Transcranial Electrical Stimulation

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Abstract

Transcranial electrical stimulation (tES) includes a range of devices where electric current is applied to electrodes on the head to modulate brain function. Various tES devices are applied to indications spanning neurological and psychiatric disorders, neuro-rehabilitation after injury, and altering cognition in healthy adults. All tES devices share certain common features including a waveform generator (typically current controlled), disposable electrodes or electrolyte, and an adhesive or headgear to position the electrodes. tES "dose" is defined by the size and position of electrodes and the waveform (current pattern, duration, and intensity). Many subclasses of tES are named based on dose. This chapter is largely focused on low-intensity (few mA) tES. Low-intensity tES includes transcranial direct-current stimulation (tDCS), transcranial alternating-current stimulation (tACS), and transcranial pulsed-current stimulation (tPCS). Electrode design is important for reproducibility, tolerability, and influences when and what dose can be applied. Stimulation impedance measurements monitor contact quality, while current control is typically used to ensure consistent current delivery despite electrode impedance unknowns. Computational current flow models support device design and programming by informing dose selection for a given outcome. Consensus on the safety and tolerability of tES is protocol-specific, but medical-grade tES devices minimize risk.

Keywords

Transcranial · Electrical · Stimulation · tES · tDCS · tACS · tPCS · Neuromodulation · Electrode design · Noninvasive · Medical devices

8.1 Basics of tES Devices and Dose

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. The electrode number, shape, and location are collectively the montage. There are minimum of two electrodes. The waveform is produced by a powered device that can be directly attached to

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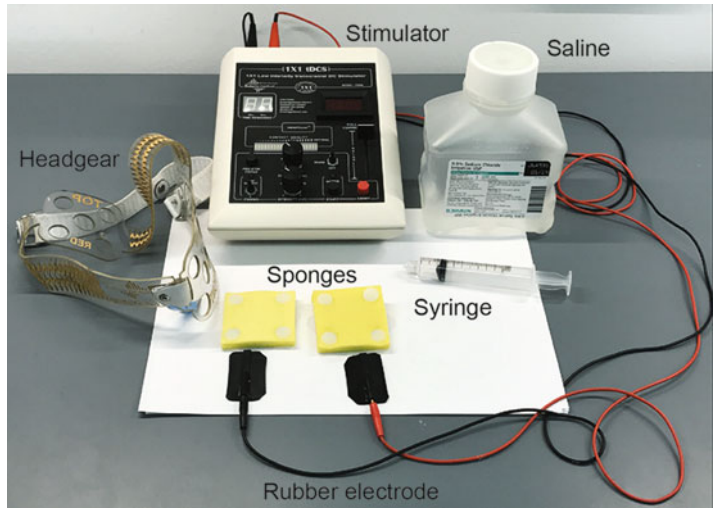

Fig. 8.1 Example of a tES device and material used for electrical stimulation with sponge electrodes. Shown are conventional sponges (yellow) soaked with a controlled volume of saline using a syringe. Each electrode is made of two layers of sponge. Conductive rubbers (electrochemical electrodes) are placed inside the sponge layers. Lead wires connect the device to the conductive rubber electrodes. Sponge electrodes are then secured on the scalp using a headgear. For the case of tDCS, the rubber electrodes are energized using corresponding anode and cathode wires connected to the stimulator

the electrodes using connector leads (Fig. 8.1). A headgear is used to hold the electrodes in the desired positions, or the electrodes are adhesive. If the device is small, it may be attached to the headgear, but more typically it is a handheld or benchtop device. Electrode design is key for tolerability (side effects) and what doses can be applied; as such electrodes are a key consideration in device design and considered in this chapter in detail.

Subclasses of tES are defined by a specific dose. 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) [1]. This chapter is largely focused on low-intensity approaches that are well below the intensity needed to produce seizures, typically only a few mA [2]. 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 (e.g., 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.

When the waveform generated by the device is sinusoidal alternating current (AC) stimulation, tES is classified as transcranial alternating current stimulation (tACS) (Fig. 8.2d). 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 a train of pulses, tES is called transcranial pulsed current stimulation (tPCS) (Fig. 8.2a). There are many further subclasses (variations) of tPCS waveform including in duration of each pulse, pulse frequency, and if pulses are monophasic or biphasic (Fig. 8.2a,b,c,e,f). 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

