8 Transcranial Electrical Stimulation (tES)

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8.1 Introduction

Transcranial electrical stimulation (tES) devices apply electrical waveforms through electrodes placed on the scalp to modulate brain function.[1] Various types of tES devices are used for a wide range of indications spanning neurological and psychiatric disorders,[2,3] blood-brain barrier polarization[4] neurorehabilitation after injury, and altering cognition in healthy adults.[5] All tES devices share certain common features, including a waveform generator (typically a current controlled source), electrodes that are either fully disposable or include a disposable electrolyte, and an adhesive to position the electrodes on the scalp (Figure 8.1). Various

tES subclasses are named based on dose. For example, electroconvulsive therapy (ECT) is a special class of tES applying high stimulation intensity. A tES "dose" is defined by the size and position of electrodes, and waveform including the pattern, duration, and intensity of the current.[6]

Figure 8.1 Example of a tES device, headgear, snap electrode, and lead wire used to connect electrodes to the stimulator. Generally, conventional sponge-electrodes are soaked with a controlled volume of saline using a syringe. Rubber electrodes are placed inside the sponge pockets. Sponge electrodes are then secured on the scalp using a headgear. The rubber electrodes are energized using corresponding anode and cathode wires connected to the stimulator.

This chapter is largely focused on low-intensity tES, which includes transcranial Direct Current Stimulation (tDCS), transcranial Alternating Current Stimulation (tACS), and transcranial Pulsed Current Stimulation (tPCS).[7] tES electrode types are 1) electrolyte-soaked sponge; 2) adhesive hydrogel;[7] 3) High-Definition (HD);[8] 4) hand-held solid metal; 5) free paste on electrode; and 6) dry.[9] Computational current flow models support device design.[10] Consensus on the tolerability of tES is protocol specific, but medical grade devices minimize risk.

8.2 Historical development of tES devices

The history of electrical stimulation dates back to the discovery of electrical phenomena, and static voltage sources are among the earliest examples of electrical technology,[11] though with unclear relation to the modern tDCS dose. There is a continuous history of transcranial electrical stimulation technology development and testing, much of it on non-DC waveforms such as pulsed stimulation (Figure 8.3).[12] Human trials investigating tDCS for neuropsychiatric disorders continued through the middle of the 20th century, typically with lower current intensities and longer du-

rations than modern tDCS.[13] The importance of canonical trials circa 2000 (showing a polarity-specific modulation of brain excitability by tDCS) is evidenced by these trials establishing the modern tDCS dose: 1 mA applied over tens of minutes with relatively large electrodes.[14] Subsequent pilot trials instituted a 2 mA intensity for therapeutic interventions[15] maintained for almost all subsequent clinical evaluation.[16] These developments established the contemporary tDCS dose and thus the specification of modern tDCS devices (Figure 8.2). Iontophoresis (transdermal drug delivery using potential gradient) devices were adopted for some tDCS trials as an off-label medical device, though they may not provide a steady output.[17]

Ongoing refinements in dose (e.g., use of 1.5 mA in cognitive neuroscience),[18] electrodes (e.g., HD-tDCS), integration with imaging (e.g., fMRI), and home-use (e.g., remote supervised) are reflected in specific tDCS device features. Usability device features such as enhanced programming (microcontroller), control systems (e.g., response to impedance changes), rechargeable batteries, disposable electrodes, enhanced headgear materials, wireless connectivity, and the integration of monitoring technology[19] reflect general progress in available technologies while maintaining the tDCS dose (Figure 8.2).

