Noninvasive Electrical Brain Stimulation of the Central Nervous System

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Contents

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Abstract

Noninvasive electrical brain stimulation of the central nervous system spans a broad range of devices and techniques that aim to change brain function with electrical current applied through electrodes on the surface of the body. The applications of such techniques span treatment of a wide range of neuropsychiatric disorders, healing of the nervous system after an injury, and experimental manipulations to study brain function. This chapter focuses on transcranial electrical stimulation (tES) which involves electrodes placed on the scalp with the goal of passing current through the skull and directly stimulate the cortex. tES itself is divided into subtechniques that are classified by the waveform applied and/or by the application of intended use. All tES devices share certain common features including a waveform generator and electrodes that are fully disposable or include a disposable component. The device applies the waveform to the electrodes through lead wires. tES "dose" is defined by the size and position of electrodes, and waveform includes the pattern, duration, and intensity of current. Versions of low-intensity tES include transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS). Impedance measurement is largely used to monitor acceptability of electrode-skin properties. Computational FEM models of current flow support device design and programming by informing how to select dose to produce a given outcome. The evidence for tES use across varied clinical applications, spanning treatment of neuropsychiatric disorders and neurorehabilitation following injury, as well as a tool to change cognition and behavior in healthy individuals is developing.

Keywords

Transcranial electrical stimulation (tES) · Dose · tES electrode · Mechanism of tES · Computational current flow model

Abbreviations

tES	Transcranial electrical stimulation
tDCS	Transcranial direct current stimulation
tACS	Transcranial alternating current stimulation
ECT	Electroconvulsive therapy
tRNS	Transcranial random noise stimulation
tPCS	Transcranial pulsed current stimulation
HD	High definition
HD-tDCS	High-definition tDCS
AC	Alternating current
DC	Direct current
CES	Cranial electrotherapy stimulation
HD-tES	High-definition tES
HD-tACS	High-definition tACS
EEG	Electroencephalogram
MHC	Multilayer hydrogel composite

ADHD	Attention deficit hyperactivity disorder
MDD	Major depression disorder
DLPFC	Dorsolateral prefrontal cortex
M1	Primary motor cortex
CSF	Cerebrospinal fluid
FEM	Finite element method
NSR	Nonsignificant risk
MRI	Magnetic resonance imaging

1 tES Devices and Providing a Dose

Electrical brain stimulation techniques encompass all research and clinical technology to modulate brain function by passing current into the brain using wire that tunnels across the skull and spinal tissues (e.g., deep brain stimulation [1, 2] and spinal cord stimulation [3, 4]) or placing electrode on the scalp to noninvasively deliver current to the brain. These noninvasive approaches are called transcranial electrical stimulation (tES), as the current passes the cranium on the way to the brain. Types of tES include transcranial direct current stimulation (tDCS; [5, 6]), transcranial alternating current stimulation (tACS; [7–9]), transcranial random noise stimulation (tRNS; [10, 11]), transcranial pulsed current stimulation (tPCS; [12, 13]), and electroconvulsive therapy (ECT; [14, 15]). During the last two decades, the noninvasive brain stimulation techniques have been expansively studied for several neurological indications and enhancing cognition, reflecting their noninvasive nature, safety/tolerability profile, ease of use, and low cost [5, 16–22]. This chapter focuses on noninvasive electrical brain stimulation techniques, and especially low-intensity tES approaches of tDCS and tACS.

tES devices are designed to provide one or multiple electrical stimulation interventions noninvasively to the brain [23]. Each tES intervention should be understood as a "dose." tES dose depends on current intensity and waveform applied to the body and the number, shape, and location of electrodes placed on the scalp. The tES device generates the waveform and passes the waveform to the electrodes through the stimulation lead wires (Fig. 1). The electrodes then guide the waveform into the head and serve as the interface between the device and the body. The dose determines how much and where electrical current flows through the body, including the brain. As such, dose is a central determinant of what a given tES device does to the body and a reliable tES device controls the dose across subjects and uses.

The electrode number, shape, and location are collectively called the montage. The electrodes need to be positioned on the scalp and this is accomplished. The electrodes are the device component that transmit electricity from the device into the body, and in so doing that must convert the current flow from electron based (in circuits) to ion based (in the body). For this reason, and others, the physical design of the electrodes places a central role in the reliability and the tolerability of ties.

In electrical stimulation, an anode electrode is defined as the electrode where current enters the body, and at a cathode electrode current exits the body [24]. Note this terminology as used in electrical stimulation literature may be different than

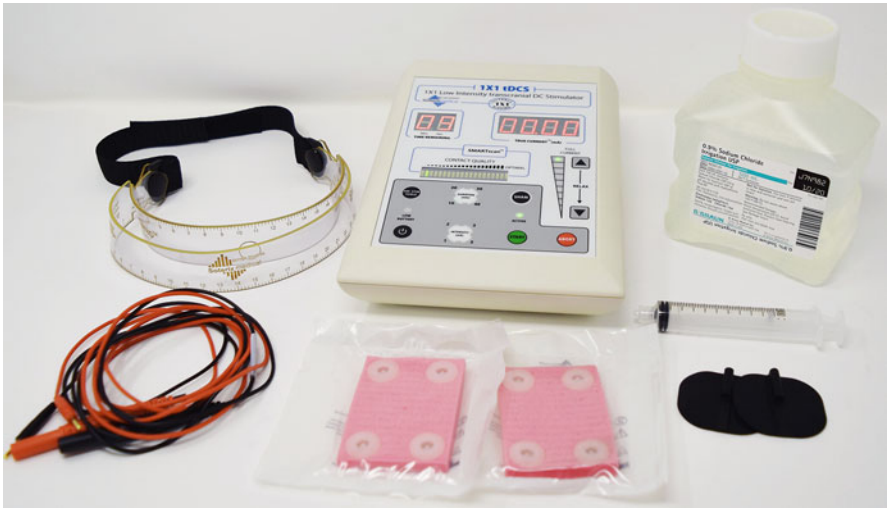

Fig. 1 Example of a tES device and a headgear used for electrical stimulation with sponge electrodes. In general, conventional sponges are soaked with a controlled volume of saline using a syringe. Rubber electrodes (electrochemical electrodes) are placed inside the sponge pockets. Lead wires connect to the device to the conductive rubber electrodes. Sponge electrodes are then secured on the scalp using a headgear. The rubber electrodes inside the saline-soaked sponge pockets are energized using a corresponding lead wire connected to the device

the way anode and cathode are used in battery literature. There must be at least one anode and one cathode, because both terminals of the tES device must be connected to the body to complete the current flow circuit.