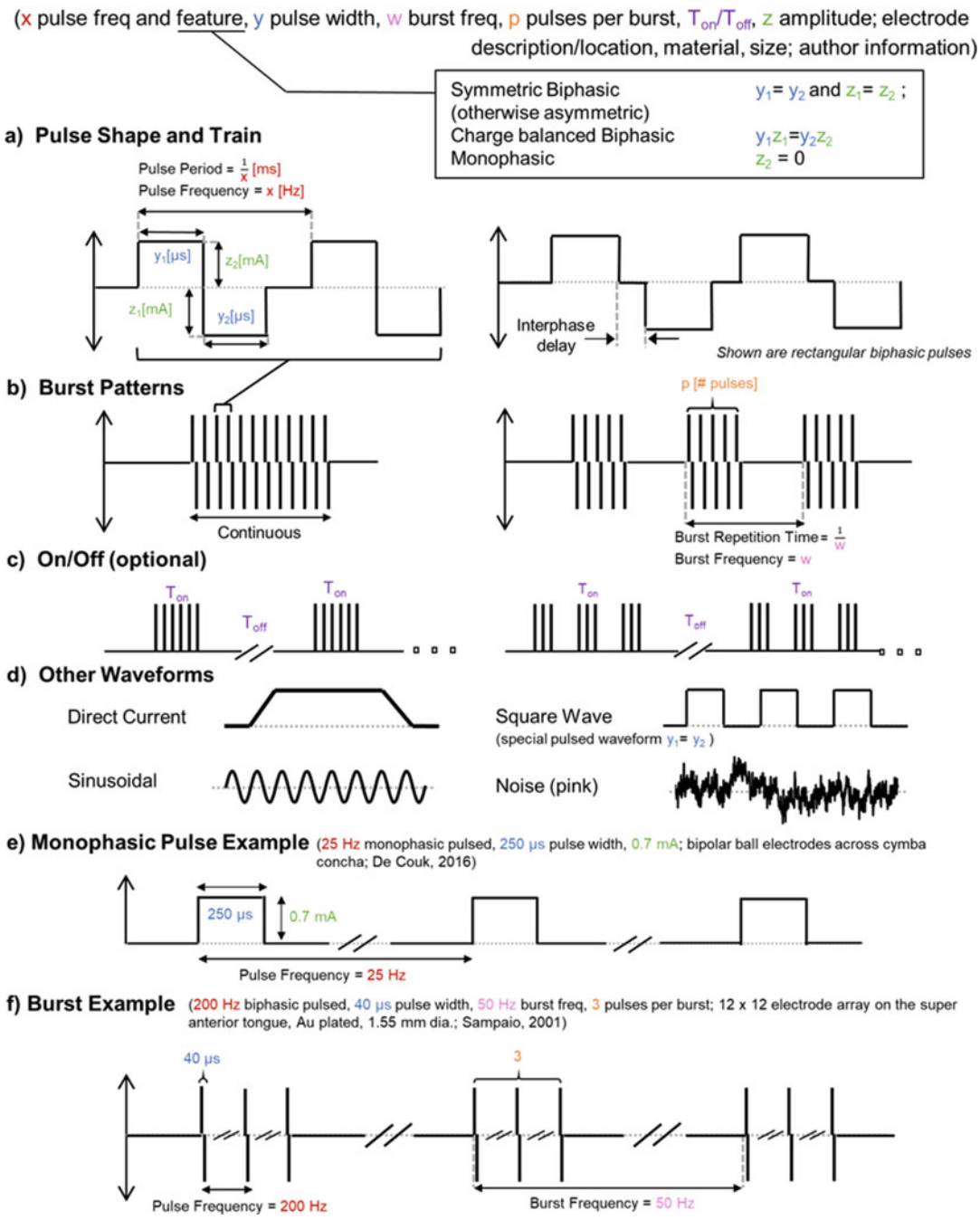

Fig. 8.2 Different types of waveforms used in tES and their parameters. (**a**) The pulse shape includes the pulse duration and amplitude. In biphasic stimulation, pulses are applied in pairs of opposite polarities. The opposite polarity pulses may have the same or different duration and amplitude. The pulses are delivered in trains with a frequency. (**b**) Pulse trains may be continuous or applied in bursts, typically on the scale of hundreds of ms. (**c**) On/off protocols indicate when stimulation is applied intermittently, typically on the scale of minutes. (**d**) Non-pulse waveforms that are applied include DC, AC, square wave, and various forms of noise. (**e**) and (**f**) show examples of how all the waveform features in aggregated define dose

that invert polarity, typically in paired opposite-polarity pulses (i.e., positive, negative, positive, negative, etc.) [3].

When the waveform is a sustained direct current (DC), tES is classified as transcranial direct-current stimulation (tDCS) (Fig. 8.2d). Additional terminology refers to further variations in waveform such as transcranial random noise stimulation (tRNS) and cranial electrotherapy stimulation (CES). A single tES device may be programmable to deliver different 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 made for treatment, especially self-application by patients, provide one or a limited number of waveforms.

Many tES devices will include an intensity ramp up and ramp down. The ramp up and down is considered to increase the tolerability of tES, as skin sensation can accommodate over time, for example, a 30-second linear increase in amplitude at the start of a session. Some tES devices include an interface for subjects or operators to adjust intensity in real time based on sensation, which then reduces the intensity if the subject reports high levels of discomfort [4].

A tES device is essentially a (medical-grade) powered 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, the use of small electrode arrays is classified as high definition (e.g., high-definition tDCS [5–7], high-definition tACS [8]).

The anode electrode is defined as the electrode where current enters the body, and at the cathode electrode, current exits the body [3]. 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. For tES devices where the waveform is biphasic, such as tACS and biphasic tPCS, each electrode alternates between functioning as an anode or cathode. 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 [9] – that is because of conservation of current where the total current entering the body must equal the total current exiting the body.

8.2 General Design Aspects of tES Electrodes

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 [10]. Because adverse events are limited to the skin, the design and preparation of tES electrodes are considered central to tolerability. Electrode design, in turn, can govern which waveforms will be tolerated. When established electrode protocols are not followed or poor electrode design used, tES produces unnecessary significant skin irritation and burns. Electrode design also underpins reliable dose delivery. In addition, electrode design should also address ease and robustness of use (e.g., potential for home use). For clinical trials, since sensations also determine effective blinding, tES electrodes also impact blinding reliability. Finally, to the extent tES electrode design (separate from montage) shapes current flow through the brain [11], and electrode selection and preparation are critical for the reproducibility and efficacy.

The typical tES devices uses just two electrodes, of comparable size, each positioned on the head [12]. However, strategies with asymmetric

electrode size, an electrode at or below the neck [13], or increasing number of electrodes (using high-definition electrodes) have been investigated to alter tES spatial focality.

Electrodes can be positioned based on head anatomical landmark. These can be modestly sophisticated requiring a trained operator, for example, using the EEG 10/10 system (e.g., anode on C3), while more simplistic placement techniques are based on gross anatomical landmarks (e.g., over the eyebrow). When a headgear is used, it is either designed to support the determination of specific electrodes positions (e.g., a cap or marked straps [14]), or the headgear is used for generic mechanical support (e.g., rubber bands [15]), and so independent measurement is used to position the electrodes. More sophisticated placement techniques such as neuronavigated [16–18], functional [19], non-neuronavigated [20], or image-based approaches (e.g., EEG reciprocity [21]) have been developed.

