14 Clinical Research and Methodological Aspects for tDCS Research

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14.1 Introduction

Transcranial direct current stimulation (tDCS) was reintroduced as a modern method for noninvasive brain stimulation (NIBS) in humans approximately 20 years ago, in 1998–2000 [1, 2]. Since its reintroduction to the scientific and clinical community, the application of tDCS across a variety of healthy, psychiatric, and neurological populations has increased exponentially. However, like many nascent fields, methods used to apply tDCS have varied over the past 20 years. This variation, together with a lack of standardized reporting methods for the field, have likely played a role in issues of reproducibility for certain effects previously demonstrated with tDCS [3]. Specifically, variability in tDCS application methodology, design, stimulation parameters, and other factors have undermined the ability to reproducibly apply tDCS within and between patients and healthy subjects. For example, inconsistent placement of electrodes alters the location and intensity of stimulation to various brain regions [4]. In contrast, different levels of stimulation intensity (e.g., 1 vs. 2 mA) result in partially nonlinear changes in depolarizing versus hyperpolarizing resting membrane potentials under anode versus cathode electrodes, respectively [5]. Furthermore, certain medications can alter excitability effects of tDCS on resting membrane potentials (e.g., serotonin selective reuptake inhibitors, SSRIs [6]) relative to effects previously shown in healthy adults not taking these medications. These are only a few examples of methodological and design factors that significantly alter the potential outcomes of clinical or research applications of tDCS. However, studies often do not provide the level of methodological detail required to guide neither clinicians and researchers new to the field of tDCS nor experienced researchers attempting to replicate study effects. These details are of critical importance for not only reproducing effects from a given study and consistent clinical outcomes, but also for educating new tDCS researchers and clinicians.

In this chapter, we will provide guidance on methodological and design aspects of tDCS, covering basic methodological issues, effective approaches, and reproducible methods for the application of tDCS in both clinical and research settings. These materials are intended to provide easily implemented and reproducible methods for both new and experienced tDCS researchers and clinicians.

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14.2 Clinical/Research Trial Designs

14.2.1 Protocol Intensity/Duration/Repetition

When designing an experimental or intervention protocol, it is important to choose tDCS parameters (i.e., stimulation intensity, electrode locations, duration, and repetition) based on the outcome being investigated (i.e., neurophysiological, cognitive, or behavioral), as well as the clinical population being studied. This is because findings with the use of particular parameters for one outcome may not directly correspond with another similar or different outcome, or in a different subject population. Neurophysiological responses (e.g., MEP amplitudes) to tDCS and other noninvasive brain stimulation techniques, for example, have been shown to have little or no correspondence to motor learning capacity [7]. As such, stimulus parameters chosen based on findings of effects on MEP amplitudes measured in the motor cortex in healthy participants may not produce equivalent effects on alternative outcomes (e.g., cognitive or behavioral) when assessed following stimulation of the same or different brain regions. This principle also can apply to the administration of stimulus parameters found effective for healthy subjects to clinical populations. While 1 mA stimulation intensity given to the left dorsolateral prefrontal cortex for 10 min improved working memory performance in healthy participants [8], 2 mA but not 1 mA stimulation intensity for 20 min was necessary to produce similar effects in patients with schizophrenia [9]. Prior research using TMS evoked MEPs consistently suggests that 1 mA tDCS produces increased excitability under the anode electrode and decreased excitability under the cathode electrode [10]. However, recent research suggests that 2 mA stimulation may result in increases in excitability under both anode and cathode electrodes [5, 11–13]. In contrast, a recent study suggests that higher doses of 3 mA tDCS (e.g., 3 mA or more) results in increased excitability under the anode and reduced excitability under the cathode, similar to 1 mA stimulation [11]. Thus, selection of stimulation intensity should be chosen carefully based on the desired change in excitability for a given application of tDCS.