Most of the tES devices have just two electrodes. 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 the summed current across the cathode electrode [25] – that is because of conservation of current where the total current entering the body must equal the total current exiting the body. For tES devices that have multiple electrodes, the electrodes should not make contact; if the electrodes contact then the current will shunt between the electrodes and does not enter the head. When using electrodes that are about 25cm^2, positioning more than three or four electrodes on the head without risk of electrodes touching can be difficult. High-definition (HD) electrodes are smaller electrodes [26], and because they are much smaller (e.g., 5, 15, and 20) can be arranged across the head.

Duration of tES various across applications. A typical single-session tES (2 mA tDCS) lasts for 20 min [22, 27]. The sponge-based electrode (soaked in controlled volume of saline) are common type of electrode in some forms of tES, such as tDCS, tACS, and tRNS (Fig. 3, [27]). In tPCS, single-use self-adhesive electrodes are often used but due to electrochemically demanding nature of DC stimulation

(Minhas et al., 2010b), adhesive electrodes are used only in limited number of tDCS trials (Paneri et al., 2016). The modulated pulse (7–11 kHz) averaged current in tPCS ranges from 5–7 mA and is injected for 17 min [28]. Similar to conventional tDCS, a single-session 2 mA HD-tDCS (high-definition transcranial direct current stimulation) lasts for 20 min [26, 29]. Here the current is injected in a 4 ×1 ring configuration (four cathodes around a center anode Ag/AgCl electrodes) and with electrode rotation, the Ag/AgCl electrodes show no visual indication of corrosion or increased impedance [30].

Subtypes of tES are then defined by a specific dose applied to the body. For example, a form of tES that delivers high intense stimulation (∼1000 mA) to intentionally produce a seizure in a anesthetized patient is called electroconvulsive therapy (ECT) [31–33]. This chapter is largely focused on low-intensity approaches where the intensity of current applied to the body are well below the amount needed to generate seizure; these low-intensity devices limit the maximum current of stimulation to a few mA [16, 34]. These low-intensity approaches are comfortable when applied to alert individuals, who may be engaged in different activities 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 overt sensations 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. Often the distinguishing feature of different subclasses of tES is the waveform – the peak intensity, options for electrode placements, and period of use are often comparable across low-intensity tES approaches (Fig. 2). 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 [17, 18, 35–38]. Because adverse events are limited to the skin, the design and preparation of tES electrodes is considered central to tolerability.

When the waveform generated by the device is sinusoidal alternating current (AC) stimulation, tES is classified as tACS. The frequency is varied typically in a range below 100 Hz, though higher frequencies have been tested. When the waveform generated by the device is train of pulses, tES is called tPCS. There are many further subclasses (variations) of tPCS waveform including duration of each pulse, pulse frequency, and if pulses are monophasic or biphasic. Pulses are typically applied repetitively in a train, where the inverse of the time between pulses equals the stimulation frequency. Individual pulses are typically rectangular with a pulse duration and amplitude. A monophasic waveform has pulses of a single polarity, while a biphasic waveform has pulses that invert polarity, typically in paired opposite polarity pulses (i.e., positive, negative, positive, negative, and so on) [24].

When the waveform is a sustained direct current (DC), tES is called transcranial direct current stimulation (tDCS). Additional terminology refers to further variations in waveform such as tRNS and cranial electrotherapy stimulation (CES). A single tES device may be programmable to deliver difference waveforms, e.g., a tDCS mode and a tRNS mode, or a device may be designed to provide a single waveform. Devices made for research typically provide more flexibility while those

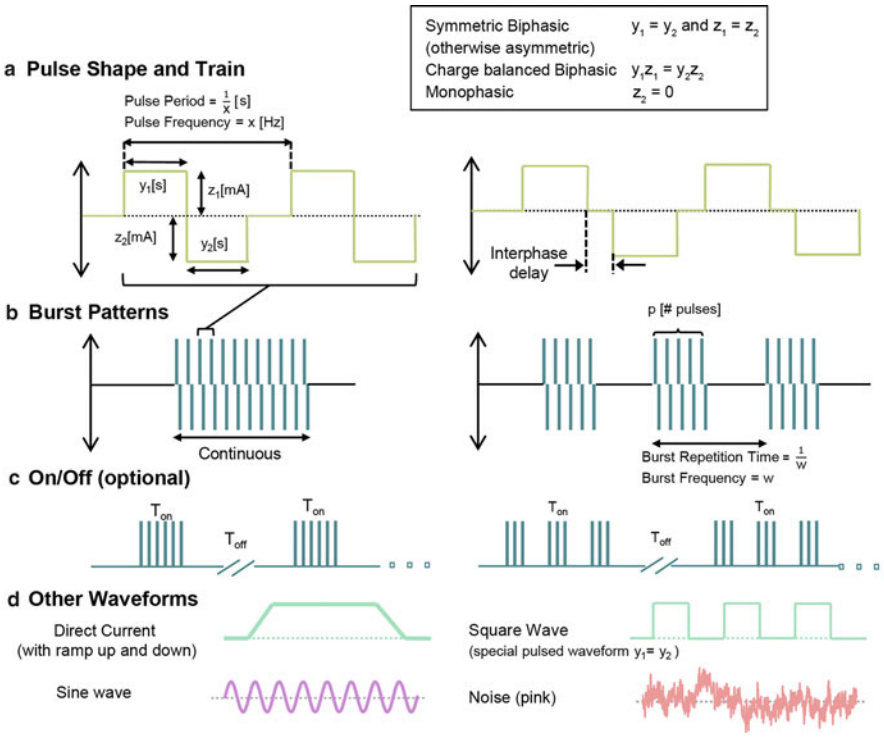

Fig. 2 Different types of waveforms used in tES and their parameters. (**a**) Represents rectangular biphasic pulses with frequency "x in Hz," period "1/x in sec," amplitude "Z_1=Z_2 in mA," and pulse width "y_1=y_2 in sec." (**b**) Illustrates continuous and discrete burst patterns of pulses where "p" is number of pulses, "w" is the burst frequency, and "1/w" is the burst repetition time. (**c**) Represents monophasic burst on (T_{on}) and burst off (T_{off}). Other waveforms such as DC, square wave, sinusoidal, and pink noise are shown in D

made for treatment, especially self-application by patients, provide one or a limited number of waveforms.

