Chapter 10
Transcranial Direct Current Stimulation Electrodes

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Importance of tDCS Electrodes

Significant contributors to the broad adaption of transcranial direct current stimulation (tDCS) are the portability and ease-of-use along with the tolerability profile of tDCS – adverse events limited to transient cutaneous sensations (e.g. perception of warmth, itching, and tingling) and erythema (Aparício et al. 2016; Bikson et al. 2016; Dundas et al. 2007; Fertonani et al. 2015). Therefore, the design and preparation of tDCS electrodes are central to tolerability, and design increasingly emphasizes ease and robustness of use. Conversely, when established electrode protocols are not followed or poor electrode design used, tDCS can produce unnecessary significant skin irritation and burns (Dundas et al. 2007). Thus, tDCS electrode design is central to understand the proper preparation of stimulation and prevent avoidable adverse events. Given that cutaneous sensation and irritation are the primary risks of tDCS, proper electrode uses and essential care at electrode preparation are vital to enhance tolerability and maximize reproducibility (Dundas et al. 2007; Minhas et al. 2011; Turi et al. 2014). Since sensations also determine effective

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H. Knotkova et al. (eds.), *Practical Guide to Transcranial Direct Current Stimulation*, https://doi.org/10.1007/978-3-319-95948-1_10

blinding, tDCS electrodes are critical for blinding reliability. Finally, to the extent tDCS electrodes design shaped the current flow through the brain, electrode selection and preparation is critical for the reproducibility of efficacy.

The conventional tDCS electrode configuration utilizes two electrodes – one anode and one cathode – of comparable size (e.g. 5×5 cm^2) positioned around the head. However, strategies scaling bipolar electrode size or increasing number of electrodes (using High-Definition electrodes) have been investigated to address concerns about tDCS spatial focality (Galletta et al. 2015; Minhas et al. 2012; Monte-Silva et al. 2010). This chapter does not address the question on montage design to target specific brain regions (instead see Chap. 9) or achieve specific neuromodulation outcomes, but only focus on the fundamental issue of electrode selection and preparation. Background on the design of electrodes is needed to guide users on electrode selection and proper application.

Technically, an "electrode" refers only to the surface of metal or conductive rubber that makes a proper contact with an electrolyte such saline or conductive gel (Merrill et al. 2005). However, in the tDCS literature, an electrode conventionally refers to the totality of entire assembly that includes (1) an actual electrode (metal snaps, pin, pellet, disk, sheet, mesh or conductive rubber); (2) a conductive electrolyte such as the saline, conductive paste, or conductive gel that serves as the contact between the electrode and the skin; (3) a sponge material, if used, has a function of holding a liquid electrolyte in place; (4) any non-conductive mechanical support material either adhesive or non-adhesive (for e.g. rubber straps, headgear, electrode holder/adapter, HD-electrode casing, adhesive layer) used to hold the assembly in place or support its shape; (5) any conductive material supporting electrical connections such as wires or metal snaps that are integrated with the electrode assembly (with some elements like a metal snap connector serving both a mechanical and electrical connection role).

An essential function of the sponge and/or other support materials (such as the HD case) is to prevent direct contact between metal/conductive rubber electrode and skin. The reason is that electrochemical reactions (including changes in pH) occur right at the metal/rubber and electrolyte interface (Merrill et al. 2005) such that a "thick" electrolyte (e.g. realized by a thick sponge, or rigid shape) minimizes these reactions from reaching the skin. Thus, the saline, conductive paste, or conductive gel is used to maintain good contact quality at the skin but also serves as a buffer between the metal/rubber and the skin surface (Minhas et al. 2010). 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 then directly impact the skin and skin irritation is likely.

An important function of electrodes used in tDCS is to protect the skin from electrochemical reactions occurred at the surface of the metal/rubber. Therefore, all electrodes designed for tDCS include some mechanism to separate the metal/rubber from the skin. As explained in the following sections, this separation can be generally facilitated by:

1. Sponge-electrode: A sponge which is saturated with the electrolyte, typically saline;
2. Self-adhesive electrode or Dry electrode: An electrolyte, typically gel, that itself has sufficient rigidity and which can either include an adhesive (self-adhesive electrode) or does not include an adhesive (dry electrode); or
3. HD electrode: A stiff mechanical support material that contains the electrolyte, typically gel and controls the position of the metal.

These choices between these general design approach also create restrictions on the size of the electrode (e.g. small HD vs large sponge) and how it is applied (e.g. self-adhesive gel or not adhesive with saline).

Sponge-Electrode

This electrode type is the most common electrode design used in conventional tDCS (Fig. 10.1, (Dasilva et al. 2011)), largely due to its apparent simplicity and historical norms – starting with the canonical tDCS studies circa 2000 (Nitsche and Paulus 2000). However, there are significant details in both the optimization of sponge-electrode design and techniques in sponge-electrode preparation (Woods et al. 2016) – especially as in their most basic form, sponge-electrode requires component assembly at every use. Most commonly in current tDCS protocols, a conventional sponge-electrode pad has a skin contact area of either 25 cm^2 or 35 cm^2 with the scalp. 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 similarly inserted into a sawn 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 conductive rubber electrodes typically include a female port which is connected to a male banana clip or pin terminated wire from the stimulator.

There are updated variants on the sponge-electrode design. The conductive rubber may be (semi) permanently 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 head-gear directly. As with other sponge electrodes, the electrodes can be re-used or are single-use – for a single-use, electrodes are further available as pre-saturated so requiring no preparation (Soterix EasyPad-2). A recent innovation is a more rigid sponge with bristles that enhances preparation through hairs and uses

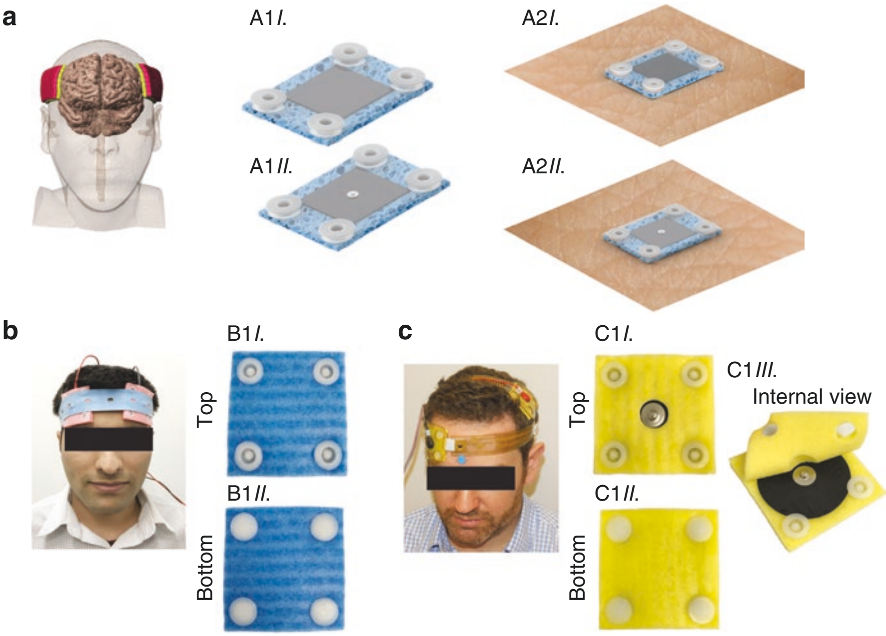


Fig. 10.1 The architecture of sponge-electrode and its variations. (**a**) An exemplary FEM model of sponge pad positioning over left and right dorsolateral prefrontal cortex (dlPFC) in a head model. (**a1I**, **a1II**) CAD exemplars of sponge assembly variations wherein both variations rubber electrode is placed in between two layers of sponges, except the later has metal snap on top of the rubber (see **c1III**) to facilitate connection with customized headgear (head strap). Both variations of sponges have rivets to minimize edge effects, hence, maximizing tolerability. (**a2I**, **a2II**) shows the computational model of the above- mentioned sponges positioned over the skin surface. (**b**) Bifrontal placement of riveted sponge electrode (as in **a1I**) on a subject forehead. (**b1I**, **b1II**) Images of actual sponge electrode (5 × 5 cm) as used in **b1**. (**c**) illustrates the positioning of updated snap-in sponge-electrode assembly on a fixed montage specific headgear, in this case, M1-SO. (**c1I**, **c1II**) depict different views of the snap-in sponge electrodes (5 × 5 cm) as in **A1II**. The shape of the rubber electrode doesn't influence the total current delivery to the brain region. (**c1III**) illustrates an internal view of the snap-in sponge electrode where the circular rubber electrode is placed exactly at the center of the sponge pad

sponge material 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 head-gear (e.g. home-use; (Kasschau et al. 2015)) 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. pre-assembled and saturated) or reliability (e.g. sponge shape).