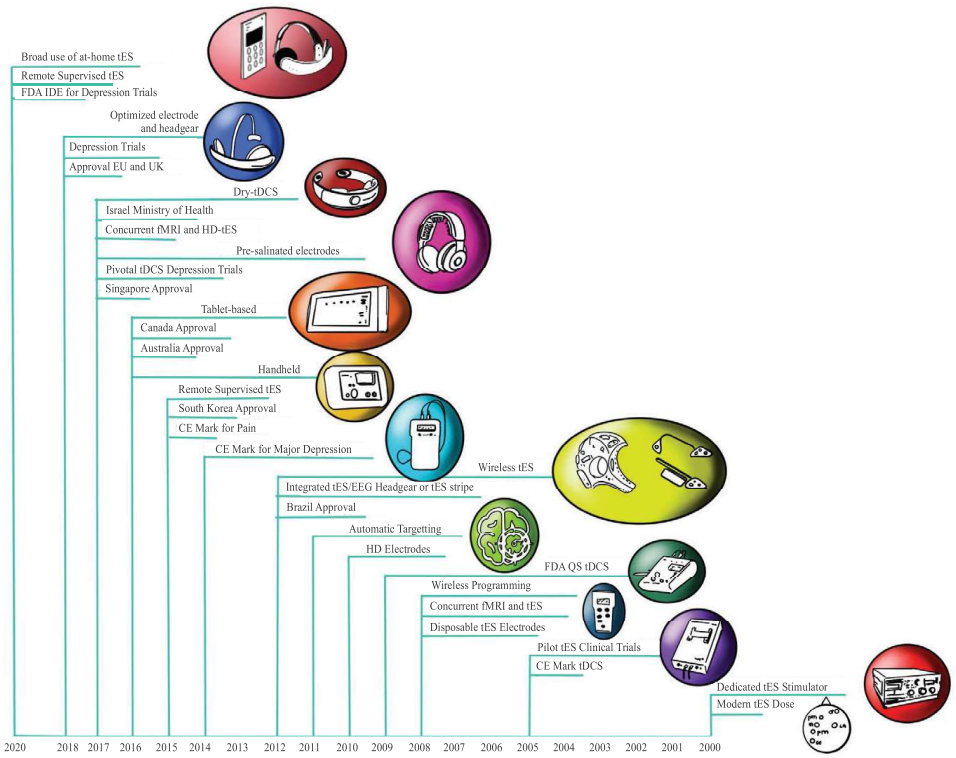

Figure 8.2 Timeline of tDCS Innovations: Technology and Regulatory Milestones. tDCS: transcranial Direct Current Stimulation. CE mark: Conformité Européenne Marking. fMRI: functional Magnetic Resonance Imaging. FDA QS: Food and Drug Administration Quality Systems. HD: High Definition/Density. EEG: Electroencephalography.

8.3 Basics of tES devices and dose

The tES device is essentially a current source connected to electrodes on the subject's scalp. A tES dose is defined as the current waveform applied to the body and the number, shape, and location of electrodes placed on the scalp. The electrodes guide the waveform into the head and serve as the interface between the device and the body. A tES device should be designed to reliably deliver the target dose, including any operator controls, safety features, and instructions for use. Electrode montage collectively refers to the electrode number, shape, and location. There is a minimum of two electrodes. The waveform is produced by a powered device that can be directly attached to the electrodes using connector lead wires (Figure 8.1). A headgear is used to hold the electrodes in the desired positions, or the electrodes can be adhesive. If the device is small, it may be attached to the headgear, but, more typically, it is a hand-held or benchtop device. Electrode design (e.g., materials) is reported separately from montage and waveform, but a central theme here is that because of reproducibility, usability, and tolerability factors, electrode design critically informs both possible dose and device form (usability) factors.

Sub-classes of tES are defined by a specific dose and intended use. For example, a form of tES that delivers high intense stimulation (~1000 mA) to produce a seizure in an anesthetized patient is called Electroconvulsive Therapy (ECT).[20] This chapter is largely focused on low-intensity approaches that are well below the intensity needed to produce seizures, typically only 1-4 mA.[21] These low-intensity approaches do not cause discomfort when applied to alert individuals who may be engaged in different activities (training, performing tasks) during stimulation. In fact, low-intensity tES typically does not provide an overt response related to brain stimulation — with any changes in brain function subtle — but can produce an overt sensation such as tingling that are not related to direct brain modulation. In most cases, stimulation is applied for several minutes (for example, 10 min) using two electrodes (typically a few cm^2) on the head. Therefore, often the distinguishing feature of different sub-classes of tES is the waveform shape and electrode montage rather than the peak intensity or period of use.[22]

tES devices that deliver low-intensity stimulation, such as tDCS, tACS, and tPCS, are typically battery-powered. tES devices used for ECT and devices that apply brief high-intensity stimulation for neurophysiological evaluation (e.g., a single 1000 mA pulse) are wall powered. In addition to waveform, electrode number and shape determine dose in some cases further inform the sub-class of tES classification. For example, the use of small electrode arrays is classified as High-Definition (e.g., High-Definition tDCS,[8] High-Definition tACS [23]).