A tES device is essentially a medical grade current-controlled stimulator that generates the stimulation waveform. 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, and in some cases further inform the subclass of tES classification. For example, use of small electrode arrays is classified as high definition (e.g., high-definition tDCS [26, 29, 39] and high-definition tACS [40, 41].

2 General Design Aspects of tES Electrodes

tES electrodes include two essential components: (1) a conductive rubber or metal not in contact with the skin by (2) a salt containing fluid, gel, or paste – which is 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 use (e.g., facilitate connection). In electrochemistry terms, the conductive rubber or plate would be the electrode, while the saline gel or paste would be the electrolyte [24], but in tES literature, the entire assembly is called the electrode. Here, we refer to the electrochemical electrode as metal or conductive rubber which includes the interface between the metal/rubber and the electrolytes. This interface is where electrochemical reactions (e.g., pH changes) occur. As noted, in tES literature when the electrode size or area is stated (e.g., 5×5 cm^2) what is being referred to is the interface (surface) between the skin and the electrolyte. Nonetheless, the configuration of all electrolyte and electrochemical-electrode dimensions and materials are important to control and document as these affect tolerability [6, 35, 42–44]. The thickness of the sponge or paste essentially controls the minimum distance between the conductible rubber or metal and the skin. Contact of conductive rubber or metal with the skin during tES is avoided as this compromises tolerability and introduces risk of significant skin irritation. This is the main reason why the more involved an electrode preparation technique is, and so the more prone it is to set up error (e.g., insufficient electrolyte thickness in a free-paste electrode), the less deployable it is. While electrodes intended for wide or deployed use should require minimum preparation (e.g., adhesive electrodes and presaturated sponge electrodes) (Fig. 4).

There are two essential functions of the electrolyte, and by extension materials used to support the electrolyte (e.g., saline and hydrogel) and any other support materials contain a viscous electrolyte (e.g., sponge case). Both functions of the electrolyte depend on preventing direct contact between metal/conductive rubber electrode and skin. The first function prevents electrochemical products that form at the metal/rubber from reaching the skin, including changes in pH [24]. For this reason, the electrolyte has a minimum thickness (saline:1–2 mm; hydrogel: 3–5 mm), which is set by the support material (e.g., thick sponge and plastic holder). The second function of the electrolyte is to normalize current flow patterns through the skin. The even coverage of the skin with the fluid/gel electrolyte (as opposed to hard metal) supports this function [6, 26, 45]. Direct contact of the metal/rubber with the skin should be avoided through robust device training and clear operating procedures.

The design of the electrolyte (any by extension all support materials used around it) is thus central in the classification of electrode types:

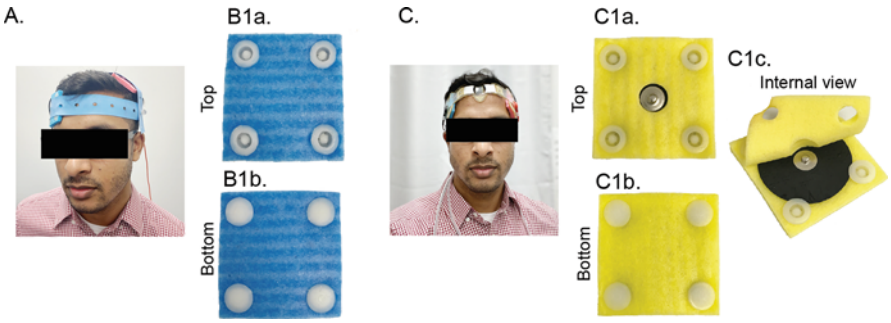

Fig. 3 Designs of conventional electrodes used for tES. Sponge electrodes are saturated with saline (electrolyte). (**a**) Standard sponge montages held with head with elastic rubber bands [27]. The electrode is a "sponge pocket" design with a conductive rubber electrode inside two sponges (B1a, B1b). Lead wires is plugged into the conductive rubber. Corner rivets serve to both package the sponge assemble and to limit current concentration at electrode edges during stimulation across the skin [65]. (**c**) Updated headgear made of plastic with electrode ports that determine electrode position on the head [19]. The sponge pocket design is updated with an exposed snap connector that connects to the headgear (C1a, C1c)

2.1 Sponge Electrode

A sponge electrode is the one that is based around sponge that is saturated with the fluid electrolyte, typically saline (Fig. 3 and 4). A metal/rubber is placed inside the sponge (sponge pocket design) or on the sponge surface opposite the skin. The sponge functions to set the electrolyte shape and conductive path (since evidently otherwise the fluid would disperse). The sponge-based electrodes are common type of electrode in some forms of tES, such as tDCS, tACS, and tRNS (Fig. 3, [27]). In these techniques electrode positions over hairline is common and the sponge electrode is especially well suited for stimulation over hairline [21]. Sponge electrode requires a headgear to hold them in place, which can take the form of a head band [46, 47].

2.2 Self-adhesive Integrated Electrode

A hydrogel electrolyte that has sufficient rigidity not to flow or spread, and either the gel and/or material around the gel including an adhesive component. Self-adhesive electrodes adhere to the skin surface and typically require minimal preparation – this makes them easy to use at locations without significant hair [28] but do not work well on hairline. Self-adhesive electrodes are often used with tPCS waveforms (Fig. 5). Because DC stimulation is electrochemically demanding [26], adhesive electrodes have been used only in a limited number of tDCS trials [28].