Similarly, this principle may equally apply when choosing the interval for repeated tDCS administrations, for example, in intervention protocols. This appears to be the case, as both the stimulus polarity and interval between sessions can interact to cause different effects on outcomes. In healthy subjects, differently spaced intervals (i.e., 0 min to 24 h) between consecutively applied tDCS given with the cathode electrode over the motor cortex has been shown to directly affect both the magnitude and duration of post-stimulation neurophysiological effects [14]. Similar differential behavioral effects due to both the polarity and duration of the spaced interval on cognitive outcomes have been found, with improvement in working memory performance following two sessions of tDCS with the cathode electrode over the left prefrontal cortex, although not when the anode electrode was placed over the same region, given 10 min apart [15]. This latter finding additionally highlighted the potential role of metaplastic effects within the stimulated region on outcomes (i.e., when tDCS is administered again during the aftereffects of a previous tDCS administration).

Unlike other noninvasive brain stimulation methods (e.g., TMS, ECT), tDCS typically applies a fixed dose of tDCS parameters across participants rather than individual dosing titration. Recent computational modeling research suggests that titration of stimulation intensity may serve as a significant factor contributing to interindividual variability of response to tDCS. Indahlastari et al. demonstrated significant variability in the distribution of current density in the brain as a function of age-related atrophy, as estimated through MRI-derived finite element computational modeling of current in a cohort of 587 older adults [16]. This work suggested that for those with the greatest signs of atrophy, the intensity of current would need to be increased by almost twofold to reach equivalent levels of current intensity induced in younger adults with-

out atrophy. Wang et al. have proposed an initial method for titrating the generated E-field generated by tDCS as a possible method for individual titration of tDCS intensity dose [17]. While robust methods for individual dose titration in tDCS is still in development, this area represents an important evolution in tDCS approaches for future studies.

Taken together these collective findings thus suggest that if no prior reference study exists when designing an experimental or intervention protocol, titration of tDCS parameters in relation to stimulus intensity, duration, and repetition should be considered. This can be achieved, for example, through a pilot study. Such piloting can also be invaluable for informing future studies.

14.2.2 Methodological Aspects of Online and Offline Protocols

A potentially important methodological consideration when designing an intervention or study using tDCS is the timing of tDCS administration in relation to task execution. That is, when tasks are given, it is important to determine whether these are performed during the application of tDCS (i.e., "online") or following tDCS administration (i.e., "offline"). This consideration is based on evidence indicating that both the physiological and behavioral effects of tDCS are different during and after stimulation. For example, functional neuroimaging has shown that while an increase in regional blood activity occurs during stimulation, activity is reduced immediately following stimulation [18]. Different behavioral outcomes have also been demonstrated with "online" compared to "offline" protocols. While improved motor learning was found to occur with "online" stimulation, decreased learning was found when the same task was performed "offline" [19]. Similarly, better performance on a cognitive training task was found with "online" compared to "offline" tDCS, with greater maintenance of learning found the following day [20]. When evaluating outcomes in interventions involving repeated tDCS administrations, these effects should also be considered as "offline" or "after"effects immediately following tDCS administration may affect task performance and/or other measurements, for example, cognitive or neurobiological changes following a course of tDCS for depression. While these after-effects have primarily been shown in the context of research studies [1, 21, 22], their impact should be carefully considered in multisession treatment studies.

A further methodological consideration is the relative effect of task related activity within stimulated regions, as this has also been shown to affect outcomes. For example, different effects on post-stimulation cortical excitability have been found depending on whether subjects were sitting passively at rest during tDCS, paying attention to a cognitive task, or actively engaging the stimulated region with performance of a motor task [23]. Further, the relative level of task-related activity has also been found to be relevant. While performance of a slow motor task during anodal stimulation over the motor cortex significantly improved learning and increased cortical excitability, poorer learning and decreased cortical excitability was found when subjects performed a fast motor task [24]. Relative activity levels during tDCS have further been shown to affect whether neuroplastic changes occur following stimulation, with ongoing background activity shown to be necessary to induce long-term potentiation in an in vitro animal model [25].