Sponge electrodes are intended to increase the contact quality even in the areas of the scalp with thick hairs because the electrolyte (saline) may penetrate under the hair and saturate the skin surface. Theoretically, the saturation of skin may also reduce inhomogeneity in current flow through the skin (Kronberg and Bikson, 2012). In some designs, where the sponges are readily accessible during the treatment session, sponge hydration must be carried out with care: oversaturated sponges with saline has indicted changes in impendence or reported tolerability (Woods et al. 2016). Some disadvantages of using sponges are that sponge is prone to leaking which distorts the "effective" electrode size making stimulation not reproducible – for this reason the volume of saline added to the sponges should be carefully calibrated (to the sponge model, size, and application) and a cap (e.g. neoprene) may be avoided since both obscure and support fluid spread.

Sponge electrode of various sizes have been used for tDCS (including 3 × 3, 5 × 5, 5 × 7, 10 × 10 cm) but smaller sizes are not practical or necessarily tolerated (but see HD electrodes). Neither changing sponge-skin contact shape from square to circular (Ambrus et al. 2011; Minhas et al. 2011) nor changing sponges-skin contact size within the conventional range (with larger electrode potentially producing slightly *more* irritation (Turi et al. 2013)) had significant effect on tolerability (Aparício et al. 2016; Fertonani et al. 2015). Potentially, more important than electrode-skin contact area/shape is the electrode design, such as material thickness and use of rivets (Kronberg and Bikson 2012) and electrolyte salinity (Dundas et al. 2007). However, changes in electrode shape and size (Nitsche et al. 2007), and even design (Opitz et al. 2015), may influence brain current flow even in the absence of significant changes in reported tolerability. Sponge electrode requires a head-gear to hold them in place (but see self-adhesive electrodes). In general, sponge-electrodes are easy to set up preferred by many researchers and clinicians worldwide (Fig. 10.1).

Self-Adhesive Electrode

Relatively uncommon but of interest for wearable technologies, self-adhesive electrodes adhere to the skin surface and require minimal preparation – making them easiest to use at a location without significant hair (Paneri et al. 2016). 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. 10.2d2). The metal may be connected to a short cable with a female pin connection and 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. Adhesive electrodes have been used in a limited number of tDCS trials (Paneri et al. 2016) but are common in other applications where pulses and AC stimulation are used such as cranial nerve electrical stimulation (Feusner et al. 2012). Although self-adhesive electrodes are easy to apply, their use is limited as they are not practical for stimulating areas of the head with hairs. Moreover, while they are many brands and designs of self-adhesive electrodes, most are not suitable for direct current stimulation and may produce skin lesions.

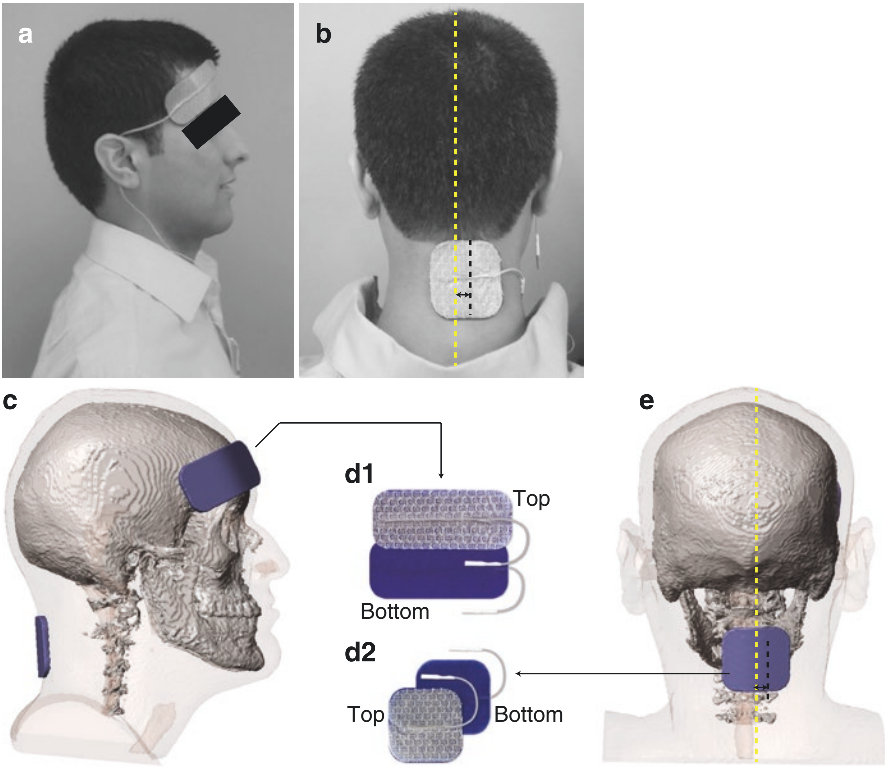


Fig. 10.2 Illustration of adhesive hydrogel electrode (left and right). (**a**) Placement of rectangular anode on the subject's right temples. (**b**) A square cathode electrode positioned about 1 cm to the right of the subject's midline on the back of the neck. (**c**, **e**) representation of analogous electrode positioning as A and B on a realistic head model. (**d1, d2**) An actual image of the anode and cathode adhesive electrode. The bottom of the electrode has an adhesive hydrogel to enhance adherence with the skin whereas, at the top, there is a mesh of fabric used to hold the conductive in place

High Definition Electrode (HD-Electrode)

High definition (HD) electrodes are another variant of the tDCS electrode assembly with a skin contact area of fewer 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 (Minhas et al. 2010). 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. 10.3). 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 (Borckardt et al. 2012; Dmochowski et al. 2011; Kuo et al. 2013). A common HD montage is the

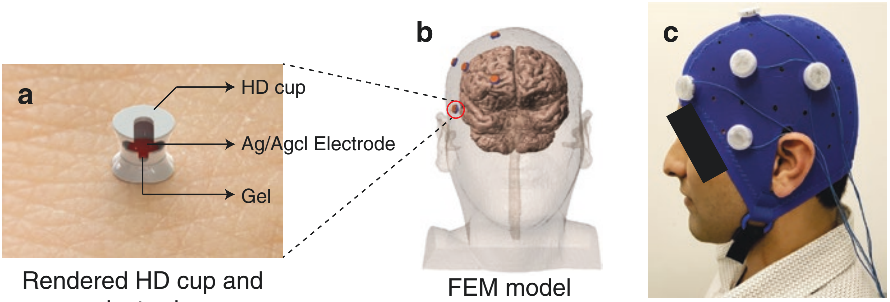


Fig. 10.3 Positioning of high definition (HD) electrode on a head model. (**a**) HD-cup with an electrode submerged in a conductive gel. (**b**) 4 × 1-ring configuration of electrode placement where four cathode electrodes are positioned around a central anode. (**c**) Illustration of HD-electrode assembly on a subject head. Electrodes are secured in a 4 × 1 configuration using a specialized head cap that follows EEG standard electrode position nomenclature

4 × 1-ring montage where a ring/circular fashion using four "return" (cathode) disk electrodes arranged around an "active" (anode) electrode at the center (Datta et al. 2009; Alam et al. 2016; Shen et al. 2016; Hill et al. 2017). The active electrode is positioned over the scalp (coinciding with the center of the active tDCS 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 (Fig. 10.3).

Electrode Preparation

The preparation and placement of tDCS electrodes remain the most critical and hence prone-to-error step in tDCS (Dasilva et al. 2011). Materials required for conventional tDCS (Fig. 10.4) are simple but the safety and tolerability of the treatment require the administrator to firmly follow standard protocols.

Monitoring of electrode resistance before and during tDCS is considered important for tolerability (Dasilva et al. 2011; Khadka et al. 2015a) where an unusually high electrode resistance is indicative of undesired electrochemical changes and/or poor skin contact conditions. However, monitoring of electrode impedance in no way reduces the need and importance of proper electrode selection and set-up- in the sense that 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

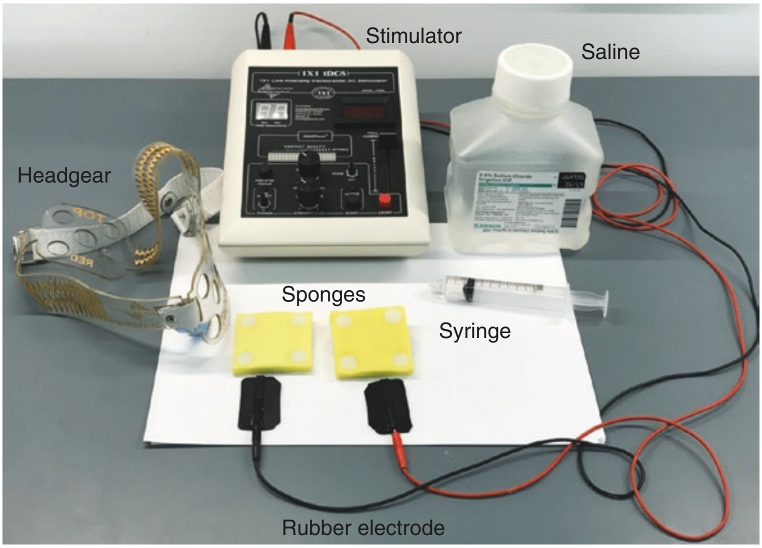


Fig. 10.4 Lists of material used for conventional tDCS sessions with sponge electrodes. Generally, conventional sponges are soaked with saline using a syringe and the rubber electrodes are placed inside the sponge pockets. Sponge-electrodes are then secured over the brain target using customized headgear or head-strap. Finally, the rubber electrodes are energized using corresponding anode and cathode wires connected to the stimulator

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 (Khadka et al. 2015a; Woods et al. 2016).