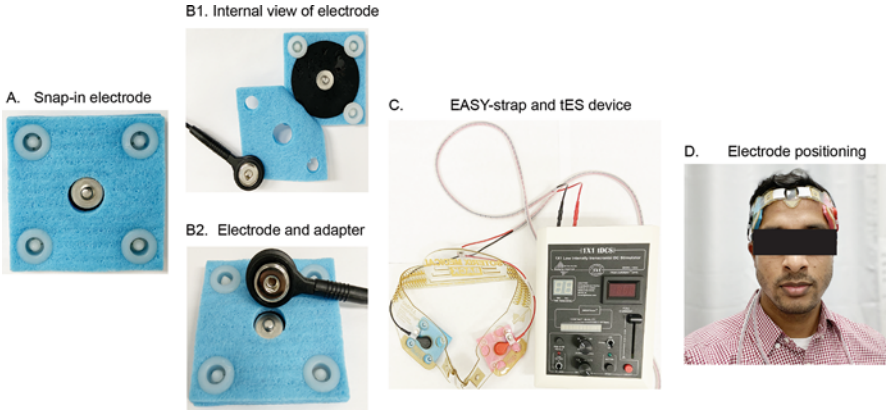

Fig. 4 Example of sponge electrode headgear for automatic electrode positioning. The components include two snap-in sponge electrode and the headgear with integrated snap lead. (**b**) The two snap sponge electrodes (**a**, B1, and B2) are connected to the two available positions on the headgear, which is connected to the tES device through lead wires (**c**). The headgear assembly can then be placed on the head (**d**). The headgear with fixed-position sponge locations ensure the electrodes are placed in the desired positions. Using different headgears, electrodes can be easily placed in different locations. Having one position per headgear reduces the possibility for setup errors [19]

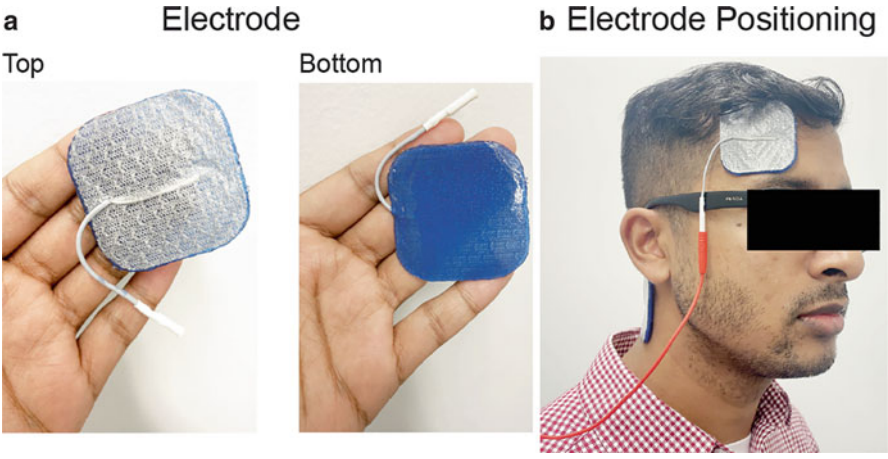

Fig. 5 Illustration of adhesive hydrogel electrode. (**a**) Top and bottom view of the adhesive electrode. (**b**) Placement of square adhesive electrodes on the subject's right temples on the back of neck. Generally, adhesive electrodes are restricted to placement below the hairline

2.3 High-definition (HD) electrode

A stiff mechanical support (short tube/cup) material that contains the electrolyte, typically gel, and also controls position of the metal. Used for smaller electrodes

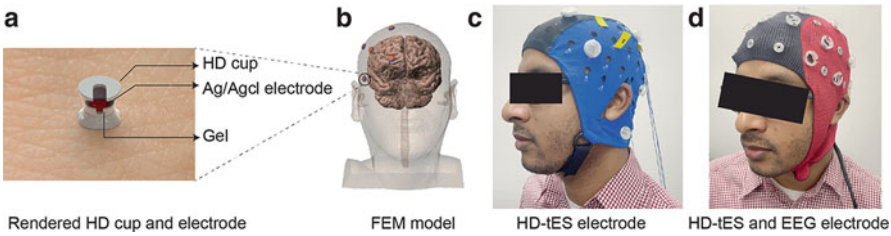

Fig. 6 High-definition (HD) electrodes. (**a**) In contrast to other types of tES electrode, HD electrodes are relatively small. (Render) A HD cup is placed on the skin and contained the metal electrodes (Ag/AgCl) and the electrolyte gel. (**b**) Because HD electrodes are smaller, they can be arranged in variation configurations on the head. Shown is the 4x1 ring configuration of electrode placement where four electrodes of matched polarity are positioned around a central electrode of opposite polarity. The render shows placement of the electrodes over the targeted brain region. (**c**) Image of a HD electrode assembly on a subject head. (**d**) HD-tES can be integrated readily with EEG in a single headgear

and so suitable for arrays, HD electrodes are electrode assembly with a skin contact area of less than 5 cm^2. The HD electrode includes a cup that sits on the skin and determines the skin contact area. The cup is filled with conductive gel or paste [26]. Suspended inside the gel is a metal ring, disk, or pellet made from Ag/AgCl. As with conventional tDCS using sponge electrodes, there are different montages of HD-tDCS but HD electrodes, by the virtue of being smaller, can be deployed in significantly higher number and/or precision of placement [25, 48, 49]. A common HD montage is the 4 × 1 ring montage where a ring/circular fashion using four "return" (cathode) disk electrodes arranged around an "active" (anode) electrode at the center [29, 39, 50, 51]. The active electrode is positioned over the scalp (coinciding with the center of the active tES sponge pad) and surrounded by four return electrodes: each at a disk distance (from center to center of the disk) of ∼3 cm from the active electrode (Fig. 6). When best practices such as electrode rotation, consistent amount of electrode gel, saturation phase, and impedance monitoring are implemented, HD electrodes can be safely used for up to ten sessions without any problematic indications [30].

Various waveforms can be applied in high-definition tES (HD-tES). HD-tDCS uses tDCS waveforms [48, 49, 52, 53]. High-definition tACS (HD-tACS) uses AC waveforms [41, 54, 55]. Still other waveforms are specific to the use or arrays such as interferential stimulation [56] or high-intensity pulses [57]. Multiple brain regions can be targeted with HD-tES [41, 58, 59].

The form factor of HD-tES cups superficially resembles electroencephalogram (EEG) electrodes (though EEG electrodes cannot be reliably used for stimulation), and indeed it is possible to combine HD-tES and EEG systems. However, while EEG recoding before HD-tES (for example, to measure baseline state of inform stimulation strategy; [60, 61]) or after HD-tES (to measure outcomes; [58, 62]) is valuable, recording of EEG during tES is confounded by artifacts [63, 64].