As such, both the timing of task execution together with the relative state of stimulated regions in relation to tDCS administration together are potentially important considerations when assessing outcomes for a particular study or intervention. Correspondingly, attempts should be made to control for potential brain state effects whenever behavioral or physiological outcomes are examined during or after tDCS administration. This could be achieved, for example, by requiring subjects to sit at rest for a given period prior to commencement of tDCS and implementing methods to standardize or restrict behavioral activity (e.g., talking) during and following stimulation.

14.2.3 Blinding, Sham, and Active Control

Appropriate blinding methods is a critical feature for interpretability of non-invasive brain stimulation studies and trials. The usual approach for blinding subjects is to apply a "sham" stimulation protocol which typically involves ramping the stimulation up and down similar to active stimulation, although only providing constant stimulation for a few seconds. The advantage of this methodology is while subjects will feel the initial itching/tingling sensation suggestive of active stimulation, the overall stimulation duration is too short to induce aftereffects, providing the stimulator is turned off after the ramping down period. If this latter step is not done, there is the potential for undesired neuromodulatory effects from the delivery of a constant very low level current with some devices when left on or in standby mode [26]. For 1 mA tDCS with an electrode size of 25 cm2, this method has been shown to reliably blind subjects [27]. As stronger stimulation intensities induce larger sensations, providing a brief constant stimulation at the maximum intensity, however, may compromise blinding [28]. An alternative approach is to apply topical anesthetics to abolish skin sensations [29]. Care should be given if this approach is taken, as local anesthetics may reduce cutaneous sensations indicative of skin damage which could in turn increase the risk for adverse side effects. However, prior research found no relationship between increased skin sensation and probability of skin burns, suggesting that the use of topical anesthetics may be a safe alternative in the sham procedure [30]. Nonetheless, care should be taken when considering the use of topical anesthetics. In recent years, the efficacy of tDCS blinding approaches has been called into question. This has been driven, in part, by insufficient assessment of blinding efficacy within studies, lack of consistent assessment of blinding efficacy across studies, and variation in sham techniques applied serving as potential sources of variability between studies [31]. To date, the most commonly used approach is the brief sham approach described above (ramp up, on for a few seconds, ramp down, and machine off).

Experimenter blinding is accomplished by use of tDCS stimulators, which include a sham stimulation function that enables the experimenter to remain unaware of the stimulation condition. However, even in this situation, it is important to note that the presence of skin erythema due to vasodilation, as well as sensations reported by subjects during and following stimulation, can nevertheless compromise experimenter blinding. Skin erythema can be reliably reduced by acetylsalicylate or topical application of ketoprofen [32]. Having one experimenter recording side effects following tDCS (e.g., skin reddening), while another one only assessing efficacy measures can further blind the primary interventionist to study conditions. Alternatively, allowing electrodes to remain in place on the participant's head for a period (e.g., 10 minutes) after stimulation has stopped can enable any skin erythema to dissipate and electrodes to return to room/body temperature levels prior to removal. This approach addresses both potential unblinding features potentially notable by experimenters. For reliable double blinding in sham/placebo-controlled studies, several different approaches should thus be considered. Any blinding procedures implemented must be accurately reported in scientific papers to facilitate replication in future studies.

On a related note, assessment of stimulation sensation and blinding efficacy is an important consideration for both clinical trials and research studies comparing active to a placebo/sham stimulation condition. Assessments of sensation should ideally evaluate a range of sensation types (e.g., tickling, burning, pain, warming, etc.) before, during, and after stimulation. This data can provide important information for direct comparison of the sensation experience between active and sham/placebo conditions of relevance for assessing sham/placebo blinding. Further, direct assessment of blinding of both participants and experimenters should occur at the end of the last stimulation session. While some studies simply inquire as to which condition the participant and experimenter believe was applied, expand-

ing this to include assessment of the confidence in their selection can provide additional useful information for assessing the integrity of blinding [33]. While a study/trial may show a significant difference in a selected outcome between active and sham/placebo conditions, this finding should be considered viable only in the context of a direct demonstration of sham/placebo-blinding efficacy within the trial/study.

