Chapter 7
Methodological Considerations for Selection of Transcranial Direct Current Stimulation Approach, Protocols and Devices

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Evidence-Based tDCS Use

Appropriately selecting a transcranial direct current stimulation (tDCS) approach, design, protocol and specific device is a multifaceted process that requires careful and iterative consideration before the most suitable (and feasible) configuration is chosen. Practically speaking, the choice of an ideal or preferred selection is often a careful balance of available resources versus targeted outcomes. Thus, it is important to carefully consider how to balance the selection of tDCS approach, without compromising integrity and quality of the outcomes. Whether tDCS is used in research or non-research applications, the outcomes (or their segment, such as adverse event occurrence) become a part of the overall pool of evidence, which iteratively advances knowledge of the tDCS field and provides foundation for evidence-based tDCS practice. Building evidence-based tDCS practice (in the means of evidence-informed tDCS use) has the following implications:

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1. tDCS users should be able to access and *critically interpret* available evidence
2. New tDCS studies or applications should be designed with consideration of their ability to *meaningfully contribute* to the existing pool of evidence
3. Standards or guidelines of tDCS use should be based on systematic review of evidence (and therefore periodically revised as the body of evidence is growing)

Clearly, all these points are highly relevant for the step-by-step process of determining the best approach, parameters or protocol. The decision-making process starts with defining the purpose of the intended tDCS application; "Why" tDCS will be used and "What" specifically should be achieved. Answers to these two questions, to a large extent, require selecting the right design, stimulation protocol or workflow for tDCS procedures. At the beginning of the planning process, the answers to Why and What are usually vague, embedded in a broader open question, issue, gap in knowledge, or need. At that stage of planning, a *critical* review of existing tDCS evidence is invaluable to help clarify the answers and prevent methodological mistakes or poor choices for the overall tDCS setup.

When critically reviewing and evaluating existing evidence, an "evidence ladder" (Fig. 7.1) can assist in navigating the process.

tDCS studies in animal models primarily provide evidence pertaining to tDCS mechanisms and safety, and association between animal models and human studies.

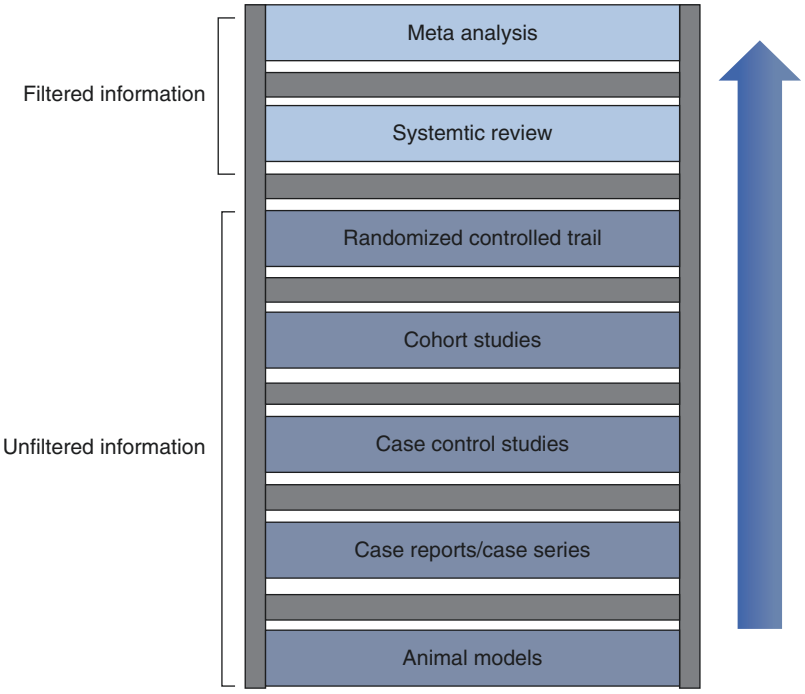

Fig. 7.1 Evidence Ladder

These studies supply evidence necessary for designing Randomized Controlled Trials (RCTs), such as initial evidence on effect size to properly power a study. The highest level of "unfiltered" evidence comes from RCTs, where the study design lacks methodological flaws. Alternatively, aggregate statistical evaluation of findings from a pool of RCT's, in the form of meta-analysis, then represents the "filtered evidence" at the top of the ladder. There are several systems available for evaluating the quality of the evidence. Although the evidence-scoring systems originate in health science/medical research, their principle fully applies to critical review of tDCS evidence as well. According to, for example, a "GRADE" scoring system (clinicalevidence.bmj.com), high quality evidence requires RCT's with only few methodological flaws. RCT GRADE quality is downgraded if RCT's have flaws, do not assess key elements, or the findings are inconsistent. Low quality evidence is usually produced by uncontrolled or observational studies; quality is upgraded if they include meticulous methods and produce moderate to large effects. Although uncontrolled studies and observations in general represent low-level evidence, they are essential as foundation for high-quality RCT's. Importantly, a carefully planned small-sample study may generate more meaningful evidence when implementing foundational support from preliminary studies. Moreover, in non-research settings, evidence-informed tDCS use may substantially facilitate progress in tDCS practice, while reckless tDCS applications not reflecting/ignoring the existing foundational knowledge may harm or set-back the field as a whole.