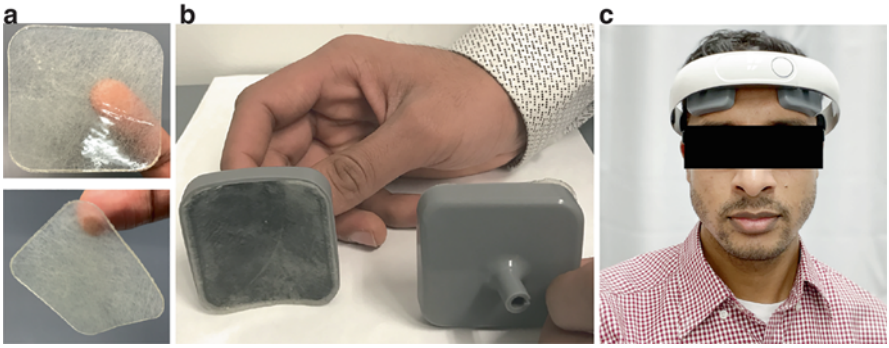

Fig. 7 Multilayer hydrogel composite (MHC) dry electrode with stimulator integrated into headgear. (**a**) Images of MHC dry electrode. The top layer is 0.6 mm thick, adhesive, and have higher conductivity, whereas the bottom layer is 1 mm thick, nonadhesive, and has low conductivity. (**b**) Dry electrode and specialized rubber adapter assembly. Dry electrodes are placed over the rubber adapter with the adhesive layer facing the rubber side and the nonadhesive layer (bottom layer) facing the skin side. The rubber adapter is encapsulated within a flexible insulated holder. (**c**) Dry electrode secured over the brain region through the specialized headgear (wearable built-in stimulator). See [10] for details

2.4 Free Electrolyte on Handheld Conductor

"Free" indicates application by the operator without strict control of thickness by the electrode assembly. Reused solid metal electrode, covered per use with a thin electrolyte layer, and an operator handle to manually press down. Used in some forms of ECT and not considered further here.

2.5 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.

2.6 Dry electrodes

Novel designs that are not adhesive and leave no residue (not liquid or paste). Dry electrodes remain in development (Fig. 7) [37].

2.7 Pre-salinated electrodes

Novel formed sponge electrode with pre-salinized foam spikes. Prior to positioning, the pre-salinated electrodes are saturated with water (Fig. 8).

Fig. 8 Formed sponge electrode with stimulator integrated into headgear. (**a**) Rectangular electrode with formed pre-salinized foam spikes. (**b**) Electrodes are incorporated in the headset with built-in stimulator. Prior to positioning, the pre-salinated electrodes are saturated with water. The foam spike design of the electrode ensures good contact between the electrode and skin, even in the region with hairs. (**c**) Headset with saturated and salinated foam spikes positioned over brain region

Table 1 Categories of tES electrodes and usability features

Electrode type	On hair?	Preparation?	Headgear required?	Focal optimization?	Electrodesizes
Sponge	Yes	Yes[a]	Yes	No	>25 cm^2
Self-adhesive	No*	No[c]	No[c]	No	>25 cm^2
HD	Yes	Yes[b]	Yes	Yes	~ 0.22 cm^2
Handheld	Yes	Yes[b]	No	No	>25 cm^2
Free paste	Yes	Yes[b]	No	No	>25 cm^2
Dry	Unknown	No	Yes	No	>25 cm^2
Pre-salinated electrodes	Yes	Yes[a]	Yes	No	>25 cm^2

[a] except single-use presaturated snap design
[b] And gel or paste residue cleanup
c except if supplement with additional preparation adding liquid gel

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

3 Electrode Resistance

The tES device is a current source with the electrodes and head completing the circuit. The resistance encountered by the tES device is the sum of the two electrodes and the head resistance, which includes the skin and underlying "internal" tissues (skull, brain, etc.). Measuring and reporting resistance is a feature of almost all tES

devices [34]. Monitoring of electrode resistance before and during tES is considered important for reproducibility and tolerability [27, 47, 66], specifically around issues related to electrode setup. An unusually high electrode resistance can indicate of undesired electrochemical changes and/or poor skin contact conditions.

The resistance measured by the device is the sum of the body resistance and the resistance of both electrodes, and the interface between the electrode and skin is included in this series [67]. Electrode resistance is typically very low, ~25 Ω. Internal body resistance is typically a few kΩ. The interface between the electrode and the skin can be relatively high and variable. It is thus the most important component of the resistance measurement by the tES device. The body resistance is a function of anatomy [68] and is not something that can be controlled or is necessarily a concern. The electrode resistance is low, unless a significant mistake has been made in setup. It is the resistance between the skin and electrode that reflects the quality of connection between the device and the body, and this resistance can increase with nonideal electrode placement. It is electrode-skin resistance that therefore provides useful information on how the device has been connected to the body. For any given tES device, there will therefore be a specific total resistance range that is considered typical and a resistance above this range may suggest nonideal electrode setup, in which case the operator may adjust the electrode setup to reduce the skin-electrode resistance. Some devices will deactivate if the resistance is atypically high, while other devices will adjust the current to compensate (e.g., "Limited Total Energy" (LTE); [67] or "Adaptive" [69]).

However, monitoring of electrode resistance does *not* reduce the need and importance of proper device design and electrode setup. For example, poor electrodes conditions may be associated with a low resistance and, conversely, in some cases (e.g., subjects with high resistance scalp) good contact may be associated with a moderately high resistance. Skin irritation and discomfort may be associated with high resistance, but not necessarily. Thus, monitoring of resistance is a supplementary tool to detect nonideal conditions at the electrode-skin interface, and *not* a substitute for quality electrode design and strict protocol adherence [6, 27, 66, 70].

4 Current Control and Voltage Limits

Electrodes play a central role in why current control (as opposed to voltage control) is typically preferred across electrical stimulation devices [24], including tES. When stimulation is applied to a body from a tES device the current must pass through electrodes before reaching the body, therefore the electrodes are always in series between the device output and the body. For the simplest case of two electrodes, the total impedance is the sum of the impedance of the two electrodes and the impedance of the body. The impedance of each electrode is unknown, variable over time, and changes with current applied [71], and can be significant compared to body impedance [24].