Alternatively, or in addition, the inclusion of an active control condition may be considered. This may be useful to determine specificity if the overall goal is to demonstrate that stimulation applied over one cortical region induces a particular effect. Application of tDCS over an alternative brain region (i.e., as an active control) therefore may provide a stronger foundation for interpretation of results. For such designs, use of high-definition tDCS electrode montages (e.g., 4 × 1) could be considered, as this enables better localization of the stimulation effects particularly for cortical regions [34–37]. Notwithstanding, the choice of the control (i.e., sham or active) should be hypothesis driven, as this can have a profound impact on study conclusions.

14.3 Patient/Participant Screening

Using modern stimulation parameters, tDCS given either over a single treatment session or over several sessions spaced apart has been safely administered to healthy subjects and patients with diverse psychiatric (e.g., schizophrenia, attention deficit hyperactivity disorder, anorexia) and neurological conditions (e.g., stroke, epilepsy, traumatic brain injury) in experimental protocols [38]. Increasingly, tDCS has also been given over multiple repeated sessions to patients as a therapeutic intervention. Careful screening, however, is critical for minimizing the risk for adverse side effects for all protocols using tDCS in both healthy and patient populations.

Prior to stimulation, it is necessary to conduct formal screening for potential comorbid neuropsychiatric and neurological conditions as well as structural abnormalities. This is important both to accurately characterize the particular patient/participant population being investigated and to determine the relative risk for unexpected side effects for particular subjects. For example, mood switching in patients with major depressive disorder and bipolar disorder have been reported in several case reports [39]. For neuropsychiatric conditions, this can be achieved using published formal structured interviews, for example, the Structured Clinical Interview for DSM-5 (SCID-5: [40]) or the M.I.N.I.6. International Neuropsychiatric Interview (M.I.N.I. 6.0: [41]). Potential neurological conditions can be screened either through either patient interview or self-report questionnaires (e.g., Transcranial Magnetic Stimulation Adult Safety Screen; TASS; [42]). Due to the potential for local enhancement of current density as a result of anatomical abnormalities (e.g., to the skull), exclusion criteria for tDCS (i.e., metal in the head, no stimulation over fissures, or cranial holes) are also typically implemented. Recent research suggests that cardiac pacemakers are not affected by tDCS [43].

Screening for concurrent medication use is also important, as particular psychoactive medications can interact with tDCS effects. For example, D-Cycloserine, a common treatment for tuberculosis, has been shown to prolong the neuromodulatory effects of tDCS [44]. Other common medications, including selective serotonin reuptake inhibitors (SSRIs; [45]), mood stabilizers (i.e., sodium and calcium channel blockers; [6]), antipsychotics (i.e., dopamine antagonists; [46]), and common pain killers and sedatives (e.g., benzodiazepines; [47]), have also been shown to interact with tDCS. Concomitant medication use should therefore be kept stable throughout the study period and ideally for at least 4–6 weeks prior to tDCS administration in therapeutic interventions. Furthermore, the experimenter should be notified immediately of any medication changes during any tDCS study, as this may affect outcomes.

Lastly, as tDCS is administered using electrodes place upon on the scalp, it is necessary to inspect the skin where the electrodes will be

placed. Skin damage to these areas (e.g., disease, irritation, or lesion) during administration of tDCS can potentially increase the likelihood of further skin damage or skin burns [48].

14.4 Electrodes and Contact Medium

The role of electrodes in tDCS is to facilitate delivery of current from the stimulation device to the scalp. Teams of clinical trial researchers have reported application of thousands of tDCS sessions without any skin injury using rigorous control of electrode selection and preparation, along with adherence to established tDCS protocols, operator training, and use of certified devices [45, 49–52]. The tDCS electrode assembly most commonly comprises (1) a metal or conductive rubber (e.g., biocarbon) electrode, (2) an electrode sponge, (3) an electrolyte-based contact medium (e.g., saline, gel, or conductive cream) to facilitate current delivery to the scalp, and (4) any materials used to shape these components or otherwise direct current flow (plastic casing, rivets).