Practical Tips for Evidence Review

Meta-analysis:

- Review inclusion criteria – if the inclusion criteria are too broad, interpretation of the findings may be problematic. Although it is well known that tDCS outcomes are parameter specific, some published meta-analyses aggregate tDCS studies with other non-invasive neurostimulation modalities, or aggregate tDCS studies across brain targets or across delivered doses, (Lowe et al. 2017). In these cases, a careful interpretation is warranted. For example, results of meta-analysis evaluating studies of tDCS placing electrodes over the frontal lobes at F3 and F4 in 10 sessions over 10 consecutive days *and* studies placing the anode electrode over M1 and the cathode electrode over contralateral supraorbital area in once-a month regimen may be misleading and have little practical significance for planning of future applications, including selection of suitable approach or stimulation protocol.
- Evaluate bias – it is important to know not only if the included RCTs were biased, but also the source of the bias. The bias may originate from selection (systematic differences in baseline characteristics of the compared study groups), carry-over effect in cross-over RCTs, reporting (reported vs unreported findings), incomplete outcome data, unsuccessful/insufficient blinding, and other factors.

- Evaluate findings on the effects – What is the size and *direction* of the effect? What is the strength of evidence for the effect? Is the effect consistent across studies?

Critical review of clinical trials:

- Consider generalizability – findings may only be applicable to narrowly defined participant-population and may not be generalizable to other contexts.
- Consider power determination – Was the study adequately powered? How was the sample size determined? Interpretation of findings is especially problematic if the study is a non-inferiority trial that does not detect a significant difference between the study groups. It may be difficult to identify if the finding is really due to non-inferiority of the compared interventions or due to insufficient sample size.
- Consider overall quality of reporting of the study – clinical trial reporting should follow the CONSORT requirements (www.consort-statement.org).

Overall, a thorough review of published tDCS literature and other available evidence pertaining to the topic relevant for the planned tDCS use is a stepping-stone that helps progress through the tDCS approach, design, protocol and device decision-making process. Considerations, as discussed below, aim to assist the reader in selecting the most appropriate approach, design, protocol and specific tDCS device.

Experimental Versus Intervention Protocols

Non-invasive brain stimulation is a tool for modulation of brain physiological functions through alterations of brain activity, and excitability. It can be used as a: (1) research tool, (2) neuroenhancement tool and (3) therapeutic tool. As a research tool, it is applied to explore the role of different cortical and/or deeper areas of the brain in behavior (Filmer et al. 2014). The approach could potentially be used to shed light on the underlying mechanisms in different fields of neuroscience, as discussed in detail in Chap. 19. As a neuroenhancement tool, it is applied on healthy individuals to affect human motor control of movement and improve cognitive/sensory-motor learning capacity in a variety of tasks including sports, music, etc. (Furuya et al. 2014; Hendy et al. 2015; Moreau et al. 2015; Picazio et al. 2015; Zhu et al. 2015). As a therapeutic tool, it is used for management of pain, symptoms of aging, and reduction of clinical symptoms in neurological and psychiatric conditions (Anton et al. 2015; Fregni and Pascual-Leone 2007; George and Aston-Jones 2010; Nitsche et al. 2009).

tDCS as a Research Tool

Better understanding the brain-behavior relationship is a central goal in neuroscience research. A large number of studies focus on correlations between brain changes (Fig. 7.2) assessed by transcranial magnetic stimulation (TMS) and imaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magneto electroencephalography (MEG), electroencephalography (EEG), and near-infrared spectroscopy (NIRS) and behavioral