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 [12]. 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 [3], 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 when electrode size is described (e.g., 5 x 5 cm^2), it is the interface (surface) between the skin and the electrolyte. Nonetheless, the configuration of all electrolyte and electrochemical-electrode dimensions and materials is important to control and document as this affects tolerability [12, 22–25]. 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 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, pre-saturated sponge electrodes).

There are two essential functions of the electrolyte and by extension materials used to support the electrolyte shape such as sponge, hydrogel polymer, and/or other support materials that contain a viscous electrolyte (such as the HD case). Both functions of the electrolyte relate to preventing direct contact between metal/conductive rubber electrode and the skin. The first function relates to electrochemical products, including changes in pH, that occur only at the metal/rubber and electrolyte interface [26] such that a "thick" electrolyte (e.g., realized by a thick sponge, gel, or holder) minimizes these reactions from reaching the skin. 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 [5, 27, 28]. 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 is 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 hot spots) and preventing any electrochemical reactions (occurring at the electrochemical electrode) from impacting the skin. Because electrochemical concerns are key concern, all electrodes designed for tES include some mechanism to separate the metal/rubber from the skin. The electrolyte being

Table 8.1 Categories of tES electrodes and usability features

Electrode type	On the hair?	Preparation?	Headgear required?	Focal optimization?	Electrode sizes
Sponge	Yes	Yes[b]	Yes	No	Large
Self-adhesive	No[a]	No[a]	No[a]	No	Variable
HD	Yes	Yes[c]	Yes	Yes	Small
Handheld	Yes	Yes[c]	No	No	Large
Free paste	Yes	Yes[c]	No	No	Large
Dry	Unknown	No	Yes	No	Variable

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

the conductive element contacting the skin thus takes on importance in general performance. As expanded on it in the following sections, the design of the electrolyte (any by extension all support materials used around it) thus features centrally in 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. The sponge sets the electrolyte shape and conductive path.
2. *Self-adhesive integrated electrode*: A hydrogel electrolyte that has 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 position of the metal. Used for smaller electrodes and so suitable for arrays.
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.
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 that are not adhesive and leave no residue (not liquid or paste). Experimental and not discussed in detail here.

These choices between these general design approaches also create restrictions (Table 8.1) 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 the hair.

8.3 tES Electrodes: Sponge Electrode

The sponge-based electrode is the most common type of electrode in some forms of tES such as tDCS, tACS, and tRNS (Fig. 8.3, [29]); notably in these techniques, electrode positions over hairline is common for which the sponge electrode is well suited [30]. Sponge electrode require a headgear to hold them in place (as opposed to self-adhesive electrodes) which can take the form of a headband. Sponge electrodes increase the contact quality even in the areas of the scalp with thick hairs because the electrolyte (saline) penetrates under the hair and saturates the skin surface skin [31]. A related concern of using sponges is that sponge is prone to leaking which distorts the "effective" electrode size making stimulation not reproducible [27] – for this reason, the volume of saline added to the sponges should be carefully calibrated (to the sponge model, size, and application), and caps (e.g.,

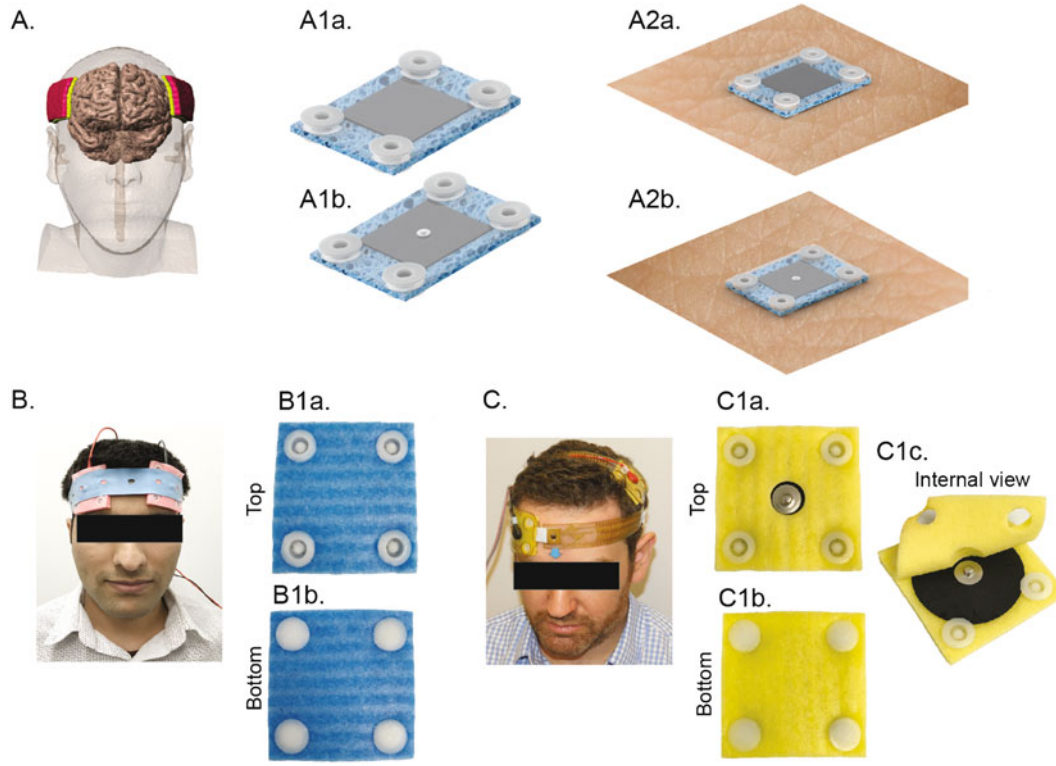

Fig. 8.3 Architecture of sponge electrode and its variations. (**a**) Example of electrodes positioned on the scalp with the intention to stimulation transcranially the brain. (A1a, A1b) Examples (CAD) of minor variations in sponge electrode design that can make significant differences in usage. Both 5×5 cm^2. In both cases, a conductive rubber electrode is placed between saline-soaked sponges (top sponge for illustration), but in one case, a metal snap is attached to the conductive rubber electrode. (A2a, A2b) Renders of same sponges positioned over the skin surface. (**b**) 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. (**c**) 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

neoprene) may be avoided since it both obscures and supports fluid spread. There are important methodological and design details in sponge electrode design and preparation [27].