As noted, direct poor contact between the metal or conductive rubber electrode (site for electrochemical reaction) and the skin can trigger skin irritation (Merrill et al. 2005). Hence, sufficient electrolytic gel, cream or saline should be used as a buffer in between. However, oversaturation of saline in the sponge-electrode is a concern. Oversaturated sponges will be leaky and can impact the reproducibility of the treatment. Sufficiently, saturated sponges maintain good contact quality between the electrode and enhance the tolerability of the treatment. Since the saline soaked sponges are exposed to the ambient room temperature and are in contact with the human body surface (convection), saline will evaporate, and dehydration will be an issue. Therefore, it is imperative to obtain good contact quality directly under the electrode while maintaining an adequate saline saturation at the sponge-electrode. For sponge-electrodes, simple methods of quantifying saline saturation (e.g. use of medical grade syringes to dispense saline) can assist in achieving a consistent and appropriate amount of contact medium.

Consistent with the issues introduced by oversaturation of sponges, the shape or size of tDCS electrodes significantly alter the distribution of current delivered to the brain (Khadka et al. 2015b; Kronberg and Bikson 2012; Minhas et al. 2011). Variation in the electrode assemblies or particularly electrode size results in differences in the distribution of the current across the surface area of the scalp and to the brain (Kronberg and Bikson 2012; Minhas et al. 2011). Thus, it is critical for investigators to consistently report not only the current intensity applied and the amount of contact medium used but also the shape and size of the electrode assembly.

Inter-individual variation in the head size and shape demands subject-specific headgears or head straps (Bikson et al. 2010). Often elastic straps are used to fasten the conventional saline-soaked tDCS electrodes over the desired location. However, the force applied to secure the electrodes over the skin might induce pressure under the electrode and thus pressure-induced erythema either under or around the edges of the electrode as observed during sham stimulation (Ezquerro et al. 2017). Moreover, excess force can cause leakage of saline from the sponge-electrode causing unnecessary mess or hindrance in current distribution over the scalp and requires frequent hydration of the sponge-electrode.

Electrode Placement

A central consideration for tDCS is determining where to place electrodes on the head (montage). Studies monitoring neuro-physiological changes following tDCS and current flow FEM prediction have demonstrated that the relative location of electrodes result in significant differences in where and how much current is delivered to the brain (Kessler et al. 2013; Minhas et al. 2012; Woods et al. 2015). For example, Nitsche and Paulus (2000) demonstrated that relative differences in electrode locations alter tDCS impacted TMS generated motor-evoked potentials (MEPs). Numerous modeling studies have demonstrated significant differences between relative locations of electrodes, with results varying from stimulation of the whole brain to selective brain targets (Kessler et al. 2013; Minhas et al. 2012; Woods et al. 2015). Hence, even a small variation in electrode location (distance between the anode electrode and the cathode electrode) significantly alters overall distribution of predicted field intensity in the brain. This chapter addresses proper electrode selection and placement, but these issues impact the control and reproducibility of dose (Woods et al. 2015). Generally, the importance of electrode location also highlights yet another critical consideration, preparation of a stable electrode placement on the head.

As head size and shape vary from person to person, it is important to use a method for common localization of electrode position. Few methods/techniques for addressing this issue includes: (1) International 10–20 (or 10–10 or 10–5) Electrode Placement System (Klem et al. 1999; Oostenveld and Praamstra 2001) or another gross anatomical coordinate system (Seibt et al. 2015); (2) neuro-navigation systems (e.g., MRI guided; (Feurra et al. 2011a, b; Santarnecchi et al. 2014); (3) physiology-based placement (e.g., TMS generated MEPs). At present, physiology-based placement can only be performed for motor and other primary cortices (e.g., sensory). However, further options may become available in the future (e.g., TMS-EEG methods). Use of EEG to guide (HD) tDCS electrode placement is investigated (Fernández-Corazza et al. 2016). Any positioning technique should specify the center of each electrode along with electrode orientation. If any special accommodations are made for individual subjects, beyond those already inherent to the positioning technique (e.g. EEG 10-10) dosage must be noted (Kessler et al. 2013). In essence, any positioning method selected must be clearly documented and reproducible allowing the study to be reproduced.

Once desired locations are identified, the electrode assembly must be affixed to the head for delivery of current. Non-conductive headgear used to position the electrodes on the body or scalp (e.g. elastic straps) are critical for appropriate electrode placement (Woods et al. 2016). For tDCS using sponge-electrodes, elastic straps or other head-gear is used to secure electrodes in place during the entire tDCS session. Pressure-induced erythema even during sham stimulation has been previously reported by Ezquerro et al. (2017). Furthermore, if electrode straps are over-tightened, there is an increased probability of saline leakage. Especially with rubber bands (elastic strips) or poorly designed caps, there is a risk with the increasing tightening of drift toward the vertex (Woods et al. 2015). Specific head-gear designs prevent drift and can provide more reliable pressure across subjects and operators (Fig. 10.5).

With conventional rubber straps, various techniques exist to mitigate the above-mentioned issues. For example, the contour at the base of the skull below the inion

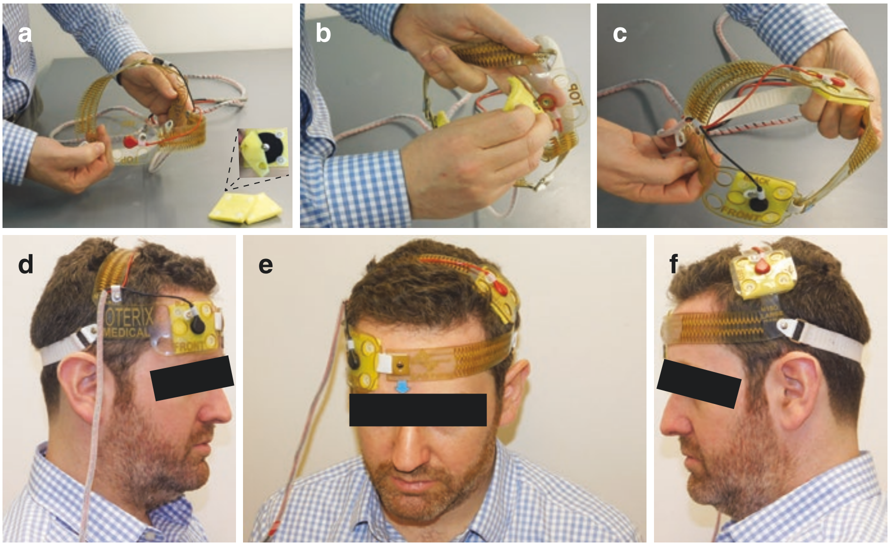


Fig. 10.5 An updated method for electrode placement using fixed position head-gear and pre-saturated snap sponge-electrode. (**a**) Example of a headgear with a build-in anode and cathode snap-in wire terminals at a fixed position (M1-SO montage). (**b**) Pre-saline-soaked sponges with snap connected are affixed to the anode or cathode terminal. (**c**) Complete assembly of sponges-electrode and a headgear. (**d**–**f**) Different views of head-strap placement on a subject head

and the flat of forehead provide stable placement of a strap around the head. For participants with long hair, placement of the back of the strap under the hairline also improves the stability of the strap preparation, whereas placement over the hair leads to a high probability of upward drift of the strap and the electrodes placed on the head. Use of cross straps over the head should also avoid over-tightening of the cross-strap to avoid this same issue. However, the use of a cross-strap under the chin can counteract this tendency but may be uncomfortable to participants. If under-chin straps are used, these should be used for all participants to maintain consistency of participant experience in the study. In totality, an advancement in the electrode assembly, particularly electrode straps can enhance the reproducibility of tDCS. One exemplar of updated snap-in sponge electrode headgear with a fixed montage (Knotkova et al. 2017) is shown above.

Further Consideration for Electrode Design and Selection

Erythema May Be Important for Blinding But Not Injurious

Skin redness (erythema) during or after tDCS is one of the most evident side-effects in tDCS trials. The causes of tDCS erythema may include but not limited to exposure to saline, iontophoresis, pressure by headgear, and the stimulation current itself. Redness resolves spontaneously after stimulation and is not injurious. Electrode design and thickness, gender, skin type, nature of stimulation (anodal or cathodal), and intensity of stimulation may mediate its strength (Dundas et al. 2007; Guarienti et al. 2014; Guleyupoglu et al. 2014). Recent studies have been conducted to characterize and control tDCS-induced erythema. Brunoni and colleagues previously reported that skin pretreatment with ketoprofen reduces tDCS-induced erythema (Guarienti et al. 2014), although such an approach inconveniently increases the preparation time. Erythema induced during tDCS varies from mild to moderate. Rater based evaluation of erythema can be overestimated which is solely based on visual inspection of the skin. Hence, a novel approach is to use the collected images for estimating a probability heat map on the skin area, which presumably represents the erythema distribution under the electrode. This model also corroborates the investigators' observation of skin redness after sham stimulation which might have occurred for some reasons such as (1) the brief period of active stimulation at the session onset; (2) pressure of the pad, depending on how it is fixed; and (3) irritation of the skin due to the saline solution.