The metal or conductive rubber electrode is the site of electrochemical reactions during tDCS [53] and should never directly contact the skin. An electrolyte must be used as a buffer between the electrode assembly and the skin. Sufficient electrolyte volume prevents chemicals formed at the electrode during the electrochemical reaction occurring during stimulation from reaching the skin [54]. The electrolyte can be placed in a sponge encasing the electrode (i.e., saline) or, in the case of electrode cream, placed directly on the electrode surface. For saline, oversaturation of the electrode sponge can significantly undermine reproducibility of tDCS application and effects. When sponges are over-saturated, saline is evacuated from the sponge and covers an area of the scalp outside of the surface area electrode sponge. Rather than delivering current through a specified surface area on the scalp under the electrode (e.g., 5 × 5 cm), the electrode surface area and area of current delivery now encompasses the entire area of the scalp that is covered in saline. This creates an unreproducible and amorphous area of current delivery within and between subjects. It is important to obtain good contact under, and only under, the electrode with the electrode sufficiently, but not overly saturated. Methods allowing quantification of saline (e.g., syringes) can assist in achieving a consistent and appropriate amount of contact medium.

Consistent with issues introduced by oversaturation of sponges, the shape/size of electrodes/sponges significantly alter the distribution of current delivered to the scalp and the brain [55, 56]. At a constant current intensity level (e.g., 1 mA), increases in electrode size or differences in electrode assembly shape result in differences in the distribution of the current across the surface area of the scalp, resulting in differences in the distribution of current throughout the brain [55, 56]. 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.

14.5 Electrode Location

Another critical consideration for tDCS is determining where to place electrodes on the head. Studies monitoring physiological changes following tDCS and computational modeling studies of predicted current flow demonstrate that the relative location of electrodes results in significant differences in where and how much current is delivered to the brain [4, 57, 58]. For example, Nitsche and Paulus [1] demonstrated that relative differences in electrode locations altered whether or not 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 more selective stimulation of particular lobes of the brain [4, 57, 58]. Woods et al. [59] further demonstrated that as little as 1 cm of movement in electrode position significantly altered the distribution of predicted current flow in the brain, as well as the intensity of stimulation in specific brain regions. Recent research using intracranial recording and careful manipulation

of electrode positioning on the scalp directly demonstrated that a 1 cm shift in electrode positioning significantly alters the underlying E-field generated by tDCS [60]. Computational modeling of electric current through the brain can be a useful tool for the a priori design of tDCS electrode positions for a given study. In this same context, the importance of electrode location also highlights yet another critical consideration, preparation of a stable electrode placement on the head.

Head size and shape vary from person to person. Thus, it is necessary to use a method for common localization of electrode position. There are several methods for addressing this issue: (1) International 10-20 (or 10-5) Electrode Placement System [61, 62], or another gross anatomical coordinate system [63], (2) neuronavigation systems (e.g., MRI guided), or (3) physiology-based placement (e.g., TMS-generated MEPs). Each method can be used to consistently center each electrode on the head, accommodating varied head shape or size, and has relative strengths and weaknesses (e.g., accuracy vs. time and cost).

For example, even when using a method like the 10–20 Electrode placement, inaccuracy of electrode placement can occur due to human error in the measurement process or in placing the EEG cap over the head. Recent work provides methods for direct measurement of electrode placement using 3D scanning of the scalp using inexpensive hardware (e.g., iPad with an attached 3D scanning camera) to capture accurate models of electrode positioning on the scalp [64]. Prior work also provides for less technologically dependent methods for capturing errors in electrode positioning using physical measurements taken on the scalp [4]. Regardless of method, these techniques provide valuable information regarding the consistency of electrode location on the scalp both within and between participants. As prior work has demonstrated that electrode locations play a central role in the distribution of the E-field generated by tDCS, these measures provide a form of quality control measurement for studies and can provide metrics for inclusion in statistical analyses to assess or control for application variability in electrode location.