As used in tDCS, tACS, and tRNS protocols, sponge electrode pads have a rectangular skin contact area of 25 cm^2.The contact area is the interface between electrolyte-saturated sponge and skin. For sponge electrodes, selection and positioning of the conductive carbon rubber sheath or metal can be varied. For example, Soterix Medical (EasyPad, Soterix Medical Inc., NY, USA) provides rubber electrode embedded inside a rectangular sponge pocket and uses plastic rivets to hold the rubber in place. In the NeuroConn sponge electrode (neuroCare, Munich, Germany), the rubber sheath is inserted into a sown rectangular sponge pocket. In both cases, the rubber electrode is smaller than the outer dimensions of the sponge. In the Amrex-style sponge electrode (Caputron, NY, USA) a metal electrode is placed behind the rectangular sponge, and an insulating rubber encases the metal and sponge, except on the skin contact side. These reusable conductive rubber electrodes typically include a female port which is connected to a male banana clip or pin-terminated wire from the stimulator. CES devices can use circular sponges soaked in tap water (Fisher Wallace electrode, New York, USA). Relatively small

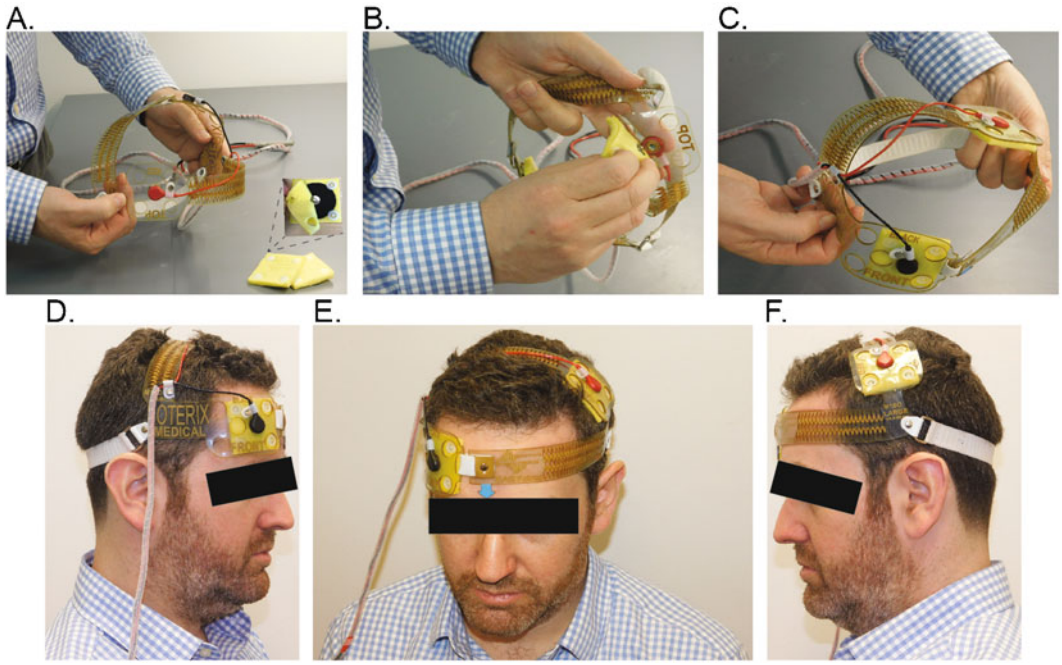

Fig. 8.4 Example of sponge electrode headgear for automatic electrode positioning. (**a**) The components include the headgear with integrated snap leads and two snap sponge electrodes. (**b**) The two snap sponge electrodes are connected to the two available positions on the headgear. (**c**) The headgear assembly can then be placed on the head. (**d**–**f**) Different views of head-strap placement on a subject head. The headgear with fixed-position sponge locations ensure the electrodes are placed in the desired positions. Using different headgear electrodes can be placed in different locations. Having one position per headgear reduces the possibility for setup errors

disposable felt electrodes that are saturated in saline are used in some CES devices with ear clip electrodes (Alpha-Stim, Texas, USA). Nonsalinized water is less common and for some applications like tDCS, it is contraindicated [27]. When water is used, residual electrolyte must be present either as impurities (tap) or absorbed from the skin.

There are updated variants on the sponge electrode design. The conductive rubber may be semipermanently embedded into a circular (Sponstim, Neuroelectrics, Spain) or rectangular (EasyPad-2, Soterix Medical Inc., NY, USA) sponge with a male metallic connector attached to the rubber and emerging through the sponge (on the side opposite the skin contact). The male connector can be affixed to a female connector on the headgear directly. As with other sponge electrodes, the electrodes can be reused or are single use – for a single use, electrodes are further available as pre-saturated so requiring no preparation (Soterix EasyPad-2, Fig. 8.4). A further variation is a more rigid sponge with bristles that enhances penetration through hairs and sponge materials embedded with salt in a manner that only water can be added over multiple uses (Halo Neuroscience, San Francisco, CA). Along with new types of associated headgear (e.g., home use) [32] and connectors (e.g., magnetic), these examples illustrate that even with the conventional sponge electrode paradigm, there is an ongoing innovation often focused on ease of use (e.g., preassembled and saturated) or reliability (e.g., sponge surface shape).