The current enters through the anode electrode into the body and exits the body through the cathode. At any instant of stimulation, there must be at least

one active anode and one active cathode. For tES devices where the waveform polarity is fixed, such as tDCS and monophasic tPCS, each electrode has a fixed assignment of either anode or cathode (Figure 8.3). For tES devices where the waveform is biphasic, such as tACS and biphasic tPCS, each electrode alternates between functioning as an anode or cathode (Figure 8.3). When there are two electrodes, the current at one electrode is always the opposite of the other (1 mA at a single anode, indicates -1 mA at a single cathode). When there are more than two electrodes, the summed current across anode electrodes must equal to the summed current across the cathode electrodes[24] — because of the conservation of current where the total current entering the body must equal to the total current exiting the body.

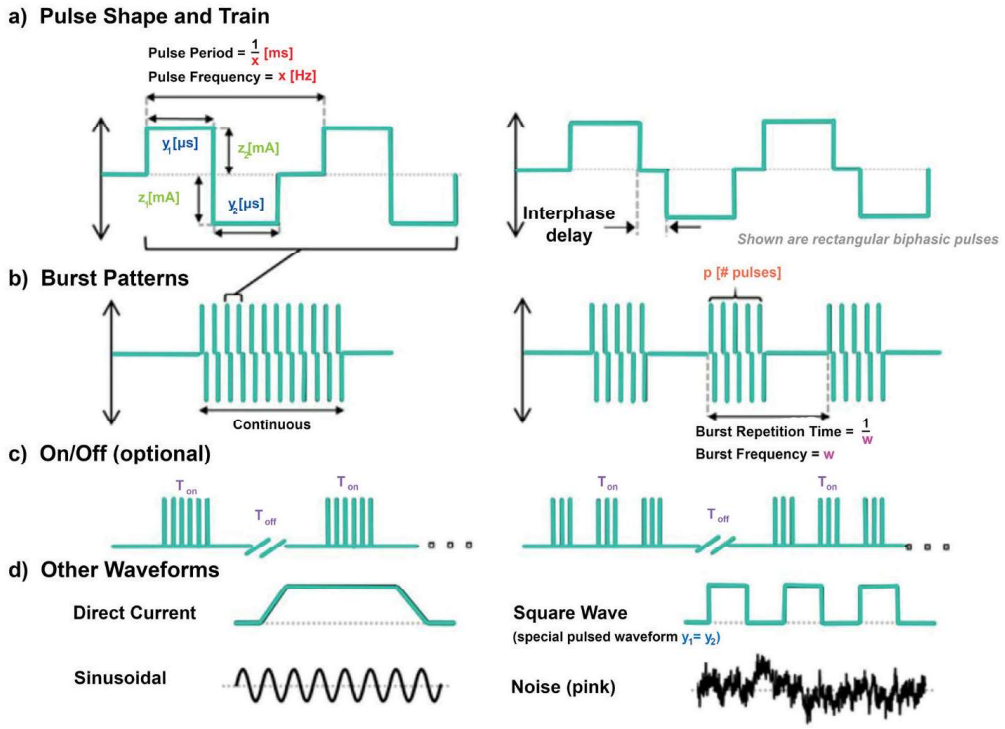

Figure 8.3 Different types of waveforms used in tES and their parameters. (A) represents rectangular biphasic pulses with frequency "x (Hz)", period " (s)", amplitude "Z1=Z2 (mA)", and pulse width "y1=y2 (s)". (B) represent burst patterns of pulses (continuous or discrete) where "P" is number of pulses, "w" is the burst frequency and "" is burst repetition time. (C) shows monophasic burst on (Ton) and burst off (Toff). Other waveforms such as direct current (DC), square wave, sinusoidal, and pink noise are shown in D.