First, we consider why voltage control is not preferred: If one used voltage-controlled stimulation, the total voltage provided by the device will be distributed across the two electrodes and the body. But since the electrode impedances are unknown and changing, the voltage across the body is unknown and changing. The total current (which reflects the voltage divide by impedance) is also unspecified and changing.

We can now contrast this with current control stimulation. Here the current output of the device is controlled. The current is passed through the two electrodes and body, all in series, so the current across the body is controlled. The voltage output of the device is therefore adjusted to keep the current controlled at the target level. This voltage divided by the current is the impedance of the system – also called dynamic impedance to specify impedance during stimulation as opposed to static impedance prior to stimulation (see resistance below). Current control therefore accommodates for the unknown, variable, and significant impedance presented by electrodes. Arguably with current control, one does not know the voltage generated across the body, but this can be predicted knowing the body's resistive properties (see "▸ Modeling "). Moreover, the voltage across the body will not depend on electrode impedances during current control, and rather will be set by the controlled applied current times the body impedance.

Since under current control the voltage will increase with total path resistance, under situations of unusually high resistance the voltage may increase to the limit of the current control device, also called device voltage compliance. For limit intensity tES devices this voltage compliance is typically on the scales of tens of volts (e.g., 40 V; [67, 69]).

The voltage compliance is conventionally set to accommodate passing the maximum target current under expected maximum resistance (e.g., with a target of 2 mA, and maximum resistance of 20 KΩ, 40 V is sufficient). In practice, the impedance may increase outside of expected or desired ranges, for example, as a result of poor electrode setup (see "▸ Resistance "). In such cases the device output may reach voltage compliance, and the device will not be able to provide the desired current. Depending on design, devices may respond to voltage compliance in different ways. Some devices may simply abort stimulation, while other devices may continue to stimulate with reduced current. Because current passage itself reduces current, maximum impedances are often encountered at the start of stimulation. Therefore, voltage compliances are often increased to accommodate this higher initial impedance. However, given that impedance would drop, one proposal for limited voltage stimulation was to provide output with moderate voltages, expecting voltage compliance to be reached at the start of stimulation, but for gradual impedance reduction to then reduce voltage, allowing target current to be reached [67]. There are various reasons to minimize voltage from simplifying circuity or power requirements, reducing stimulation energy, or providing redundant tolerability measures in susceptible populations or use cases [72].

5 Applications That tES Is Used for (Clinical Indications)

tES spans many clinical and behavioral interventions, and as noted many subtechniques [73] such as tDCS, tACS, and tPCS. What these different techniques share is that they all apply electricity to the brain through electrodes on the scalp [6, 13, 74–76]. tES can then lead to measurable changes in behavior and cognition ([39, 77–79]. Since tES changes brain function, the clinical indications for tES are neurological or psychiatric disorders such as depression [14, 80–82], schizophrenia [83, 84], attention deficit hyperactivity disorder (ADHD) [85, 86], addiction [87–89], and chronic pain [90–92].

From the perspective of the device, the dose is designed and selected to achieve specific changes in brain function and so clinical or cognitive outcomes. There is a large parameter space of dose, including the electrode montage (e.g., how many, what size, and where) and features of the waveform (e.g., intensity and frequency). The electrode montage is generally considered to determine which brain regions are influenced, by placing electrodes over or near parts of the brain that are targeted, whereas waveform determines how those targeted brain regions 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 [5, 93–97]. tES clinical trials intending to treat pain disorders, such as migraine [98–101], fibromyalgia [102–104], and craniofacial pain [105, 106], often target the primary motor cortex (M1) with an electrode [107]. In reality, where to place electrodes to get current to targeted brain regions is not simple, and computational models of current flow, discussed next, are used in montage design.

6 Current Flow Modeling Informs Device Design and Setup

Current that is injected through the tES electrodes takes a path through the head that is determined by the head anatomy and the resistivity of each tissue type. The resistivities of different tissues in the head (such as skin, skull, and brain) vary. Resistivity of each tissue is expressed in ohms meter. A fraction of the current is "shunted" between the electrodes by the skin, so never crosses the resistive skull to reach the brain [108]. Of the current fraction that crosses the skull, a further portion is shunted by the highly conductive cerebrospinal fluid (CSF) that surrounds the brain. Finally, the fractional current component that reaches the brain crosses the grey and then the white matter. As current crossing the brain spread outs, each brain region may receive a different amount of local current. This is measured as current density, current per unit area (A/m^2). Alternatively, the current reaching each region can be expressed as an electric field (V/m). The electric field equals the current

density times the resistivity (1/conductivity) [97]. The electric field is thus induced around the neurons in the brain, and leads to change in their membrane voltages, being polarized.

Electrode size positioned on the scalp along with the current applied to each electrode defines the tES dose [109]. Not only tES dose but also individual head anatomy determines the resulting current flow intensity and pattern through the brain [110, 111], and so resulting neurophysiological and behavioral changes [112]. However, the current flow pattern in the head is complex and is not simply "under" the electrodes and will vary across individuals. The task of current flow models is to relate dose (as controlled by the device) and resulting brain current flow. While dose is what is specified, it is brain current flow that underpins interpretation of outcomes.

Computational models are a key tool in relating dose (controlled at the scalp by how the device is placed and programmed) with resulting brain current flow. However, for current flow models to be accurate, they must correctly represent the shape and resistivity of head tissues (e.g., skin, skull, CSF, and brain). Computational models have been developed [25, 29, 113–118], and repeatedly validated [108, 110, 119–121] over a decade. Approaches invented using computational models, such as HD-tDCS, has been validated [39, 57, 74, 108, 119] and applied [41, 52, 53, 122, 123]. Models can optimize a montage to target specific brain regions [25, 124, 125] which can be done at the population average or individual level [126]. Because the same dose will produce different brain current flow patterns across subjects, models can also support individual analysis [57, 127, 128]. Current flow models can also be compared with imaging data [129].

Thus, computational model is a key software used to inform the design, setup, 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 a new device technology. For example, a home-based system relying on adhesive electrodes would restrict positional electrode location to explore with models below hairline [130], which in turn simulate the development of simple-to-use electrodes that can go over hairline [47]. The potential for focal transcranial stimulation was suggested first by models [29], but it was not until practical HD electrodes were developed [26] that approaches to optimize transcranial stimulation using HD arrays could be tested.