8.4 tES Electrodes: Self-Adhesive Electrode

Self-adhesive electrodes adhere to the skin surface and typically require minimal preparation – this makes them easy to use at locations without

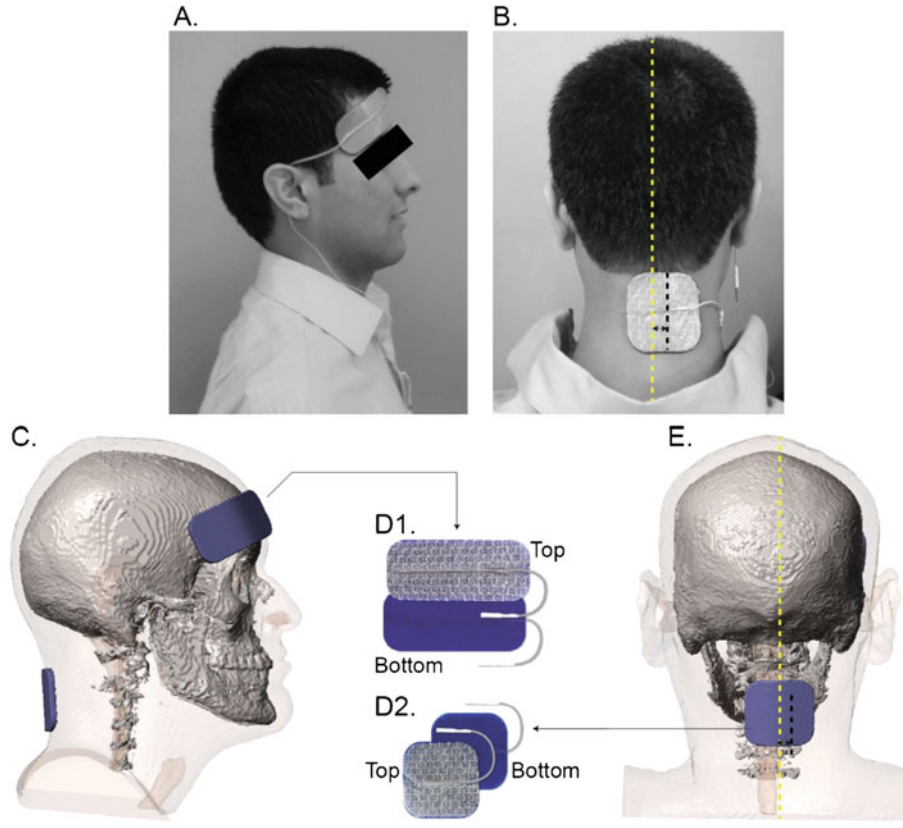

Fig. 8.5 Illustration of adhesive hydrogel electrode (**a**, **b**) placement of rectangular anode on the subject's right temples. Generally, adhesive electrodes or restricted to placement below the hairline. In this case, a square cathode electrode positioned about 1 cm to the right of the subject's midline on the back of the neck. (**c**, **e**) Representation of analogous electrode positioning as **a** and **b** on a head model. (**d**) Image of the adhesive electrode is in the middle column. The bottom of the electrode has an adhesive hydrogel for adherence with the skin, whereas at the top, there is electrochemical metal mesh electrode

significant hair [33] but do not work well on hairline. Self-adhesive electrodes are often used with tPCS waveforms (Brainpod, Caputron, NY, USA) and also with ECT (Thymapad, Somatics, FL, USA). In their simplest design, the bottom of the electrode has a layer of conductive hydrogel along with an adhesive material; over this layer is a conductive wire, rubber, or metal; and over either of them is a layer of insulation (see Fig. 8.5D2). In some designs, the metal may be connected to a short cable with a female pin connection (the cable from the stimulator can be connected to this female pin), or the metal may be connected to a snap connector that protrudes through the insulation layer. When the device is handheld, the lead wire from the device extends to the connector on the electrodes. When the device is "wearable," it may connect directly to the adhesive electrode, and the adhesion may, in some cases, be sufficient to hold the device to the head.

Because DC stimulation is electrochemically demanding [5], adhesive electrodes have been used only in a limited number of tDCS trials [33] and devices (Zendo E-Meditation), but self-adhesive electrodes are common in other applications where biphasic pulses and AC stimulation are used such as cranial nerve electrical stimulation [34]. Self-adhesive electrodes designed and validated for one stimulation dose may not be tolerated for other doses.

Many approaches that use adhesive electrodes for head stimulation are intended to activate cra-

nial nerves (or peripheral nerves) so as such are not "transcranial" and are, therefore, outside the scope of this chapter. Still, insights from cranial stimulation devices can inform tES devices. Cranial nerve stimulation devices have used handheld device form factors (Monarch, NeuroSigma, CA, USA) but also compact device that snap directly the adhered electrodes (Thync pad, CA, USA, and Cefaly, CT, USA) – making the entire system wearable. Technologies intended to stimulate cranial nerves can have electrodes of varied separation, ranging from distant electrodes across the head to proximal (adjacent) electrodes. The latter case produces local superficial current flow-suited stimulation of cranial nerves at the skin, but not transcranial. In the former case, the two distant electrodes are presumably stimulating two targets – though this is also increased current through the head (transcranial). For this reason, transcranial systems with adhesive electrodes avoid adjacent electrode placement (e.g., placed as a distance across the forehead) [33]. These last points relate to a broader debate within the noninvasive neuromodulation [35]; regardless of whether a system is called "transcranial" or claimed to target cranial nerves, there can be significant overlap in dosage between such systems. With verification of target engagement (what nervous system element is activated and correlated with outcomes), the targets of these devices can be speculative. For CES devices which include models of adhesive electrodes (Caputron, Mindgear, NY, USA), there may be indefinite target engagement (cranial nerve, brain [36], or a combination of both).