8.4 Design aspects of tES electrodes

The key technical contributors to the broad adaption of tES are the portability and ease of use, along with the tolerability profile of most tES techniques. For limited-intensity tES techniques, adverse events are largely limited to effects that occur at the skin such as transient skin sensations (e.g., perception of warmth, itching, and tingling) and redness[25,26] that might be related to skin current flow.[27] Because adverse events are limited to the skin, the design and preparation of tES electrodes are considered central to tolerability.[9] Electrode design, in turn, can govern which waveforms will be tolerated. When established electrode protocols are not followed or poor electrode design is used, tES produces significant skin irritation and burns.[28] Electrode design also ensures reliable dose delivery. In addition, the electrode design should also address the ease and robustness of use (e.g., the potential for home use). For clinical trials, since sensations also determine effective blinding, tES electrodes impact blinding reliability.[21] Finally, to the extent that tES electrodes design shapes current flow through the brain, electrode selection and preparation are critical for reproducibility and efficacy.

The typical tES device uses just two electrodes of comparable size, positioned on the head.[6] However, strategies with asymmetric electrode size,[29] an electrode at or below the neck,[30] or an increasing number of electrodes (using High-Definition electrodes) can alter tES spatial focality.[8]

Electrodes can be positioned based anatomical landmarks on the head. These can be modestly sophisticated requiring a trained operator and tape measure, for example, using the EEG 10/10 system (e.g., anode on C3). Other more simplistic placement techniques are based on gross anatomical landmarks (e.g., over the eyebrow). When head gear is used, it is either designed to support the determination of specific electrode positions (e.g., a cap or marked straps[31]) or generic mechanical support (e.g., rubber bands[32]) so independent measurements can be used to measure the position of electrodes first (Figure 8.4). More sophisticated placement techniques include neuronavigated,[33] functional,[34] specialized head-straps,[35] or image-based approaches (e.g., EEG reciprocity[19,36]).

tES electrodes include two essential components: 1) a conductive rubber or metal separated from the skin by 2) a saline-soaked sponge, gel, or paste — which are collectively called the electrolyte.[6] Additional components of the electrode are often intended to provide mechanical support to the conductive rubber/metal or electrolyte, or otherwise facilitate electrode use (e.g., adhesion). In electrochemistry terms, the conductive rubber or plate would be the electrode, while the saline, gel or paste would be the electrolyte.[24] However, in tES literature, the entire assembly is called the electrode.[22]

Here we refer to the “electrochemical electrode” as metal or conductive rubber which is defined at the interface between the metal/rubber and the electrolytes. This interface is where electrochemical reactions (e.g., pH changes) occur.

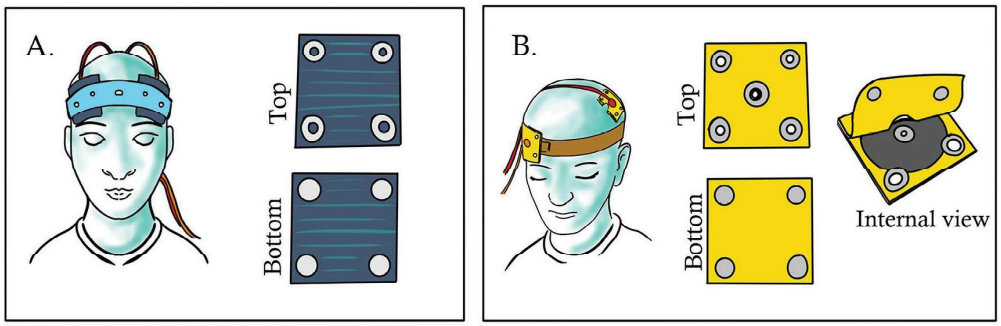

Figure 8.4 Architecture of sponge-electrode and its variations. (A, B) Examples of electrodes positioned on the scalp with the intention to stimulate the brain transcranially. Variations in sponge electrode design can make a significant difference in usage (both 5x5 cm2). In both cases, a conductive rubber electrode is placed between saline soaked sponges, but in one case, a metal snap is attached to the conducive rubber electrode. (A) For sponges without the metal rivet, a wire needs to be inserted inside the sponges to connect to the conductive rubber electrodes. A rubber band is then used to hold the electrodes to the scalp. (B) For sponges with a metal rivet, a lead with a snap connector may be used. In this case, the snap connector can be integrated into a head gear. This example is intended to show how seemingly small changes in electrode deign can have significant impact on overall usability.