Clinically applied tES protocols are generally designed and optimized in finite element method (FEM) forward models [39, 111, 131–133]. These FEM models educate researchers about the resulting current flow (intensity and pattern) [29, 39] and so the resulting neurophysiological and behavioral changes are based on tES dose (mA), resistivity of head tissues (e.g., skin, skull, CSF, and brain), and head anatomy [132, 134]. Computational models are thus an ancillary tool used to inform the design, setup, and programming of tES devices, and investigate the role of parameters such as electrode assembly, current directionality, and polarity of tES in optimizing therapeutic interventions.

Forward modeling results are generally interpreted under the quasi-uniform assumption [4, 111, 131]; however, note that the prediction of the clinical efficacy

requires additional insights about the underlying brain functions. The quasi-uniform assumption is based on a proportional relationship between neuronal excitation and the local electric field magnitude [135–138]. The quasi-uniform electric field/current density representation is only an approximation for predicting the effects of tES, which is nonlinear, time-dependent, and coupled system. Nonetheless, for conceptual and practical reasons, most tES models depend on the quasi-uniform assumption (as evident by the predictions of electric field/current density distributions). Moreover, the fact that it is nearly impossible to replicate tES-induced electric field gradient across even a single hypothetical neuron between species – much less across the entire population of neurons – makes the quasi-uniform assumption a technical necessity in translational animal models.

Furthermore, computational modeling is the framework to rationally organize empirical data, formulate quantitative hypothesis, and test new interventions [29, 37, 42, 119, 139, 140]. However, developing *useful* computational models requires the right balance of detailed multiscale model with appropriate reductionism [141–146]. A central motivation for modeling of stimulation devices is that the interventional parameter space (stimulation dose, timing, task, subject selection, etc.) is too wide, given the cost and potential risk of human trials [126] – there are simply too many device design and treatment protocol decisions to test (for every possible combinations). Computational model is thus necessary for rational optimization of neuromodulation protocols to target specific brain regions [147, 148]. Especially at an early device design and optimization stages, such efforts are especially constrained [141, 149].

Computational FEM modeling is also the bridge by which data from animal studies (preclinical testing) can be rationally incorporated into methods for interventions. The reason for this is when trying to adapt a successful tES intervention from an animal model (e.g., effective control of epilepsy in a rat model), it is not appropriate to simply scale the dose from animal size to human size (e.g., if a human is 5.5 times bigger than a rat, we cannot simply apply 5.5 times the current intensity), rather models are needed to decide on how all aspects of dose (intensity, electrode size, and position) should be designed for human experiments based on animal trials. This also applies when relating animal safety data to guidelines for human tES [4, 18].

When new devices and electrodes are tested, computational modeling is used to interpret results and inform future design iterations [37, 71, 91]. Finally, computational models can be stand-alone tool to address mechanisms of action or safety concerns [66, 150], with the need for any human or preclinical testing.

Across the various uses, the computational modeling pipeline of tES starts with segmentation of an anatomically precise (voxel size: 1 x 1 x 1 mm^3) magnetic resonance imaging (MRI)-derived head model into multiple tissue compartments, typically scalp/skin, fat, skull, CSF, brain gray matter, brain white matter, and air. The basic MRI-derived pipeline was established in 2009 [29] and continues to be used to date with various enhancements [140, 151–154]. Electrodes of variant shapes, dimensions, and materials are then positioned over the brain target (just as they would be on a real person), and a volumetric mesh is obtained with optimal

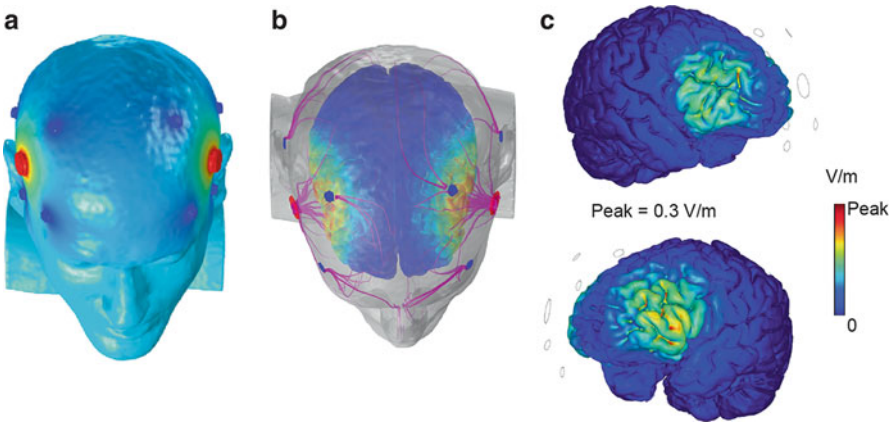

Fig. 9 Computational FEM head models and predicted field intensity of dual-hemisphere tES montage. (**a**) Customized HD-tES electrodes (center large and surrounding standard size) positioned bitemporal on an MRI-derived segmented head. (**b**) Represents an orientation of magnitude controlled electric field streamlines inside the head tissue layers during tES. (**c**) Volume plot of predicted field intensity and different views (side views) of brain under stimulation conditions. Predicted results plotted at same color range (Peak = 0.3 V/m) indicated comparable and focal field intensity on both sides

mesh quality (quality determined by multiple mesh density refinement approaches). The volumetric mesh is later imported into a numerical solver to generate a FEM. Tissues and electrode conductivities are assigned based on prior literatures [131, 133]. Boundary conditions are applied as a normal current density (inward current flow: *Jnorm*) at the top exposed surface of the anode and ground, at the top exposed surface of the ground electrode (cathode) – though the physics of current flow are symmetric and this can be reversed. Remaining other external surfaces of electrode are electrically insulated. The model is then solved using Laplace equation for electric current physics under steady-state assumption ($\nabla\ (\sigma \nabla V) = 0$; where V is the potential and σ is the electric conductivity of each compartment), and the current density/electric field is predicted (Fig. 9).