8.5 tES Electrodes: High-Definition Electrode (HD Electrode)

High-definition (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 [5]. Suspended inside the gel is a metal ring, disk, or pellet made from Ag/AgCl. The gel and metal are thus positioned by the interior dimensions of HD cup. The design of the HD cup controls the important factors of gel contact area with the skin and the distance between the metal and the skin (Fig. 8.6). 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

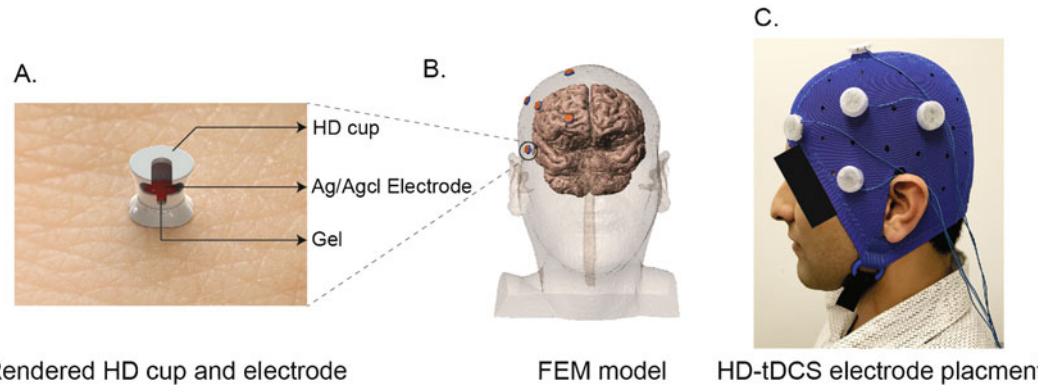

Fig. 8.6 High-definition (HD) electrodes. (**a**) In contrast to other types of tES electrode, HD electrodes are relatively small. (Render) An HD cup is placed on the skin and contain the metal electrodes (Ag/Agcl) and the electrolyte gel. (**b**) Because HD electrodes are smaller, they can be arranged in variation configurations on the head. Shown is the 4 × 1 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 4 × 1 HD electrode assembly on a subject head. Electrodes are secured in a 4 × 1 configuration using a specialized head cap

and/or precise placement [9, 37, 38]. A common HD montage is the 4 × 1 ring montage where a ring/circular fashion using four "return" (cathode) disk electrodes is arranged around an "active" (anode) electrode at the center [6, 7, 39, 40]. 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. The HD electrodes are held in place using a cap headgear, and a conductive electrolytic gel is filled into the electrode holders. Note that in contrast to sponge electrodes, here a cap does not introduce issues related to electrolyte spread since the gel is well confined by the HD cup.

Various waveforms can be applied in HD-tES. HD-tDCS uses tDCS waveforms [37, 38, 41, 42]. HD-tACS uses AC waveforms [8]. Still other waveforms are specific to the use or arrays such as interferential stimulation [43] or high-intensity pulses [44]. Multiple brain regions can be targeted with HD-tES [8].

The form factor of HD-tES cups superficially resembles 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 recording before HD-tES (e.g., to measure baseline state of inform stimulation strategy; [45]) or after HD-tES (to measure outcomes; [46]) is valuable, recording of EEG during tES is confounded by artifacts [47, 48].

8.6 Electrode Resistance

Monitoring of electrode resistance before and during tES is considered important for reproducibility and tolerability [29, 49], specifically around issues related to electrode setup. An unusually high electrode resistance can indicate undesired electrochemical changes and/or poor skin contact conditions. tES devices will therefore include a resistance measurement circuit. However, monitoring of electrode impedance in no way reduces the need and importance of proper electrode selection and setup in the sense that poor electrode 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 an adjunct tool to detect not only ideal conditions at the electrode skin interface but also a substitute for quality electrode design and strict protocol adherence [27, 49].

The resistance measured by the device will be the sum of both electrodes including the underlying electrode-skin resistance and the body resistance. Body resistance is typically a few KΩ but will vary depending on electrode position on the body and the conditions of the skin (e.g., calloused skin). Electrode-skin resistance will vary depending on the electrode design and waveform applied [50]. 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 not ideal electrode setup, in which case the operator may adjust the electrode setup to reduce the skin-electrode resistance. Some device will deactivate if the resistance is atypically high.

8.7 Current Control, Voltage Limits

Electrodes play a central role in why current control (as opposed to voltage controlled) is broadly preferred across electrical stimulation applications [26], including tES. Voltage limits, and protocols to address voltage compliance, and settings then reflect device specifications. 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 [51] and can be significant compared to body impedance [26].

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. Though in tES we're not aware of modern devices that use voltage control in other brain stimulation applications, there may be situations where voltage control is practical such as stimulation of the vagus nerve through electrode on the neck (GammaCore, Electrocore, NJ, USA) or traditional invasive stimulation technologies such as SCS and DBS (Medtronic, Fridley, MN, USA).

We can now contrast this with current controlled 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.

The analogy for why current control provides more specificity can be extended to accidental electrical exposure. An individual contacting a high-voltage line but wearing insulative rubber gloves would be protected, since the gloves provide a high resistance path in series with the body, hence the expression "it's the current, not the voltage, that kills you." While the stimulation intensities used in neuromodulation are much lower than hazardous accidental exposure, and electrodes are designed to be conductive (metal/rubber and electrolyte), the analogy is valid in the sense that they dampen the voltage at the body under voltage-controlled stimulation.

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).

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 simple 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 [50]. There are various reasons to minimize voltage from simplifying circuitry or power requirements, reducing stimulation energy, or providing redundant tolerability measures in susceptible populations or use cases [52].

8.8 Indications for tES Use

tES spans many clinical and behavioral interventions, and as noted, many sub-techniques [53], such as transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial pulsed current stimulation (tPCS). What relates these different techniques is that they apply current through electrodes on the scalp with the intention of directly stimulating the cerebrum, rather than the periphery [27, 36, 54]. Research that uses tES focuses on direct cortical modulation as an explanation for changes in behavior, cognition, neurophysiology, and imaging studies [6, 55].