Skin redness (erythema) compared between rater-based and software-based data has demonstrated a very mild erythema occurred after sham stimulation although it was significantly higher after active stimulation, and even higher for the thick compared to thin sponge-electrodes (Fig. 10.6). In the stimulation groups: stimulation using both thin and thick electrode of the same size, erythema was comparable between the groups. Moreover, redness did not concentrate around the pad edges but it was rather diffuse under the electrode (Ezquerro et al. 2017). Assuming that

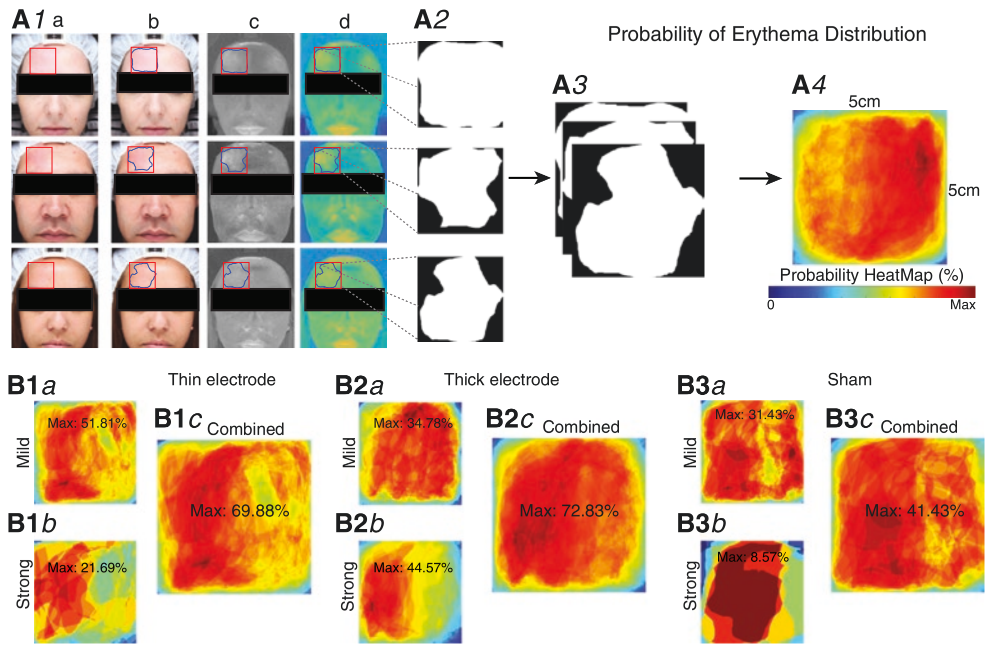


Fig. 10.6 Erythema distribution analysis in the ROI (site of stimulation) for active (using thin and thick sponges) and sham stimulation. (**A1a**) An Illustration of high definition images of the subject photographed before and after the stimulation. (**A1b**) represents ROI and traced erythema distribution. (**A1c**, **A1d**) Representation of filtered Images to isolate erythema from regular skin color tone. (**A2**) illustrates the binary image of erythema traces in the ROI. (**A3**) Illustration of the probability of erythema distribution calculation via stacking equi-dimensional binary images. (**A4**) Probability heatmap of erythema distribution (in percentage) across the ROI. Max represents 100% probability in the color bar. (**B1a**) Graphical illustration of the calculated mild erythema distribution for the "thin" sponge. Mild erythema distribution had a higher probability than strong (**B1b**). The calculated maximum combined probability (B1c) was diffused across the ROI. Strong erythema distribution (**B2b**) was slightly higher than mild (**B2a**) for "thick" sponges. (**B2c**) represents a maximum combined probability of erythema distribution. For sham, mild erythema (**B3a**) had a higher probability than strong erythema (**B3b**). (**B3c**) illustrates the maximum combined probability of erythema distribution. The probability of the erythema distribution in sham compared to the active stimulation sponge types was significantly lower

the electric current causes redness, it seems that current density is fairly homogeneous below the pad, and redness would be caused by an increase in blood perfusion among the tissue. This contrasts with a previous modeling study that showed that a thin sponge would have the current concentrated in the center of the sponge and a thick sponge, on the edges (Wagner et al. 2007). However, that model did not fully capture the inhomogeneity and anisotropy within the skin; for instance, skin/scalp was considered a combined mass of muscle, skin, fat and connective tissues.

The implications of erythema results in informing tDCS trial design should be taken with caution. First, the results can be specific to the headgear (e.g., presuming sham erythema reflects pressure), electrode technologies, electrolyte (gel/saline/cream) used, subject demographics, and waveforms tested. In fact, a prior study has shown dependence on electrode design and skin type. Trial-specific considerations would determine the need and value to mitigate erythema-related sham concerns. At a minimum, researchers should be rigorous in controlling and reporting the relevant headgear and electrode, as well as other factors that could induce erythema. Simple methods to conceal exposed skin areas can be implemented. If appropriate, erythema intensity can be reduced by treating skin with 2% ketoprofen before stimulation (Guarienti et al. 2014). Importantly, a protocol that involves either trained operators or quantified segmentation, with optimal lighting and image capture, and with the targeted intention to identify erythema difference across arms, is something impractical for regular use in tDCS trials. The finding from the respective tDCS erythema study (Ezquerro et al. 2017), therefore, do not necessarily contradict conventional experience in tDCS trials where sham was found effective by operator and subject reports, but rather raise a need for more detailed report of procedures used in future research to conceal stimulation group allocation, since it is now well documented that erythema is an independent factor for breaking investigator blinding in within-subjects design.

Technical Comments on Resistance (Impedance) in tDCS

The simplest way to minimize skin irritation is through limiting current applied (e.g. peak current, total charge per session), use of well-designed electrodes (e.g. designed for tDCS), and following protocols for electrode and skin preparation. None-the-less, none ideal conditions can arise. Subject reporting of sensation, general observation of electrode/skin conditions, and the monitoring of "electrode resistance" during stimulation (Wagner et al. 2007) are the only methods to monitor electrode conditions – and of these, electrode resistance is the only device controlled and objective measures. Electrode resistance is thus, universally relied on tDCS. However, the "electrode resistance" is, in fact, the voltage at the current stimulator output (as the voltage is adjusted to maintain a constant current) divided by the applied current. This voltage reflects many non-linear processes at both electrodes and the tissue (shown as Rt and RE in Fig. 10.7). While valuable in tDCS monitoring, since large excursions in voltage are indicative of non-ideal electrode conditions, this is not a first measure of "skin conditions" nor a measure of single

