tissue type. A fraction of the current never crosses the resistive cranium, instead shunting across the relativity-conducive (low resistivity) scalp.[91] Of the current fraction that crosses the skull, a further portion is shunted by the high-conductivity cerebrospinal fluid. The current component that reaches the brain crosses the gray and then white matter. As current crosses brain tissue, it generates an electric field on the local tissue. Neurons are exposed to and so stimulated by local electric field. The current intensity is not uniform across the brain, and so the electric field intensity is also distributed. The peak electric field in the brain during 2-mA tDCS is 0.5 to 1 V/m based on intracranial recording in subjects validating current flow models.[33,92,93] For conventional tDCS, this peak may be in a brain region between electrodes.

The direction of current flow across the gray matter can be radial inward (from the pial surface toward gray/white matter boundary), radial outward, or tangential (along the gray matter).[99] Current flow will polarize neuron in a compartment-specific manner (ie, the soma, dendrites, axon of a single neuron may be polarized differently[100,101]). The magnitude and direction of the electric field generated in the gray matter determine the polarization of neuronal compartments.[102] Radial inward current will depolarize the somas of cortical pyramidal neurons ~0.2 mV per V/m of electric field, whereas radial outward current will hyperpolarize the cortical pyramidal neurons somas by −0.2 mV per V/m.[103] Radial inward/outward current is expected to increase/decrease the firing rate of these neurons because of somatic polarization.[104,105] Each neuronal compartment will be polarized, depending on the morphology of the neuron.[106,107] Electric field will polarize axon terminals (synapses) oriented parallel to the field direction ~1 mV per V/m,[108] which can then influence synaptic function.[107,109–111]

The neurophysiological and so behavioral consequences of tDCS will depend on how this polarization influences excitability and plasticity.[112] Because tDCS produces only incremental membrane polarization, the cellular effects of tDCS on brain function will depend on ongoing activity.[82,113–115] These effects may then be amplified over time (tens of minutes[116–118]). The organization of neurons in active networks with emergent properties such as oscillations will influence the aggregate effects of tDCS.[114,119] The ultimate consequences of tDCS on macroscopic measures of neurophysiology (eg, transcranial magnetic stimulation) and behavior (eg, therapy) will be complex,[54,120–123] but ongoing research about such changes should not be confused with debate about the biophysics of current flow and resulting membrane polarization.

SAFETY AND TOLERABILITY OF tDCS DEVICES

The tolerability of any intervention depends not simply on the device and dose, but on protocol including the subject's demographic and clinical characteristics (ie, inclusion/exclusion criteria [eg, age, preexisting condition], operator training and certification, ongoing monitoring, and parallel interventions). Therefore, the scientific consensus that tDCS is safe and tolerated[12,15,31,124–126] is explicitly limited to those protocols tested. Human trials of tDCS in the United States are almost always considered nonsignificant risk (risk comparable to daily activities). But this risk designation—whether made by the Food and Drug Administration or by an institutional review board—must be made on a protocol-specific basis, emphasizing that recommendation on safety and tolerability cannot be made on any device, but must also specify the methods of use.

Transcranial direct current stimulation device design may be considered to minimize risk to the extent they reliably control dose and allow consistent electrode setup, when used within the limits of established protocols. Medical-grade tDCS devices and accessories, which are designed and manufactured to internationally recognized medical standards, regardless of region specific approval for

treatment,[12,28,127] provide the highest standard of control in regard to reliability.

HOME-BASED tDCS DEVICES

A theoretical advantage of tDCS is deployability. Factors such as cost, portability, safety, and ease of use allow tDCS to be used in a wide range of clinical environments and at home.[128] However, devices designed for use by certified operators at research or clinical centers may not be suitable across deployed conditions. To address this concern, standards for remote-supervised tDCS have been developed[129] and validated.[129,130] The principle of remote-supervised tDCS is, under continuous medical or research supervision, to control compliance, proper dose control, and risk. Features of suitable device include mechanisms to limit dose (eg, one 2-mA, 20-minute session per day) and simple and robust method to prepare and apply electrodes (eg, single-use presaturated snap electrodes and single-position headgear). While the ethics and merits of self-administered tDCS (outside medical or research supervision) are discussed,[131–133] specifications for tDCS devices that minimize risk have been developed.[28]

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