In tES when electrode size is described, (e.g., 5 x 5 cm^2) it is the interface (surface) between the skin and the electrolyte, not the electrochemical electrode surface. None-the-less, the configuration of all electrolyte and electrochemical-electrode dimensions and materials are important to control and document as this affects tolerability. [28,37,38]

The thickness of the sponge or paste essentially controls the minimum distance between the conductible rubber/metal and the skin. Contact of conductive rubber or metal with the skin during tES is always avoided as this compromises tolerability and introduces the risk of significant skin irritation. This risk is the main reason why the more involved an electrode preparation technique is, the more prone it is to set-up error (e.g., insufficient electrolyte thickness in a free-paste electrode), and the less deployable it is. Electrodes intended for wide or deployed use should require minimum preparation (e.g., adhesive electrodes, pre-saturated sponge electrodes).

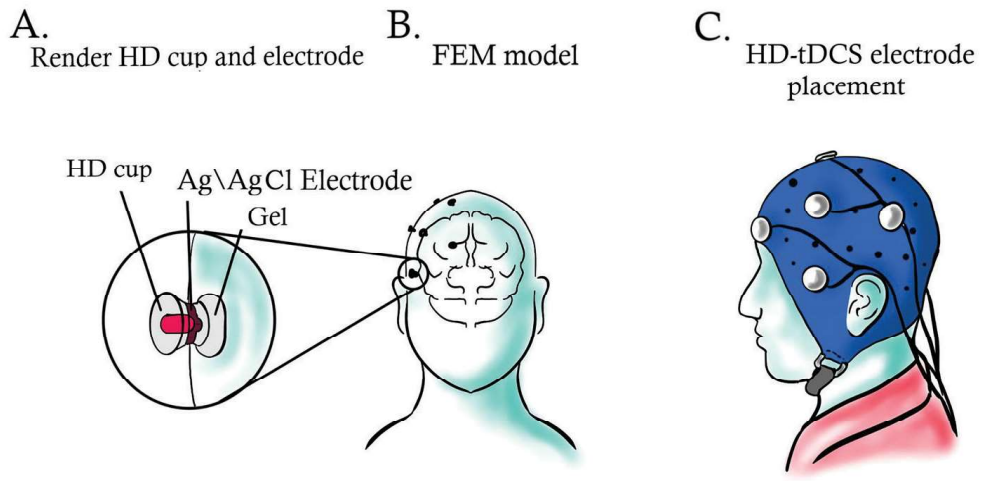

Figure 8.5 High definition (HD) tES device and electrodes. In contrast to other types of tES electrode, HD electrode are relatively small. A HD-cup placed on the skin contain the metal electrodes (Ag/AgCl) and the electrolyte gel. Shown is the 4x1-ring configuration of electrode placement where four electrodes of matched polarity are positioned around a central electrode of opposite polarity. Electrodes are secured in a 4x1 configuration using a specialized head cap.

There are two essential functions of the electrolyte, and by extension, the materials used to support the electrolyte shape such as sponge, hydrogel polymer, and other support materials that contain a viscous electrolyte (such as the HD case (Figure 8.5)). Both functions of the electrolyte relate to preventing direct contact between metal/conductive rubber electrode and skin. The first aforementioned function relates to electrochemical products, including changes in pH that occur only at the metal/rubber and electrolyte interface[24] such that a "thick" electrolyte (e.g., realized by a thick sponge, gel, or holder) minimizes these reactions from reaching the skin and causing irritation. The second function relates to normalizing current flow patterns through the skin; related to this, the saline, conductive paste, or conductive gel is used to maintain good contact quality at the skin.[37,39] If, as result of poor electrode design (e.g., conductive metal/rubber not fully protected from the skin) or preparation (e.g., a metal/rubber electrode pushed through paste), the metal/rubber contacts the skin, these electrochemical changes or poor current density patterns can adversely impact the skin and aggravated skin irritation is likely.