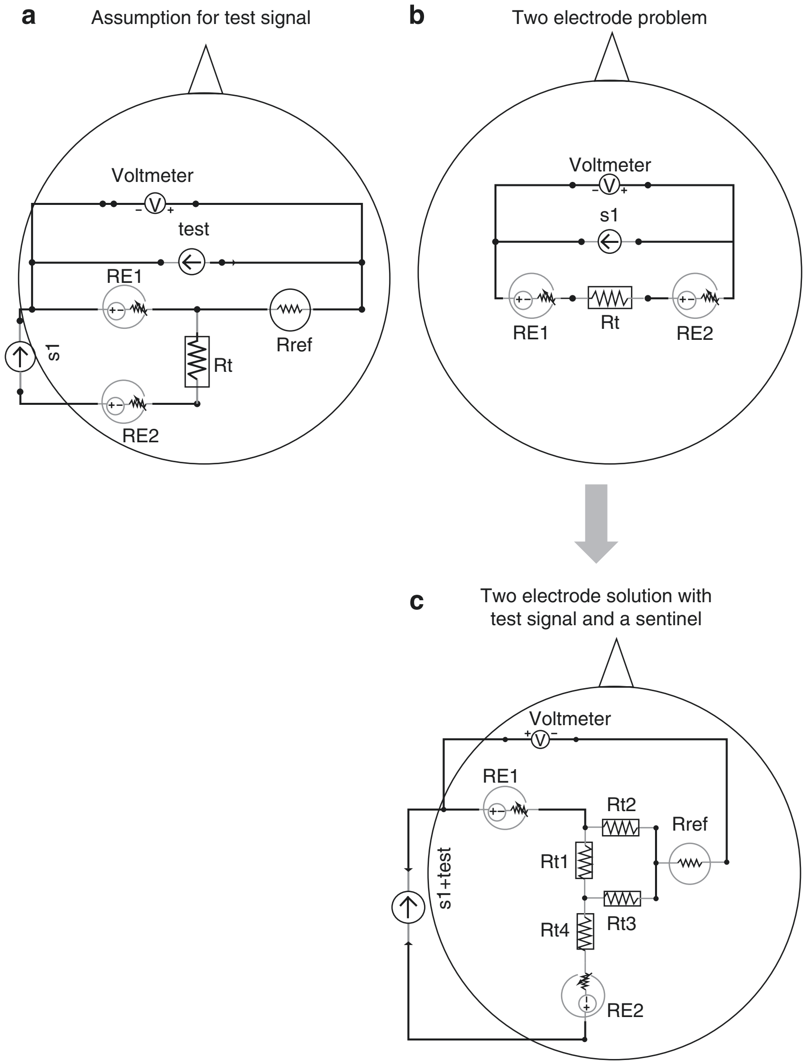


Fig. 10.7 Lumped circuit analysis of tDCS using two electrodes with an additional sentinel electrode (not carry direct current). (**a**) represents an exemplary circuit using a test signal (test) and a sentinel (R_{ref}) to predict DC voltage. This example includes two sources, S1 (DC) and a test AC signal, two active electrodes used for DC simulation: RE1 and RE2, and a sentinel electrode (R_{ref}) to test the assumption that the AC voltage detected across RE1 and R_{ref} can predict the DC voltage (hence, DC-resistance) of RE1. (**b**) Illustrates methodology to detect single electrode resistance changes. The schematic has two electrodes (RE1 & RE2) and a DC source (S1). The resulting voltage across these electrodes is the function of tissue impedance (Rt) and the resistance of both electrodes. (**c**) Presents a solution for the problem indicated in B based on the assumptions outlined in A, where a sentinel electrode (R_{ref}) is used to selectively monitor a stimulating electrode (in this case RE1) of interest. Here, a single source produces a combined direct current with superimposed test AC signal and the sentinel electrode (not used for DC stimulation) is required, but not additional current sources

electrode resistance, or even strictly resistance – since electrode over-potentials contribute as well. Rational development of tDCS can benefit from recognizing the non-triviality of this "electrode resistance" measurement.

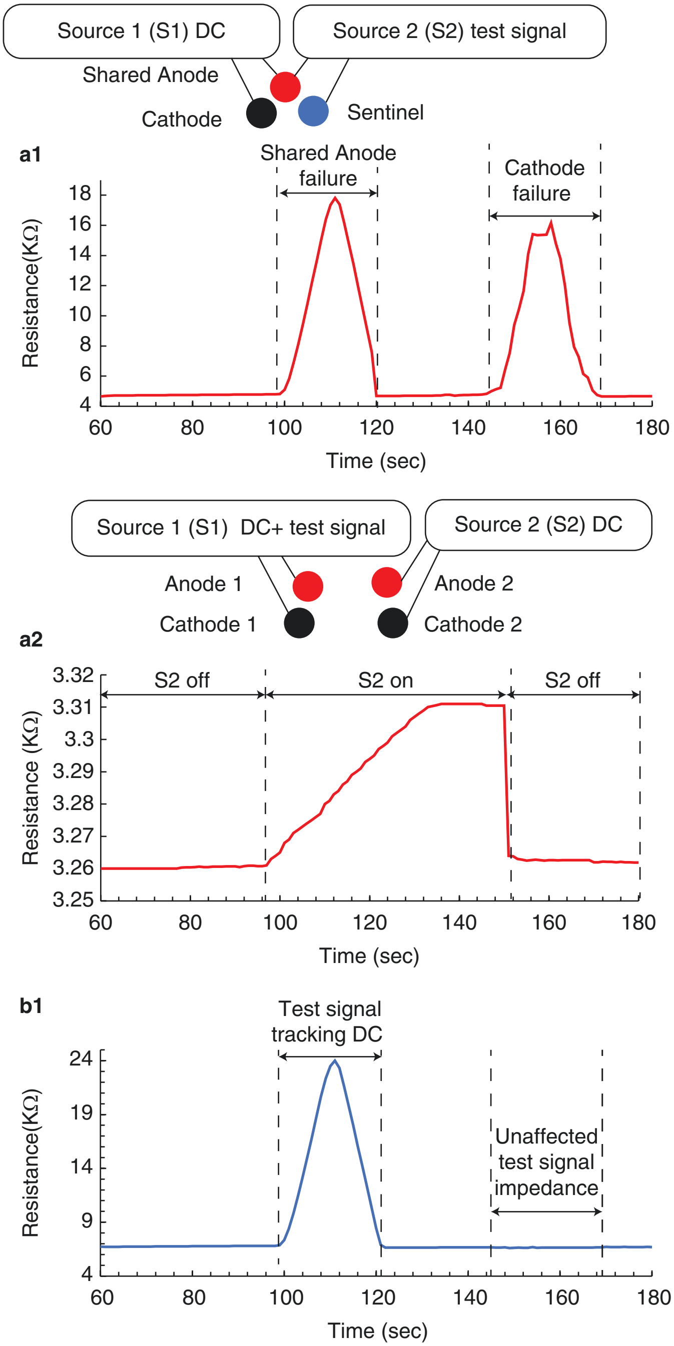
Before and after tDCS, measurement of resistance requires the application of a low-intensity test current. Even prior to stimulation, the resistance reported by a device will speak about the properties of the test current used. Minor variations in the waveform of the test current (e.g. pulses vs DC test waveform, 10 vs 20 μA test current) can significantly change the calculated resistance (Hahn et al. 2013). Therefore, the pre/post resistance reported by different tDCS devices, even under exactly identical electrode and skin contact conditions may vary. Since resistance during stimulation is measured under relatively high current (e.g. 1 mA), the pre/post resistance also does not simply predict resistance during stimulation, though a general correlation is expected (e.g. very high pre-resistance is associated with high during resistance). None of this diminishes the value of testing resistance in tDCS, but compounded by the issues discussed next, raises cautions about interpreting resistance values in strictly absolute terms.

A relevant outcome of tDCS is that the passage of current itself across the skin may lower the skin resistance. This means that the effective resistance measured during tDCS is less than before tDCS. This feature can be taken advantage of in a situation where it is desired to limit the voltage (energy) generated by a tDCS device (Hahn et al. 2013). It also has important consequences for blinding. If the active tDCS arm produces a distinct current-dependent change in resistance that is absent in the sham arm, then devices that report resistance to the operator during stimulation are not strictly blinded. However, one does not want to remove resistance reporting since its value is warning of non-optimal conditions. One solution is to replace resistance measured during stimulation with more categorical indicators of resistance (e.g. "Good", "Moderate" or "Poor"), that can further be calibrated to be even across active and sham conditions (Alonzo et al. 2016; Russowsky Brunoni et al. 2015). The source of this resistance drop is likely a decrease in skin impedance (Hahn et al. 2013).

The electrochemical performance of electrodes under DC, as well as tissue, has been addressed elsewhere (Merrill et al. 2005). None-the-less, context is necessary to inform rational design. tDCS is current controlled with the voltage output (total source-voltage) of the stimulator adjusted to maintain a controlled current application. The electrode and tissue have complex non-linear impedances. For example, the impedance may change over time and both electrodes and tissue may generate internal potentials. For electrodes, this is the overpotential from the electrode interface (Minhas et al. 2010) and for tissue, this includes skin potentials (Nitsche and Paulus 2000). How then does this complex system of impedance inform monitoring of "electrode resistance" for tDCS safety? It is accepted that during tDCS, significantly increased voltage (at the current source output), which is associated with increased cell impedance, suggests non-optimal conditions at the electrode or electrode-skin interface. This is biophysically justified since maintaining a low electrode over-potential voltage (Minhas et al. 2010) for a detailed discussion) at the electrodes and high conductivity (e.g. good gel/saline contact with the electrode and skin) are associated with minimized chemical reactions and good contact. These, in turn promote, but do not guarantee, tolerated stimulation. In multiple electrode scenarios, the challenges in measuring single electrode resistance still exist where electrode impedances are confounded through crosstalk. Measurements of “electrode resistance” (as extrapolated from the voltage as one of the current sources) may be misleading such that poor electrode conditions are not detected (false negative) or good electrode conditions as reported as poor (false positive). Thus, individual electrode impedance measurement is valuable for two electrode tDCS, for multi-electrode tDCS it becomes essential (Fig. 10.7).

Isolation of individual electrode resistance has been previously demonstrated, based on tested fundamental assumptions: (1) passage of a low-intensity and low-frequency sinusoid current (test signal) across a tDCS electrode produces a sinusoid voltage across an electrode that predicts the DC voltage across that same electrode. Hence, the sinusoid test impedance should predict the DC impedance of the electrode (Fig. 10.8a1, b1), (2) electrode resistance (for both DC and test signal) is greater than tissue impedance. Rational to this assumption is that poor electrode conditions will result in high electrode resistance and therefore will be detected. High electrode resistance is indicative of poor electrode conditions whereas a low or comparable tissue resistance is not a matter of concern, (3) administration of test current (Fig. 10.7 “test”) does not itself confound either tolerability of tDCS or electrode performance (Fig. 10.8a2, b2). This assumption appears to be valid as physiological actions on the skin or peripheral nerves could be resulting from a change in sensation or resistance. Moreover, current densities at the brain are much lower than skin (Dasilva et al. 2011) where changes could not be detected, and experimentally, it has been validated by prior observations (Antal et al. 2008; Nitsche and Paulus 2000) that a low amplitude and frequency test signal as used in this study do not influence brain function (Fig. 10.8).