7 Mechanisms of tES

The brain is an electrical organ, and the characteristic cells of the brain, neurons, are each electrical. Neurons in the brain have an electrical voltage across their membranes (polarization) where changes in this polarization underpin how neurons, and so the brain, function. All brain functions, such as attention, learning, and memory, are in this sense electrical processes. Similarly, all disease of the brain can be conceived of as nonoptimal electrical processing of the brain. Given the brain is an electrical organ, it is not surprising that brain function is responsive to tES. While there are open questions about the detailed mechanisms of tES, the general mechanisms of tES related to current delivery to the brain and the resulting changes in the neuronal membranes voltages ("polarization") are well known [155, 156]. The

polarization produced by tES is the initial mechanism of action, with subsequent more complex changes in function secondary to this polarization [157, 158].

The peak electric field in the brain during 2 mA tES is about 1 V/m [110, 119, 121]. In contrast, ECT applies ~700 mA or current producing electric field of about 300 V/m [159–161]. This difference is important. Whereas ECT (and most invasive brain stimulation techniques) produces high-intensity electric fields in the brain (> 100 V/m), low-intensity tES approaches, including techniques like tDCS [157, 162] and tACS [9, 163–165], produce weak electric fields (< 1 V/m). Low-intensity tES produces a small amount of membrane polarization, about 1 mV, which modulates ongoing brain activity. ECT produces much more polarization, about 100 mV or more, which overrides brain activity.

The neurophysiological and so behavioral consequences of tES will depend on how the resultant neural polarization then influences excitability and plasticity [157]. ECT produces so much polarization that it overruns ongoing brain function to such an extent that ECT can, by design, produce seizures. The seizures due to ECT act as a "reset" for the brain, intended to lead to improvement in symptoms of disease like severe depression. Because low-intensity tES produces only incremental membrane polarization, it does not overrun existing brain activity, rather it adjusts ongoing activity [9, 162, 166–170]. The activity of the brain during low-intensity tES therefore influences how low-intensity tES changes brain function [9, 171–175]. For example, if an individual is learning a task during tES, the brain processes activated by the task could be modulated by tES.

The ultimate consequences of low-intensity tES on macroscopic measures of neurophysiology (e.g., TMS) and behavior (e.g., therapy) will be complex [176–180], and subject to extensive ongoing research [10, 126, 181–183]. There is currently enough basic science supporting tES to inform how devices can be designed and programmed in order to test hypothesis related to brain function and therapy [41, 54, 184–186]. At the time, there is tremendous potential for new and improved tES technology to change how technology interfaces with the brain and can be used to deliver personalized therapy.

8 Safety and Tolerability

One of the factors driving testing and adoption of low-intensity tES is the perceived tolerability [48, 187–190]. Low intensity is considered safe in the sense that there is no evidence for long-term harm or serious adverse effects associated with the stimulation [16, 18, 191, 192]. For the most common types of tES, side effects (adverse events) are considered minor and transient, such as tingling or itching perceived under the electrodes that ceases at the end of the stimulation. Indeed, more human trials of tES are conducted on the designation of nonsignificant risk (NSR), which is comparable to the risk of simple day-to-day activities. Because of the well-known safety and tolerability profile of tES, it is also tested widely on the healthy subjects for any changes in cognition or behavior [28, 193–199] – implicitly it is therefore understood that low-intensity tES trials would not be common among

healthy volunteers (e.g., college students) if there were any real perceived risks. Finally, in this sense, any decisions about the clinical use of low-intensity tES (as with any medical intervention) would balance the perceived benefit with this NSR risk [16, 20, 87, 200].

The aforementioned points are to suggest that one should be cavalier about safety. When established protocols [6] are not followed and/or poor equipment are used, a significant skin irritation can occur. Equipment, headgear, and electrode designed for tES by trained professionals may not be suitable for home use, such that special protocols (e.g., remote supervised tDCS; [85] and equipment may be preferred [201]. For example, while multistep electrode preparation with manual fluid application is common for at-center tDCS/tACS protocols [27], fully prepackaged electrodes are preferred for home use (Fig. 4, [19]). In general, it should be emphasized that safety and tolerability do not apply universally to a device, but rather to a device in the context of how it is used. The use of new devices or devices in new ways require consideration if any changes introduce new risks.

9 Discussion: Controversies and Future Directions

Low-intensity tES, including tDCS and tACS, is among the most actively developed, investigated, and debated emerging technologies to change and study the brain. These techniques have been tested for a very broad range of clinical disorders and to modulate various brain function in healthy individuals. The sheer breadths of application have led some outsiders from the field to broadly criticize tES. However, for those working in the field, it has always been recognized that low-intensity tES is a form of neuromodulation that interacts with ongoing activity – and in this way, specificity derives not just from selecting a tES dose but from how stimulation interacts with an underlying brain activity [166, 167]. Another concern raised by individuals not familiar with the techniques is that the electric field produced in the brain are too "weak" to stimulate neurons. However, this fact not only has been exhaustively quantified by researchers in the field [29, 119] but in fact substantiates how these techniques are hypothesized to work – *not* by triggering (pacing) action potentials, but by *modulating* ongoing brain activity [171, 174, 202–205]. Thus, that low-intensity tES is "weak" in regard to brain electric fields is considered a feature supporting specificity, while the low power required as a result of low-intensity tES devices underlies their usability (e.g., battery powered) and tolerability.

There are several important areas of ongoing development and research. (1) Device technology continues to be enhanced: on the one hand making devices simpler and deployable (e.g., for home use; [19, 37, 206]), while on the other hand increasing device sophistication with more channels and feedback [41, 207–209]. (2) Interindividual variability in responses should be minimized, which can be accomplished using computational models to normalize dose [132, 134, 210] or functional imaging to identify personalized targets [41, 211–214]. (3) In this last regard integration of tES with EEG is compelling since both technologies can be in the same headgear [207, 215, 216] and the principle of "reciprocity" can be used to

guide stimulation to active brain regions, provided artifacts can be managed [63, 64, 217]. (4) A further area of research is increasing dose [218], however high currents should be linked to optimized hardware/electrodes to maintain good tolerability [69, 190].

Conflict of Interest The City University of New York (CUNY) has IP on neurostimulation systems and methods with authors NK and MB as inventors. MB has equity in Soterix Medical. MB served on the advisory boards and/or consulted for Boston Scientific, Mecta, Halo Neuroscience, and GlaxoSmithKline Inc.

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