The overall cardinal functions of electrodes used in tES are to 1) support reliable delivery of the desired dose; and 2) protect the skin from electrochemical reactions occurring at the surface of the metal/rubber, including normalizing current density across the skin (e.g., minimize hotspot) and preventing any electrochemical reactions (occurring at the electrochemical electrode) from impacting the skin. Because electrochemical reactions are key concerns, all electrodes

designed for tES include some mechanism to separate the metal/rubber from the skin. The electrolyte, being the conductive element contacting the skin, takes on importance in general performance. As expanded upon in the following sections, the design of the electrolyte (and by extension all support materials used around it) is central to the classification of electrode types:

1) *Sponge-electrode*: A sponge saturated with the fluid electrolyte, typically saline, with a metal/rubber inside the sponge (sponge pocket design) or on the sponge surface opposite the skin (Figure 8.4). The sponge sets the electrolyte shape and conductive path.

2) *Self-adhesive integrated electrode*: A hydrogel electrolyte with sufficient rigidity not to flow or spread, and with the gel or material around the gel including an adhesive component.

3) *HD electrode*: A stiff mechanical support (short tube/cup) material that contains the electrolyte, typically gel and also controls the position of the metal (Figure 8.5). Used for smaller electrodes and so suitable for arrays.

4) *Free electrolyte on hand-held conductor*: "Free" indicates application by the operator without strict thickness control by the electrode assembly. Re-used solid metal electrode, covered per-use with a thin electrolyte layer, and an operator handles to press down. Used in some forms of ECT and not considered further here.

5) *Free paste on conductive rubber electrode*: The paste may also provide adhesion. Used in some investigational forms of tDCS/tACS and not considered in detail here.

6) *Dry electrodes*: Novel designs that are not adhesive and leave no residue (not liquid or paste). Experiments are not discussed in detail here.

These general design approaches create restrictions on 1) the size of the electrode (e.g., small HD vs. large sponge) that can impact the ability to leverage electrode arrays for targeting; 2) how much preparation is required and the need for headgear; 3) if the electrodes can be applied to the hair regions of the scalp.

8.5 Indications for tES use

The tES spans many clinical and behavioral interventions, and as noted, many sub-techniques,[22] such as tDCS, tACS, and tPCS. What relates these different techniques is that they apply a current through electrodes on the scalp to stimulate the brain directly, rather than the periphery.[6] Research that uses tES thus focuses on direct cortical modulation as an explanation for changes in behavior, cognition, neurophysiology, and imaging studies.[40]

From the perspective of the device, the dose is designed and selected to achieve specific changes in brain function and thus clinical or cognitive outcomes. While

this is a large parameter space, it can be reduced to parameters of the electrode montage (e.g., how many, what size, where) and features of the waveform (e.g., intensity, frequency). The electrode montage is generally considered to determine *which* brain regions are influenced, and waveform determines *how* they are influenced — though, in practice, montage and waveform will integrate to determine where and how the brain is influenced.

For example, tDCS is applied as a possible treatment for major depressive disorder (MDD). A brain region of interest in MDD research is the dorsolateral prefrontal cortex (DLPFC), which is targeted with tDCS by placing electrodes bilaterally on the forehead.[3] tES clinical trials intending to treat pain disorders (e.g., migraine, fibromyalgia, craniofacial pain) often target the motor cortex (M1) with an "active" electrode, while the "return" electrode is placed on the contralateral forehead (called the "supra-orbital" or SO position) (Figure 8.4C).[14]

8.6 Current Flow Modeling Informs Electrode/ Device Design and Set-up

Computational models predict the resulting current flow (electric field distribution) in the brain for a given dose and anatomy (Figure 8.6). Computational models have been developed[41–43] and validated[44] over a decade. It is important not to conflate established montage-specific effects (e.g., "shaping" the outcomes of stimulation) with a demonstration of focality (e.g., current delivery to one region of interest). Rather, models of conventional tDCS[45] and HD-tDCS[8] support testing hypothesis that links brain regions to neurophysiologic or behavioral changes.[10] This includes registering results from computational current flow models with the imaging data.[46]

Computational models are ancillary software used to inform the design,[26] set-up, and programming of tES devices. Device specifications limit the dose range that can be explored by a model, while conversely, models can encourage the creation of new device technology.[42] For example, a home-based system relying on adhesive electrodes would restrict the positional electrode location to explore with computational models to position them below the hairline,[47] which in turn, simulates the development of simple-to-use electrodes that can go over the hairline.[31] The potential for focal transcranial stimulation was suggested first by computational models,[45] but it was not until practical HD electrodes were developed[48] that approaches to optimize transcranial stimulation using HD arrays could be tested.