Fig. 10.8 Demonstration of failures to detect single electrode impedance changes (electrode faults) with specificity and methods to correct (**a1**, **b1**) Type A error and method of correction using a sentinel electrode and test signal in *in vitro*. A constant source (S1) energizes an anode and cathode with 2 mA whereas a second source (S2) delivers a test sinusoidal current (38 μA peak-peak at 10 Hz) across the anode (shared) and a sentinel electrode (not used for direct current). At any instance (in above illustration around 100–120 s of stimulation; **a1**) when the anode electrode becomes faulty – here, intentionally made defective through reduced electrode gel contact area – the voltage/resistance increases across the DC current source and at the time the AC voltage/impedance increases across the second test source. In contrast, when a fault is created at the cathode, DC-resistance across the first source again increases but AC-impedance at the second course is unaffected. (**a2**, **b2**) Type B error and method for correction using a sinusoidal test signal. Two independent sources pass direct current (DC) across independent pairs of electrodes. S1 generates a superimposed test signal (38 μA) on top of a DC (0.5 mA) while S2 generates 2 mA DC. S2 is activated transiently (around 100–150 s) whereas the DC voltage/ resistance across S1 is contaminated by the voltage produced when S2 is energized, the AC voltage/impedance is not affected


Source 1 (S1) DC
Source 2 (S2) test signal
Shared Anode
Cathode
Sentinel
a1
Shared Anode failure
Cathode failure
Resistance(KΩ)
18
16
14
12
10
8
6
4
60
80
100
120
140
160
180
Time (sec)
Source 1 (S1) DC+ test signal
Source 2 (S2) DC
Anode 1
Cathode 1
Anode 2
Cathode 2
a2
S2 off
S2 on
S2 off
Resistance (KΩ)
3.32
3.31
3.3
3.29
3.28
3.27
3.26
3.25
60
80
100
120
140
160
180
Time (sec)
b1
Test signal tracking DC
Unaffected test signal impedance
Resistance(KΩ)
24
19
14
9
4
60
80
100
120
140
160
180
Time (sec)

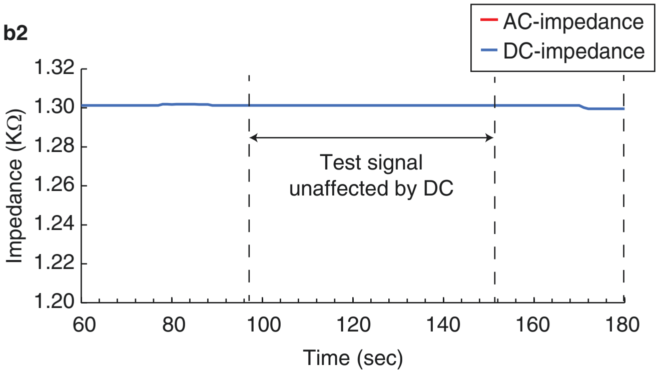


Fig. 10.8 (continued)

Tingling, Itching, and Related Sensations

Tingling is yet another common adverse effect reported in tDCS studies, observed in almost 3 out of 4 subjects (Kessler et al. 2012; Poreisz et al. 2007). Generally, the severity of adverse events is low across all condition (Brunoni et al. 2012), however, the frequency of tingling is significantly higher under thin vs. thick sponge stimulation (88% vs. 64% incidence, respectively) (Minhas et al. 2010). As discussed above, electrode size and salinity of sponge-electrodes may influence sensation (Dundas et al. 2007). 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 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 (Ezquerro et al. 2017). 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.

Heating, No Evidence in tDCS

One of the concerns to be addressed during tDCS is the change in temperature at the skin surface. These changes might be stimulation polarity (anode or cathode) specific, contributed due to passive heating, or due to a change in blood perfusion. Small non-injurious changes in skin temperature during tDCS may influence cutaneous sensation (Lagopoulos and Degabriele 2008) and even influence current flow patterns to the brain (Dasilva et al. 2011; Gholami-Boroujeny et al. 2015). Such changes may also confound blinding of subjects (e.g., a sensation of warmth that is based on real temperature changes) or operators (e.g., in the active case sponges are warmer). Although higher temperature changes may be injurious and contribute to less tolerable treatment, prior experimental and FEM modeling studies have curtailed a role for significant temperature increases during tDCS. Datta et al. (2009) predicted no significant temperature rise at the sponge-electrode and the scalp interface deploying 4 × 1 ring HD-tDCS and conventional tDCS, however, this temperature increase phenomenon was not reported using experimental measures. A recent study conducted by Khadka et al. (2017b) indicated a moderate and non-hazardous increase in temperature (~1 °C) at the skin surface during 2 mA tDCS that was independent of polarity and resulted from stimulation induced blood flow rather than passive heating (Fig. 10.9).

Any electrical stimulation might produce temperature changes; reflecting complex interactions between joule heat due to applied current across the resistive tissue, changes in metabolism (neuronal activation) or perfusion (flare), and heat conduction (Abram et al. 1980; Elwassif et al. 2006). Temperature changes in the body are typically considered insignificant in the efficacy or safety of neuromodulation technologies (Balogun et al. 1996; Cramp et al. 1999). Skin surface temperature changes of 1 °C are none injurious and within normal variation (e.g., due to exercise, environment; (Elwassif et al. 2006; Scudds et al. 1995)). Moreover, as this small increment is, in fact, compensating for a reduction in surface temperature following application of room-temperature sponges, and since the core body temperature of the blood limits perfusion-based heating, this mechanism is not hazardous. Warmth sensation felt under the tDCS electrode can be attributed to electrical nerve activation rather than heating, and any significant skin irritation (that occurs only when standard protocols are not followed) being electrochemical in nature (Minhas et al. 2010). Any warming of sponges observed by subjects or operators touching the electrode surface would reflect passive heating from the body and it is unlikely that the difference between active and sham can be resolved, hence, not a confound to blinding.

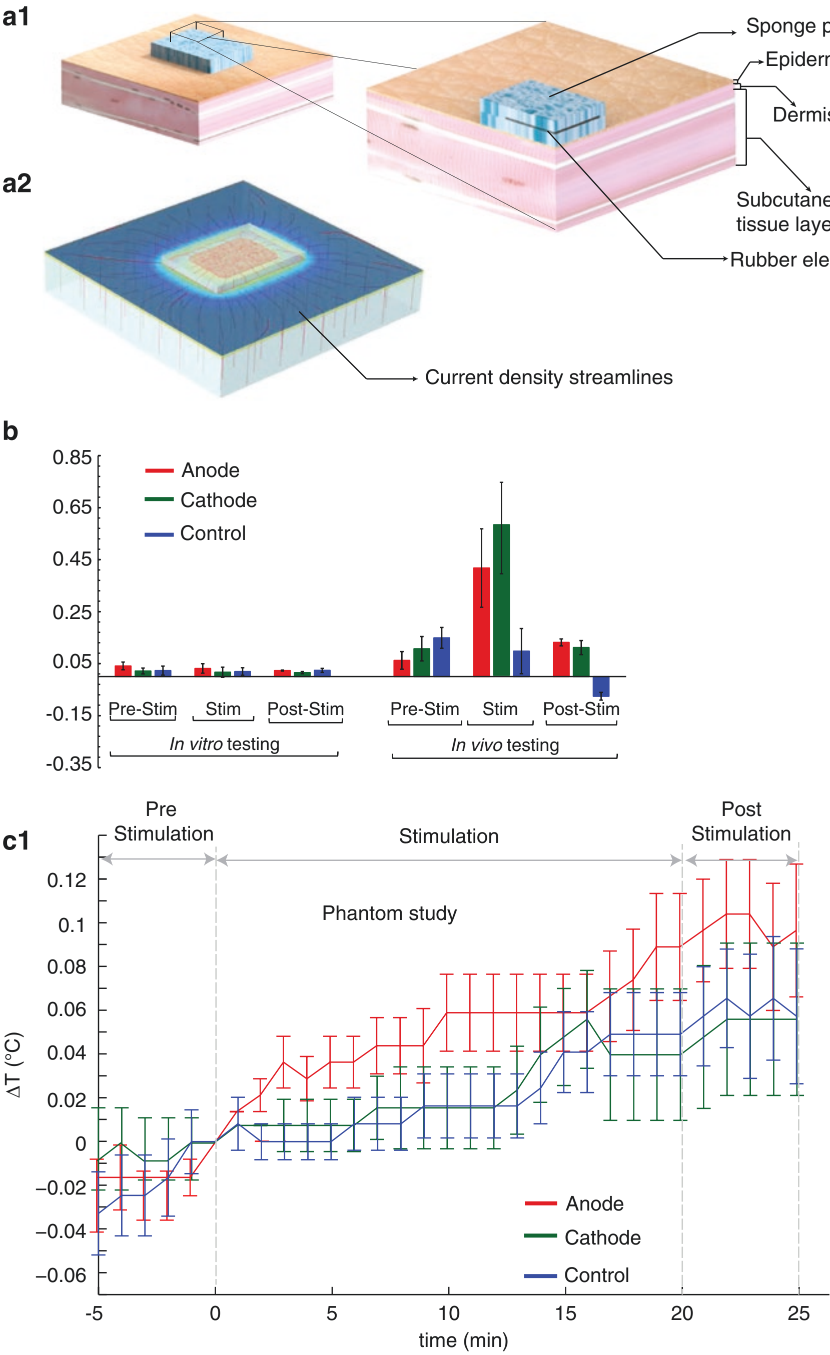
Future Electrode Advancement

Within Electrode Current Steering (WECS)