From the perspective of the device, the dose is deigned and selected to achieve specific changes in brain function and so clinical or cognitive outcomes. As described above, while this is a large parameter space, it can be reduced to features 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, whereas 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 [20, 56–59]. tES clinical trials intending to treat pain disorders – e.g., migraine [60], fibromyalgia [61], craniofacial pain [62, 63]) – often target the motor cortex (M1) with an "active" electrode, while the "return" electrode is placed on the contralateral forehead (called the "supraorbital" or SO position) (Fig. 8.4) [64].

8.9 Current Flow Modeling Informs Device/Electrode Design and Setup

Electrode size and position on the scalp along with the current applied to each electrode define tES dose [65]. tES dose, along with head anatomy, determines the resulting current flow (intensity and spatial pattern) in the brain [66, 67] and so resulting neurophysiological and behavioral changes [68]. 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 the resulting brain current flow intensity and spatial pattern. While dose is what is specified, it is brain current flow that underpins interpretation of outcomes.

For current flow models, also known as volume conduction models, to be accurate, they must correctly represent the shape and resistivity of head tissues (e.g., skin, skull, CSF, brain). The physics governing volume conduction models of tES mirror those used in electroencephalography, though more anatomically detailed variants have been developed over time. Computational models have been developed [9, 11, 69–74] and repeatedly validated [66, 75–78] over a decade. Approaches invented using computational models, such as HD-tDCS, have been validated [6, 44, 54, 75, 77] and applied [8, 41, 42].

Models support the optimization of montages to target specific brain regions [9, 79] which can be done at the population average or individual level [80]. Different montages and electrode designs can be tested [81–83]. The effect of invasive scenarios such as skull burr holes, lesions, or weight gain on brain current flow can be tested hypothetically [70, 84, 85]. Because the same dose will produce different brain current flow patterns across subjects, models can also support individual analysis [44, 86, 87]. The intensity of brain current flow can also vary across individuals, susceptible populations (e.g., age, stroke, tumor), or species in the case of animal experiments [88]. Current flow models can be used to compare the effect of stimulation protocols. Current flow models can also be compared with imaging data [89].

Thus, computational models are ancillary 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 new device technology. As examples, a home-based system relying on adhesive electrodes would restrict explorable electrode locations in models to locations below the hairline [90], which in turn simulate the development of simple-to-use electrodes that can go over the hairline [91]. The potential for focal transcranial stimulation was suggested first by models [71], but it was not until practical HD electrodes were developed [5] that approaches to optimize transcranial stimulation using HD arrays could be tested.

Some important aspects of computational models are to investigate the role of parameters such as electrode assembly, current directionally, and polarity of tES and use them to optimize therapeutic interventions for improving their risk/benefit ratio. A computational modeling pipeline of tES starts with segmentation of an exemplary magnetic resonance imaging (MRI) scan of a head into multiple tissue compartments, namely, scalp/skin, fat, skull, csf, gray matter, white matter, and air, to develop a high-resolution (<1 mm) MRI-derived finite element method (FEM) model. Electrodes of variant shapes, dimensions, and materials are then positioned over the brain target (e.g., a 35 cm^2 scalp contact area electrode positioned over inferior frontal gyrus (Fig. 8.7)) and meshed at different mesh densities using appropriate mesh refinement procedures (e.g. Simpleware Synopsys, CA, USA). The final volumetric mesh of the head with electrodes comprising >10,000,000 degree of freedom (DOF) and >12,000,000 tetrahedral elements, specific to this exemplary head model (DOF and no. of elements are inter-individual variant), is then imported into an FEM solver (i.e., COMSOL Multiphysics 5.1 MA, USA). For electrical stimulation, a quasistatic approximation [67] (steady-state solution method) is implemented and solved for electric current physics. The boundary conditions are applied as normal current density at the top exposed surface of the anode and ground (0 V) at the top exposed surface of the return electrode (cathode). The remaining other external surfaces of electrode are electrically insulated, and the model is solved. Predicted results are represented as electric field/current density streamlines to show the current flow trajectories across different brain regions or volume plot of field intensity/current density at desired brain tissue (Fig. 8.7).

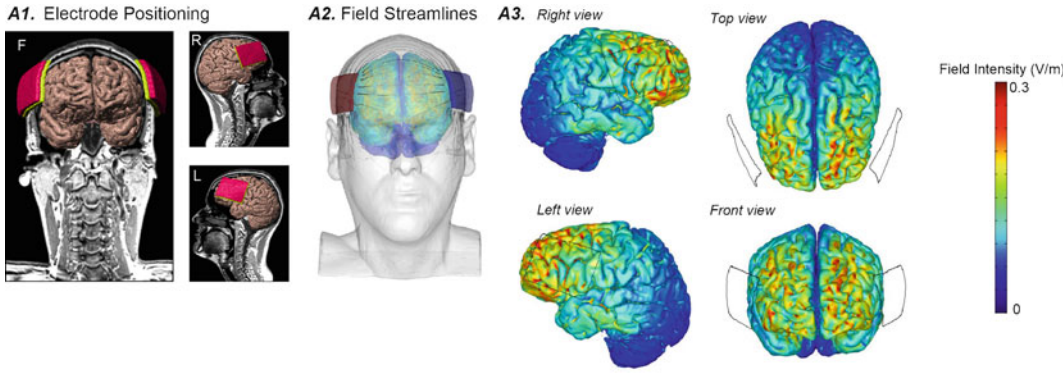

Fig. 8.7 Computational FEM head models and predicted field intensity of dual-hemisphere tES montage. (A1) 3D image of a segmented brain generated from an MRI scan of a healthy adult and different views (F, L, R) of electrode placement over the inferior frontal gyrus. (A2) represent an orientation of magnitude controlled electric field streamlines inside the head tissue layers during tES. (A3) Volume plot of predicted field intensity and different views of brain under stimulation conditions. Predicted results plotted at same color range (peak = 0.3 V/m) indicated comparable field intensity under both anode and cathode

8.10 tES Biophysics/Mechanisms

Neurons in the brain have a potential across their membranes (polarization) where changes in this polarization (most dramatically action potentials) underpin brain function. 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 mechanisms and efficacy of tES for varied indications, the biophysics of tES related to current delivery to the brain (see current flow modeling) and the resulting polarization of neuronal membranes are well established [92, 93]. The polarization produced by tES is the initial mechanism of action, with subsequently more complex changes in excitability and plasticity secondary to this polarization [94, 95].