14.6 Electrode Placement

Once desired locations are identified based on specific study design needs, the electrode assembly must be affixed to the head for delivery of current. Nonconductive headgear used to position the electrodes on the body or scalp (e.g., elastic straps) are not typically included in the electrode assembly but are critical for appropriate electrode placement [4]. For tDCS using sponge-covered electrodes, elastic straps are the most commonly used headgear for electrode placement. If these straps are under- or over-tightened, electrodes have a strong tendency to move/shift over the course of a tDCS session. Thus, the distribution of current delivery changes over the duration of a tDCS session [4]. This too undermines tDCS replicability. Furthermore, if electrode straps are over-tightened, there is an increase in the probability of evacuation of saline from the electrode sponges. Regardless, the contour at the base of the skull below the inion and the flat of forehead provide for 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 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. 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.

As the field of tDCS has progressed, a wider array of electrode positioning systems has become available. Some of these systems provide rigid systems for placement of electrodes on the scalp, while others are individually adjustable. Other approaches have worked to integrate electrodes within EEG-like cap systems. Thus, a variety of electrode placement methods now exist. Regardless of selected electrode positioning approach, the user must evaluate whether the selected system provides a stable and consistent positioning and placement of the electrodes on

the scalps of participants/patients—evaluating these methods across different head sizes.

In addition, at-home based approaches to delivery of tDCS has significantly advanced over the past 5 years [65]. At present, there are a number of different available options for at-home approaches. Typically, at-home approaches involve a remote-supervision component where staff can remotely observe self-application of tDCS head-gear by the participant/patient. These systems typically involve a head strapping system with integrated electrodes that stretch to fit the electrodes over the desired target locations. Some of these available options require participants to individually prepare electrodes for each session, while others come with pre-prepped electrodes that are attached to the placement headgear. Commonly, participants will receive at least one or more in-clinic/lab or home visit training sessions on self-placement of at-home equipment prior to remotely supervised sessions. In addition, at-home systems typically involve controlled access to stimulation features on the at home device. For example, some systems provide single use stimulation cartridges while other involve input of a stimulation code that is only active for a dedicated period of time (e.g., 1 day) to activate a stimulation session. This provides the clinic/study staff with a level of control in terms of the interval at which participants/patients can deliver stimulation to themselves. At-home methods continue to advance, but may provide a viable remote option for delivery of multisession stimulation treatment in the future—for example, for depression [66].

14.7 tDCS Stimulator Selection

A limited but growing number of certified tDCS-stimulators are currently available [67]. These devices are designed to deliver constant current through two or more electrodes [68, 69]. Available stimulators differ based on specific features, such as: suitability for alternative stimulation protocols (e.g., transcranial alternating current stimulation, transcranial random noise stimulation, transcranial pulsed current stimulation), custom programming capabilities, number of stimulation channels, available stimulation intensity level, stimulator size, stimulator weight, stimulator portability, compatibility with magnetic resonance imaging (MRI), blinding options, and sham options. Certified tDCS stimulators provide the basic features required to deliver tDCS. Thus, selection of a stimulator depends on the planned application and study protocol (e.g., number of electrodes, requirements for blinding, desired stimulation intensity, sham options, etc.). In any case, exactness of delivered current, as programmed, is of crucial importance and should be tested at a regular interval (e.g., by aid of an oscilloscope), as minor deviances can result in prominent alterations of experimental outcomes. Thus, while a certified stimulator from a manufacturer may be delivered performing to exact specifications, repeated stimulation may result in alteration of the exactness of delivered current (i.e., delivery of less than or more than 2 mA when stimulator set to 2 mA) and should be tested for consistent delivery of tDCS to patients and participants. Certified tDCS stimulators also have the advantage of limiting the intensity of current to, typically, less than 3 mA, and limiting the duration of stimulation. In contrast, many stimulation devices repurposed for tDCS (e.g., iontophoresis stimulators) provide the ability to deliver stimulation up to and beyond 1 mA. This is a significant safety concern regarding skin lesions/burns, for example, if an error is made with stimulation settings. Stimulators should be chosen that provide optimal safety for participants and patients, as well as based on the specific features required for a given stimulation protocol.