Conventionally, tDCS employs rectangular saline-soaked sponge pads (25–35 cm^2) placed on the scalp, with an internal electrode (carbon rubber electrode) connected to the direct current source. In many cases, impedance measurement across the current source output may fail to recognize any non-uniform conditions at the electrode-skin interface such as an uneven content or saturation. Hence, there is a need to have a technology that enhances the sophistication of electrode design, and further augments tolerability and promote broad use (for e.g., remotely supervised use or in-house use). Within electrode current steering (WECS), a novel method by Khadka et al. (2015b), is distinct from across electrode current steering as developed for implanted devices technology such as deep brain stimulation (DBS), where current is steered between electrodes that are in contact with the deeper brain tissues with the goal of changing desired brain regions that are activated. In WECS, current is adjusted between electrodes, not in contact with tissue but rather embedded in an electrolyte on the body surface (Fig. 10.10a2). The goal here is 'not' to alter brain current flow (Fig. 10.10e), but rather compensate for non-ideal conditions (Fig. 10.10b) at the electrode-skin interface. This technology also leverages methods for independently isolating electrode impedance and over potential during multichannel stimulation (Khadka et al. 2015a). Having presented this novel idea through an exemplary case, WECS supports the need of future studies in the optimization of tDCS electrode design, automation of algorithms to control current (including using impedance measurement), and ultimately validation using experimental measures.

In principle, WECS applies to noninvasive electrical stimulation with two or more electrodes (metal-rivets) embedded in an electrolyte (saline or gel)) on the skin (Poreisz et al. 2007). Each electrode is independently powered by a current source. Success in the implementation of WECS depends on geometry and material of each component of the assembly and an algorithm for current steering between electrodes. Changing the diameter and distance between the electrodes, the distance between the electrodes and skin, or electrolyte conductivity will discriminate how

Fig. 10.9 Skin surface temperature increases under tDCS electrodes during pre-stimulation, stimulation, and post-stimulation phases in the phantom, *in vivo* studies, and FEM simulations. (**a1**) An architecture of a skin model showing three skin layers (epidermis, dermis, and subcutaneous layers) and an electrode positioned on the skin surface. (**a2**) illustrates uniformly seeded current density flow streamlines inside the different skin tissue layers from the top surface of the anode electrode. (**b**) represents an average temperature change in subjects (*in vivo* testing) and phantom (*in vitro* testing) normalized to a temperature at $t = 0$. In the phantom, ΔT was approximately identical across test samples and mode of stimulation, whereas in the subject testing, maximum ΔT was measured under the active electrode (max. under cathode) during stimulation. (**c1**) Analysis of normalized average ΔT in the phantom study ($p < 0.01$). No significant difference in ΔT was found in the control, compared to the anode and the cathode. (**c2**) shows predicted ΔT for the non-stimulation (control) and stimulation cases in the phantom FEM model. Predicted findings indicated no significant effect of stimulation on the phantom. (**d1**) *In vivo* analysis of temperature difference over time within subjects during pre-stimulation, stimulation, and post-stimulation. Red and green asterisks symbolize a statistical significant difference ($p < 0.01$) between anode and control, and cathode and control, respectively. There was a significant difference in ΔT under the anode ($p < 0.01$) and the cathode ($p < 0.01$), compared to the control. Temperature under both anode and cathode gradually increased due to stimulation. (**d2**) FEM representation of the predicted ΔT in the skin model. A maximum ΔT of 1.36 °C was predicted by the computational model during direct current simulation


a1
Sponge pad
Epidermis
Dermis
Subcutaneous tissue layer
Rubber electrode
a2
Current density streamlines
b
0.85
0.65
0.45
0.25
0.05
-0.15
-0.35
Anode
Cathode
Control
Pre-Stim
Stim
Post-Stim
In vitro testing
Pre-Stim
Stim
Post-Stim
In vivo testing
c1
Pre Stimulation
Stimulation
Post Stimulation
Phantom study
0.12
0.1
0.08
0.06
0.04
0.02
0
−0.02
−0.04
−0.06
ΔT (°C)
Anode
Cathode
Control
-5
0
5
10
15
20
25
time (min)

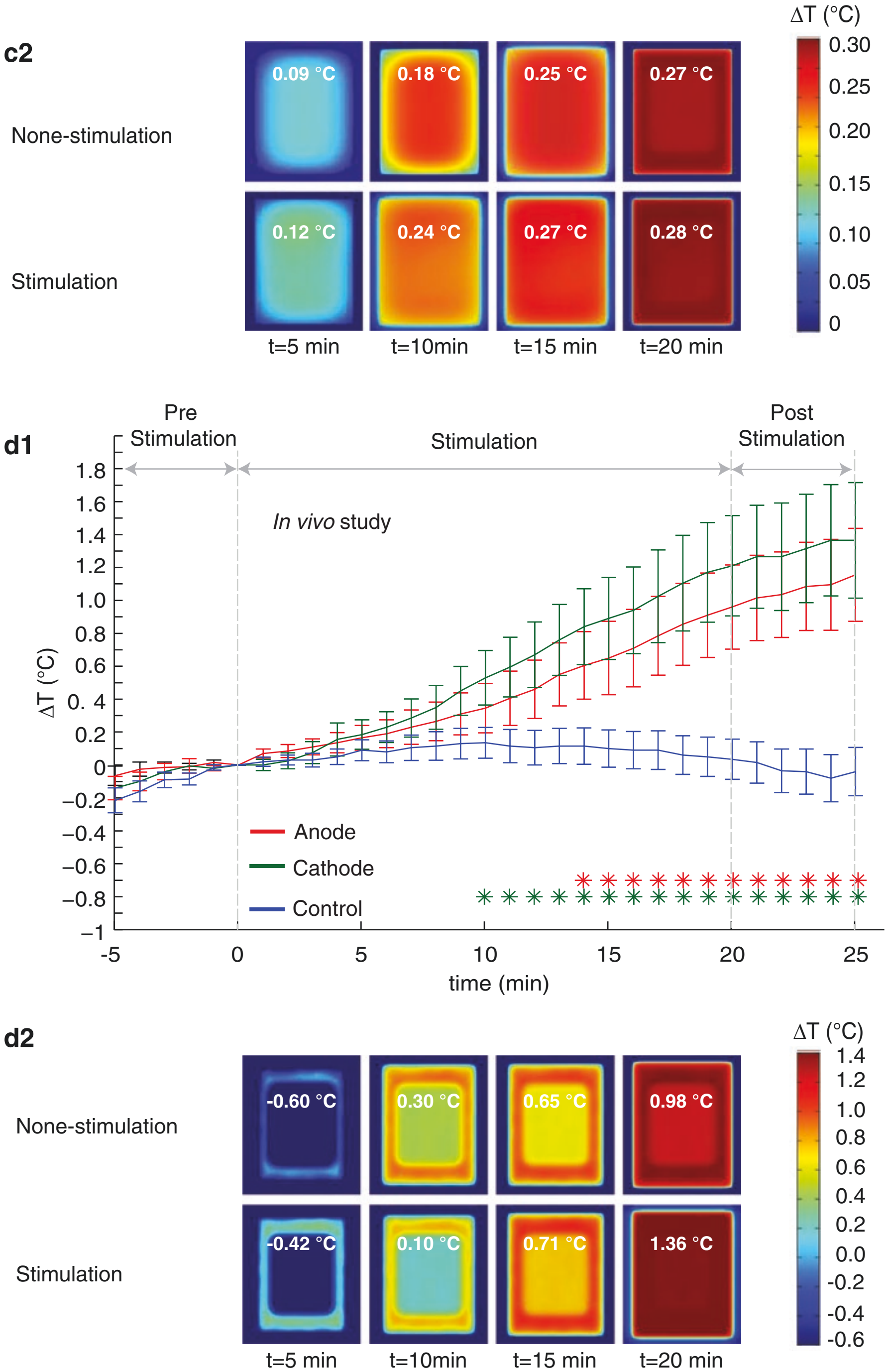


Fig. 10.9 (continued)