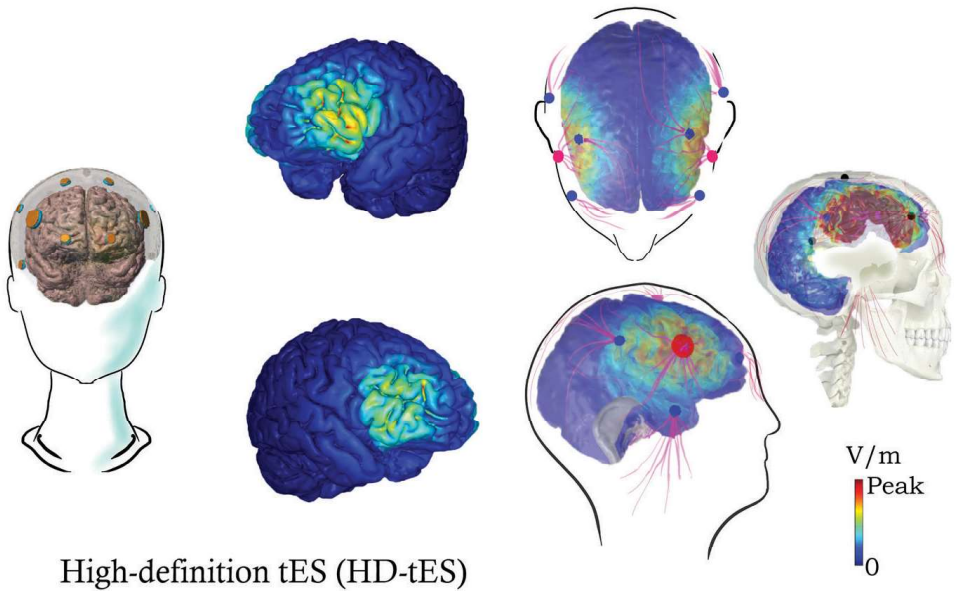

Figure 8.6 Computational FEM head models and predicted electric field magnitude of dual-hemisphere HD-tES montage. (Left) 3D image of a segmented brain generated from an MRI scan of a healthy adult and electrode placement over the cortex. (Middle) electric field magnitude and current density stream inside the head's tissue layers during HD-tES. (Right) Dissected view of skull with activated brain region by HD-tES.

8.7 Safety and Tolerability of tDCS Devices

The tolerability of any intervention depends not simply on the device and dose but the protocol, including the subject's demographic and clinical characteristics (i.e., inclusion/exclusion criteria (e.g., age, preexisting condition), operator training and certification, ongoing monitoring, and parallel interventions). Therefore, the scientific consensus that tDCS is safe and tolerated is explicitly limited to those protocols tested. Human trials of tDCS in the USA are almost always considered Non-Significant-Risk (risk comparable to daily activities). However, this risk designation — whether made by the Food and Drug Administration (FDA) or by an Institutional Review Board (IRB) — must be made on a protocol-specific basis. Recommendations on safety and tolerability cannot be made on a blanket level to any device but must also specify the method of use.

The tES device design may be considered to minimize risk to the extent that the device can reliably control the dose and allow consistent electrode setup when used within the limits of established protocols. Medical grade tES devices and accessories designed and manufactured to internationally recognized medical standards — regardless of region-specific approval for treatment – provide the highest standard of control with respect to reliability.