Current that is passed through tES 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 skull (cranium) instead shunting across the relativity conductive (lower resistivity) scalp [77]. Of the current fraction that crosses the skull, a further portion of this is shunted by the highly conductive cerebrospinal fluid. The remaining current component that reaches the brain and 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. For low-intensity tES, the current intensity is not uniform across the brain, and so the electric field intensity is also distributed. For conventional tES using two large pad electrodes, this peak may be in a brain region between electrodes [20].

The peak electric field in the brain during 2 mA tES is 0.5–1 V/m based on intracranial recording in subjects and validated current flow models [66, 75, 78]. In contrast ECT applies 700 mA or current producing electric field of 300 V/m [96]. This contrast is important. Whereas ECT and most invasive brain stimulation techniques produce high-intensity electric fields in the brain (>100 V/m), low-intensity tES approaches produce weak electric fields (<1 V/m). This is well known and directly support a "subthreshold" modulation mechanism of low-intensity tES technique such as tDCS [94] and tACS [97–99].

The neurophysiological and so behavioral consequences of tES will depend on how this next polarization (across neurons and their compartments) influences excitability and plasticity [94]. Because low-intensity tES produces only incremental membrane polarization, the cellular effects of low-intensity tES on brain function will further depend on ongoing activity [99–102] and may be amplified over time (tens of minutes [103–105]). The organization of neurons in active networks with emergent properties like oscillations will influence the aggregate effects of tES [99, 106–110]. The ultimate consequences of low-intensity tES on macroscopic measures of neurophysiology (e.g., TMS) and behavior (e.g., therapy) will be complex, but ongoing research [80, 111, 112] about such changes should not be conflated with the well-established biophysics of current flow and resulting membrane polarization of low-intensity tES. As with any single aspect of brain function and disease, and every intervention, "open questions" remain – and, again, open questions should not be conflated with the lack of scientific basis for tES. Specifically, 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.

8.11 Tolerability of tES Devices

The tolerability of any intervention depends not simply on the device and dose but on protocol including subject inclusion/exclusion (e.g., age, preexisting condition), operator training and certification, ongoing monitoring, and parallel interventions. For example, the scientific consensus that tDCS is safe and tolerated [12, 33, 113–116] is explicitly limited to those protocols tested. In the same vain, human trials of tDCS in the USA are almost always considered nonsignificant risk (risk comparable to daily activities). But this risk designation – whether made by the FDA or by an institutional IRB – 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.

tES device design may be considered to minimize risk to the extent that they reliably control dose and allow consistent electrode setup, when used within the limits of established protocols. Medical-grade tES devices and accessories that are designed and manufactured to internationally recognized medical standards – regardless of region-specific approval for treatment [2, 114, 117] – provide the highest standard of control in regard to reliability.

Tingling is a common adverse effect reported in low-intensity tES studies [118, 119]. For low-intensity techniques like tDCS, the severity of adverse events is low across all conditions [59]; however, the frequency of tingling is significantly higher under thin vs. thick sponge stimulation (88% vs. 64% incidence, respectively) [5]. As discussed above, electrode size and salinity of sponge electrodes may influence sensation [120]. In principle, electrode design must be optimized to reduce the frequency and intensity of tingling and related sensations in clinical trials, which enhances blinding effectiveness. For this same reason, studies which have focused on the effectiveness of 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 [121]. A potential reason may be that the thick sponge produces more uniform current density at the skin surface, resulting in evenly diffused erythema distribution and, hence, lower tingling sensation.

Conflict of Interest The City University of New York has patents on brain stimulation with MB and NK as inventor. MB advises Boston Scientific, GlaxoSmithKline, and Mecta. MB has equity in Soterix Medical Inc. DQT has no conflict to declare.

Homework

1. What stimulation parameters define tES dose?
2. Name at least three tES device types. What distinguishes them from each other?
3. A tES device provides a DC current through three electrodes. One electrode is an anode and provides 2 mA. A second electrode is a cathode and collects 0.5 mA. Is the third electrode an anode or cathode? How much current does it provide or collect?
4. Approximately how much current is used to produce a seizure during ECT? How much current is used in techniques such as tDCS and tACS?
5. In a tES setup, the body resistance is 2 kOhm, one electrode-skin resistance is 1 kOhm, and the second electrode-skin resistance is 10 kOhm. What is the total impedance measured by the tES device? If the second electrode is adjusted such that the second electrode-skin resistance is now 1 kOhm, what is the new total impedance measured by the tES device?
6. In tES with two electrodes, what is the reason for not placing the electrodes proximal (almost touching) each other? For what kind of head electrical stimulation devices is proximal placement rational?
7. A tES electrode assembly is made from a cylindrical gel compartment contacting the skin with a circle interface of 1 cm radius. The gel is encased in a hard plastic material of 0.5 cm thickness and held inside a cap with a circumference of the head. The side of the gel opposite from the skin makes contact with a metal disk of 0.5 cm2 radius. When this is used in a tES publication, what is the "electrode area" that is practically reported in describing the stimulation dose?
8. If one knows the dose and head anatomy, what is the use of computational models (e.g.,

what aspects of brain current flow are models used to predict)?

9. What are the two essential functions of the electrolyte used in tES?
10. Only a fraction of current reaches the brain in tES. Given that current is conserved, where (what tissues) does the remainder of the current go?

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