14.8 Assessment of Safety/Adverse Events and Monitoring During Stimulation

It is important to make the distinction between tolerability and safety aspects in relation to tDCS. While tolerability refers to the presence of uncomfortable and unintended effects (e.g., tin-

gling and itching sensation under the electrodes), safety refers to damaging effects. Using modern protocols, comfort ratings for tDCS have generally shown a favorable tolerability profile [70, 71]. The most frequently reported side effects are tingling and itching sensations under the electrodes, headache, and tiredness [52]. The sensation of phosphenes elicited by abrupt current on- or offset is avoided by ramping current intensity in both active and sham conditions. Erythema under the electrodes is caused by tDCS-induced vasodilation and hence is not a safety issue [72].

In relation to safety aspects, no structural damage of brain tissue as examined with diffusion-weighted and contrast-enhanced MRI [73] or neural damage as assessed using neuron-specific enolase [73, 74]have been reported using the modern protocols introduced by Nitsche and colleagues. Nevertheless, caution should be taken to systematically assess safety when using protocols with stimulation settings beyond those typically used in modern research studies (e.g., higher current intensities), including those involving prolonged multisession treatment in clinical settings. To date only one seizure, which potentially may be attributed to tDCS, has been reported since the introduction of modern tDCS protocols. This occurred when repeated tDCS sessions in combination with administration of escitalopram was given to a 4-year-old boy who had a prior history of epileptic activity and a recent adjustment to his antiepileptic medication regime [75]. This report thus further highlights the importance for careful patient screening and monitoring, as well as titration with the use of both novel tDCS protocols and established protocols used in different clinical populations.

Another potentially relevant aspect to safety is the application of tDCS using an extracephalic reference electrode based on adverse side effects reported in an early study [76]. Computer modeling of the use of an extracephalic electrode placed upon the shoulder suggests that cardiac or brainstem activities should not be affected [77, 78]. Data in healthy subjects suggests that using an extracephalic electrode reference does not modulate brainstem autonomic activity [79]. Notwithstanding, this assumption does not necessarily apply for any tDCS protocol, independent from current intensity, and stimulation duration, and without regard for inclusion/exclusion criteria. Hence, careful patient monitoring to demonstrate safety is recommended particularly for novel protocols.

The most immediate safety risk for tDCS is the potential for skin lesions or burns following repeated treatments [30, 80]. Risk to subjects, however, can be substantially ameliorated through the implementation of several previously outlined recommendations [81, 82]. (1) Subjects should be screened for skin disease, irritation, or lesions underneath where the electrodes will be placed to minimize focalization of current density. Skin should also be checked prior to every tDCS administration. (2) A single-use sponge should be placed between the electrode and the scalp, as repeated use of sponges may lead to the build-up of substances, which could cause electrochemical reactions [80]. (3) Sponges should be evenly saturated with contact medium (e.g., saline) so that no dry portion of the sponge is in contact with the skin. If using electrolyte cream directly on an electrode, the thickness of the cream application should be consistent (~5 mm) and should cover the electrode completely, preventing direct contact of the electrode with the skin [82]. (4) Care should be taken to ensure adequate and even contact of the electrode skin interface is achieved. (5) Finally, standardized monitoring of patient comfort (e.g., discomfort/pain during stimulation) and side effects following stimulation should be implemented [81, 83], to regularly assess subjects' skin condition and risk for burns.

14.9 Monitoring Functional Effects of tDCS

There are several possible approaches to monitoring the functional effects of tDCS. Effects on motor cortex plasticity and motor cortex excitability, for example, are typically examined through experimental designs which involve firstly determining the motor cortex hotspot for a targeted muscle (e.g., first dorsal interosseous)

using single pulse TMS, obtaining a measure of baseline excitability, and then measuring physiological changes following tDCS stimulation [74, 84]. Another commonly used approach is to examine cognitive effects either during or following tDCS administration (for review, see [85]).