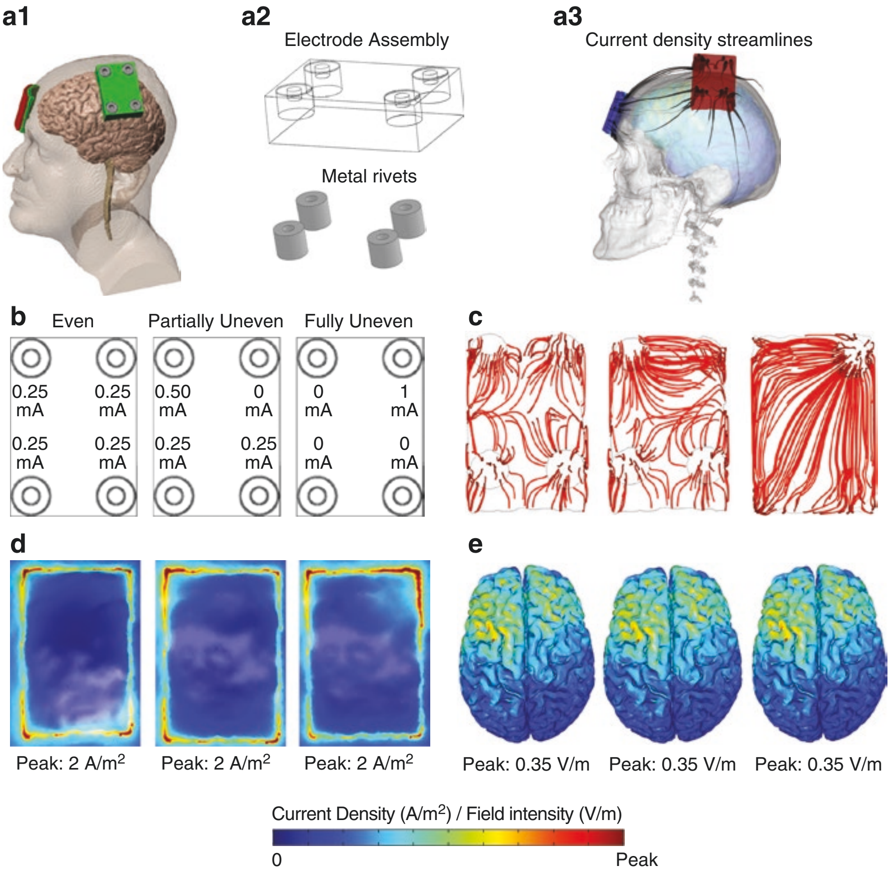


Fig. 10.10 Validation of the underlying assumption of within electrode current steering (WECS) using FEM simulation. (**a1**) represents a realistic head model with an electrode assembly. (**a2**) illustration of an exemplary electrode assembly for WECS. (**a3**) Uniformly seeded current density streamlines originated from within electrodes to the head tissues. (**b**) An “Even”, “Partially Uneven”, and “Fully Uneven” current administration mode through metal rivets of an electrode assembly keeping total current constant was considered. (**c**) Current flow isolines from each energized metal rivets. (**d**) Predicted current density at the electrode-scalp interface. (**e**) Presents an even electric field distribution in the brain target, even under different current administration conditions

current from the electrode reaches the skin (Kronberg and Bikson 2012), however, the total brain current flow remains unaltered and is independent of electrode configuration (Fig. 10.10e). In WECS technique, an entire electrode assembly receives a fixed total current (intensities vary based on application). Current is evenly divided across the electrodes within the electrode assembly. For example, if an assembly has four electrodes, under an “even” current split of 2 mA, each electrode receives 0.50 mA current (Fig. 10.10b).

WECS can be generalized to other noninvasive electrical stimulation techniques and potentially invasive techniques where an artificial or natural electrolyte barrier

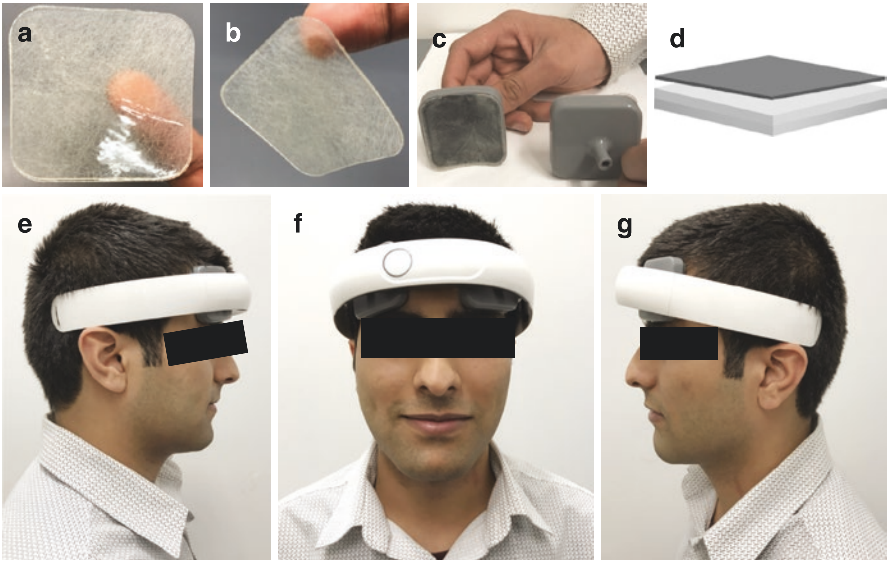


Fig. 10.11 Future electrode advancement in tDCS, multilayer hydrogel composite (MHC) dry electrode. (**a**, **b**) Images of actual MHC dry electrode. (**c**) illustrates placement of the dry electrode over the specialized rubber electrode with the adhesive layer facing the rubber while the non-adhesive layer on the opposite side (skin side). The rubber holder is encapsulated in a flexible insulated holder. (**d**) shows an electrode assembly (CAD model render) – rubber electrode positioned over the MHC electrode. (**e**–**g**) Images of MHC dry electrode secured over the brain region through the specialized headgear (wearable built-in stimulator)

exists between the electrode and the tissue. For invasive techniques, WECS may complement traditional current steering but be used to protect electrode and tissue from injury. A further consideration is how current flow at the skin (scalp) is altered. On the one hand, current steering should avoid significant increases in current density at the skin, maintaining as uniform a current density at the skin as practical. On the other hand, when non-ideal conditions at the electrode or skin arise, including increasingly non-uniform current flow or electrode failure, current steering may be used to compensate. For example, if a given electrode fails and a high overpotential at the electrode is detected, current may be steered to other electrodes to minimize electrochemical hazard (Kessler et al. 2012) or if one region of the sponge becomes dry during use, current may be diverted to the most distant electrodes. Inherent to the above concept is the ability to detect non-ideal conditions and program appropriate corrective measures. The simplest feedback is the voltage at each current source, which using signal processing and “test signals” (superimposed currents not used for neuromodulation) or a “sentinel electrode” (not used for DC) may be used to calculate single electrode impedance (Khadka et al. 2015a). Additional information can be derived by using test signals to isolate the impedance of the sponge/electrolyte between the electrodes, generating a prediction for current density patterns that can be corrected.

Multilayer Hydrogel Composite (MHC) Dry Electrode

Dry electrodes are defined as electrodes that exclude: (1) any saline or other conductive hydrogel based paste or gel, that is prone to leaking; (2) an adhesive at the electrode-skin interface or 3) any electrode preparation steps. The Multilayer Hydrogel Composite (MHC) electrode design fulfills these criteria. A dual layer structure of the MHC dry electrode was adopted by independently optimizing mechanical, electrical, and chemical properties of each layer to get some novel characteristics. First, in order to attain a dry surface, a non-adhesive bio-compatible polymer hydrogel containing Poly-Vinyl Alcohol (PVA) was used as a bottom surface layer (thickness 1 mm) and an adhesive polymer hydrogel was used in an inner layer (top layer, thickness 0.6 mm) (Fig. 10.11). The top layer was optimized to have a low impedance to redistribute the current within the electrode, whereas the bottom layer was optimized to have a high impedance to avoid current clustering at the skin defect sites. Further pH changes at the non-ionic/ionic conduction interfaces within the electrodes were optimized by using the top layer as a diffusion barrier and the rubber electrode/top layer interface was designed to avoid skin surface exposure.

Preliminary analysis of the performance of this MHC electrode using experimental measures on skin-phantom and FEM predictions has shown a comparable voltage and current/current density distribution under the MHC dry electrode when compared to the state-of-the-art conventional sponge-electrode, however, the FEM model of the former predicted more homogeneous current density distribution at the electrode-skin interface. tDCS using MHC dry electrode and conventional sponge-electrode was equally tolerated with comparable VAS ratings and adverse event reporting (Khadka et al. 2017a). In general, this study reveals a potential alternative of saline-soaked sponge-electrode in wearable devices with comparable performance.

Summary

Electrodes represent a critical component of tDCS application. In this chapter, we have described technical and practical considerations for electrode preparation, design, and application. While, at present, sponge-covered electrodes and Ag/AgCl electrodes are the most commonly applied variety, this too will change with material science and engineering advances. We also described the state-of-the-art work in this domain as well as appropriate practices for the common electrode types. Regardless of an electrode type, careful consideration must be given in preparation and application procedures to maximize safety and reproducibility. Common mistakes in electrode preparation and placement can significantly alter outcomes and in the worst cases (e.g., over-saturation leading to the distribution of saline beyond the electrode, bridging of electrodes, etc.) interfere with the ability to deliver tDCS that penetrates the skull. However, appropriate use of electrodes can provide safe and effective delivery of tDCS in a variety of study designs and application settings.

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