Tingling is a common adverse effect reported in low-intensity tES studies.[7] For low-intensity techniques like tDCS, the severity of adverse events is low across all conditions (Figure 8.7). As discussed above, electrode size and salinity of sponge-electrodes may influence sensation.[28] In principle, electrode design must be optimized to reduce the frequency and intensity of tingling and related sensations in clinical trials, enhancing blinding effectiveness. For this same reason, studies that focus on the efficacy of the tES (tDCS) blinding technique but provide little attention to the electrode design and preparation techniques (including document operator training) are of limited generalized value. There is a dissociation between erythema and tingling — tingling being higher under thin sponge stimulation than thick electrodes.[25] A potential reason may be that the thick sponge produces a more uniform current density at the skin surface, resulting in evenly diffused erythema distribution and lower tingling sensation.

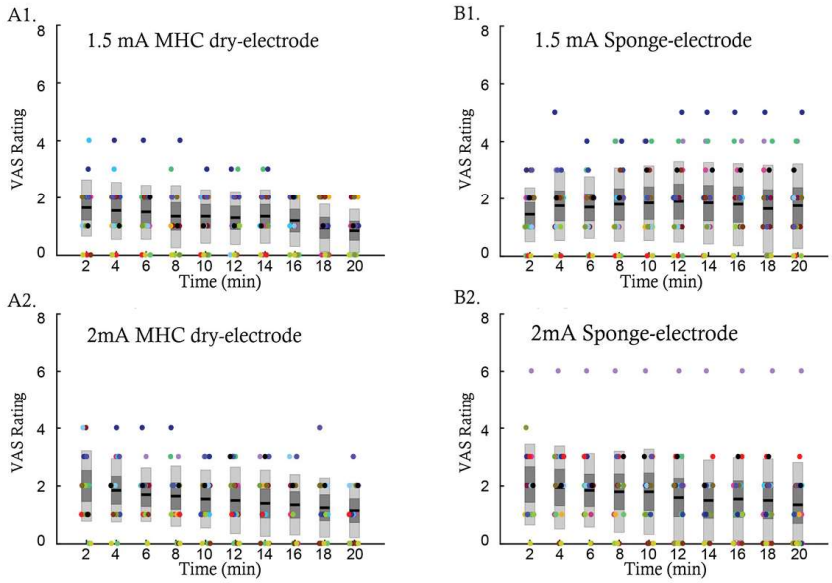

Figure 8.7 Visual Analogue Scale (VAS) pain score at different stimulation intensities (1.5 mA and 2 mA tDCS) for a conventional sponge and MHC dry electrode. Participants were color-coded as the cumulative adverse events and relationship to tDCS data, and the VAS pain score (1-10 scale; 1: no pain, 10: unbearable pain) was collected every 2 minutes during each stimulation session. There was no significant difference ($P < 0.05$) in the VAS rating across all four stimulation sessions. Adapted from Khadka et al., 2018.[9]

8.8 Home-based tDCS Devices

The advantage of tES (including tDCS) is deployability. Factors like cost, portability, safety, and ease-of-use allow tES (tDCS) to be used in a wide range of clinical environments and at home.[49] However, devices designed for use by certified operators at research or clinical centers may not be suitable across deployed conditions. Standards for remote-supervised tDCS have been developed and validated[50] to address this concern. 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 (e.g., one 2 mA 20-minute session per day) and simple and robust method to prepare and apply electrodes (e.g., single-use pre-saturated snap electrodes and single position headgear). While the ethics and merits of self-administered tDCS (outside of medical or research supervision) are discussed, and specifications for tDCS devices that minimize risk have been developed.

8.9 Conclusion

The tES device is a current source connected to electrodes on the subject's scalp. tES dose is defined as the current waveform applied to the body and the number, shape, and location of electrodes placed on the scalp that guide the waveform into the head. Approaches using low-intensity tES, limited to a few milliamperes, include tDCS and tACS. A practical tES device is equipped to reliably deliver the dose, including any operator controls, safety features, and instructions for use. The waveform is produced by a powered device and may be hand-held or benchtop and connected, or the device may be integrated into a headgear that includes an electrode. Other than the waveform, device features such as shape, weight, power supply, and user interface are not explicitly part of dose but can be critical for usability (e.g., ability to apply correctly, acceptability and compliance). The applications of tES are diverse and expanding, spanning treatment of neurological and psychiatric disorders, neurorehabilitation, and mental health and performance. The level of evidence for the efficacy of different tES doses across different applications varies.

Endnotes

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