Increasingly, investigators are additionally employing neuroimaging tools (e.g., EEG and fMRI) to further explore functional effects. EEG, while lacking the spatial resolution of other techniques, has the advantage of allowing for enhanced temporal resolution for assessing tDCS-related functional effects. EEG measures voltage fluctuations resulting from ionic current flow via scalp recorded activity and thus is useful for elucidating changes in processing over time within specific regions or across circuits [24]. Similar to the assessment of functional cognitive changes, functional effects can be measured "online" or "offline" following stimulation. Both methods, however, are associated with methodological challenges. Firstly, the tDCS electrodes will need to be integrated together with the EEG electrodes, so as to avoid both types of electrodes being in direct contact and potential bridging between tDCS and nearby EEG electrodes via spreading of the conductive medium. The latter can be potentially avoided through the use of small-sized electrodes, similarly to those used with HD-tDCS [34]. Secondly, for "online" protocols, as tDCS involves the application of an electrical current and EEG directly measures very small electrical changes within the brain, there is the potential for direct interference from tDCS. This can thus result in saturation of an EEG recording amplifier that does not have sufficient range. Artifacts related to the tDCS device can also introduce external noise. Such effects may potentially be accounted for by the use of a phantom head so as to identify potential artifacts introduced by the tDCS device [86]. Recent research on the integration of tDCS and EEG has also evidenced that tDCS during EEG can produce local changes in skin impedance around the site of stimulation electrodes [87]. This, in turn, may significantly alter the amplitude of EEG data through improvement of impedance for the recording electrodes—which may be entirely unrelated to effects of tDCS on the brain and EEG signal therein. Continuous recording of impedance from recording electrodes may provide for methods to covary out artificial changes in impedance and recover interpretability of EEG data during tDCS. In addition, prior work also demonstrates that recording electrodes are able to detect a significant and variable heartbeat artifact around the site of stimulation electrodes [87]. This artifact is presumably produced by changes in local blood flow response under the stimulating electrodes and appears as a variable ~1 Hz signal within EEG data. Filtration/processing methods have been proposed as a possible method for addressing this artifact source. Nonetheless, EEG provides a promising method for integrated assessment of tDCS effects on the brain, but special considerations are required for production of interpretable data.

Functional effects may further be investigated using magnetic resonance imaging (MRI), which incorporates several methods including blood-oxygen-level-dependent (BOLD) fMRI [88, 89], arterial spin labeling [18], as well as proton and nonproton MR spectroscopy [90]. tDCS can be applied within the bore of the magnet, with the option of assessing effects either during "online" or "offline" stimulation, where subjects are removed from the scanner, have tDCS applied, and then are returned in the scanner. There are several methodological considerations in regards to the use of tDCS within the MR bore [91]. Firstly, due to the potential for premature drying out of the electrodes during concurrent scanning (which may last up to or over an hour), biocarbon electrodes should be attached to the participant using thick electrical conductance paste (e.g., Ten-20 paste), rather than saline soaked sponges or low viscosity electrode gel. Secondly, electrodes should be marked with oil capsules, so their position can be checked on the resulting images. It is also very important that electrodes are not in contact with the head coil, or sound attenuating headphones, to prevent electrode displacement and unexpected interactions between the stimulator and the scanner. Specially designed MRI-compatible (nonferrous or appropriately shielded) tDCS cables and electrodes passed

through the magnet suite waveguide and into the magnet bore are also necessary, with loops avoided and placed away from subjects to avoid the risk of eddy current induction and potential RF burns. Lastly, when analyzing data, consideration should also be given to the potential warping of the magnetic field due to the introduction of tDCS resulting in false positive findings.

14.10 Concluding Remarks

In this chapter, we deliver guidance for technically sound application of tDCS. Although the technique is seemingly simple and easy to apply, specific aspects must be taken into careful consideration to perform reproducible application and obtain reliable results. In the absence of careful consideration for the topics covered in this chapter, it is difficult, if not impossible, to interpret study findings, and difficult to facilitate attempts to replicate prior findings. In addition to other available technical guides to tDCS [92], this chapter will arm researchers and clinicians new to tDCS with insight into methodological considerations necessary for consistent application of tDCS in both clinical and research settings. For experienced researchers, this chapter provides a critical review of methodological aspects of tDCS important for consideration in attempts to replicate existing effects in the literature and important for inclusion in reports of tDCS effects. In summary, with careful consideration of the topics covered in this chapter, clinicians and researchers should be well equipped to perform consistent and reproducible tDCS in clinical and research settings.

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