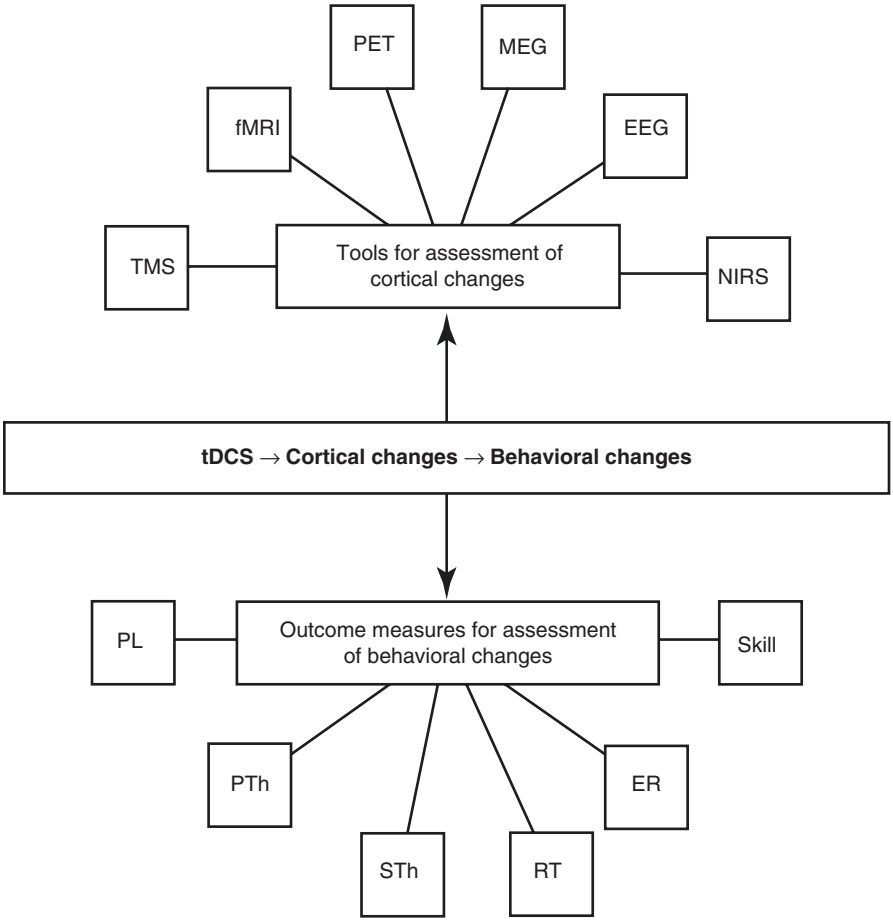

Fig. 7.2 Cortical and behavioral effects of tDCS. TMS transcranial magnetic stimulation, fMRI functional magnetic resonance imaging, PET positron emission tomography, MEG magneto electroencephalography, EEG electroencephalography, NIRS near infrared spectroscopy, PL Pain level, PTh pain threshold, STh sensory threshold, RT response time, ER error rate

changes assessed by a wide variety of outcome measures (Fig. 7.2) during sensory, motor or cognitive tasks. Combination of these methods and tDCS can convey significant insight for current basic and clinical research.

In this field of research, tDCS has been used to reduce or enhance the activity or excitability of cortical areas:

- To probe stimulation effects on near and far cortical regions (Vaseghi et al. 2015a, b), which helps to establish functional connectivity between different cortical areas.
- To measure stimulation effects on sensory, motor or cognitive functions (Apolinário-Souza et al. 2016; Nakagawa et al. 2016; Pope et al. 2015; Woods et al. 2014). This helps to establish the causal links between one specific cortical area and the task performed.
- To investigate hemispheric differences in processing of behavioral tasks (Bardi et al. 2013). When using certain parameters, the function of a cortical area in one side of the brain can be enhanced while the same area in the other side of brain is inhibited. The outcome of this interhemispheric imbalance can then be measured and used as evidence for communication and or rivalry between two hemispheres.
- To assess two or more behavioral outcomes to investigate if they are affected in the same way by tDCS to shed light on the functional organization of the brain (e.g., Iuculano and Cohen Kadosh 2013).
- To examine how it affects EEG power spectrum (Soekadar et al. 2014) and cortical excitability.

Blinding and Sham/Placebo Effects of tDCS

Blinding is a research procedural step for reduction of bias in modern RCTs. In double blinding, both participants and/or researchers are kept unaware of the allocation group. Without proper researcher blinding, they are more prone to bias during evaluation of the participants (Boutron et al. 2007; Brunoni et al. 2014). Lack of participants blinding is also problematic because it can increase the chance of placebo responses and treatment non-compliance (Noseworthy et al. 1994; Turner et al. 2012; Woods et al. 2016). Blinding integrity in any controlled trial or research study involves two main aspects: concealment allocation and a sham/placebo treatment.

Concealed allocation is not hard to achieve and technically is blinding during screening and separation of the candidates into two (or more) arms of a study. None the less, care should be taken in operator blinding including device options for coded programming (Alonzo et al. 2016; Russowsky Brunoni et al. 2015) and with subtle factors such as active-arm specific impedance changes or skin erythema considered (Ezquerro et al. 2017). On the other hand, it is not trivial to develop a

reliable method of sham tDCS, as it should be very similar to the active tDCS condition (Fig. 7.3a), yet free of neuromodulatory effects (Boutron et al. 2007).

Literature suggests the following techniques for sham tDCS in randomized trials:

1. The fade in, short stimulation, fade out (FISSFO) approach (Fig. 7.3b). In this method, the Direct Current (DC) is initially increased incrementally over several seconds (e.g., 10 or 30 s) until reaching the current density of choice (Hummel et al. 2005; Iyer et al. 2005; Nitsche et al. 2003). In active tDCS, stimulation is

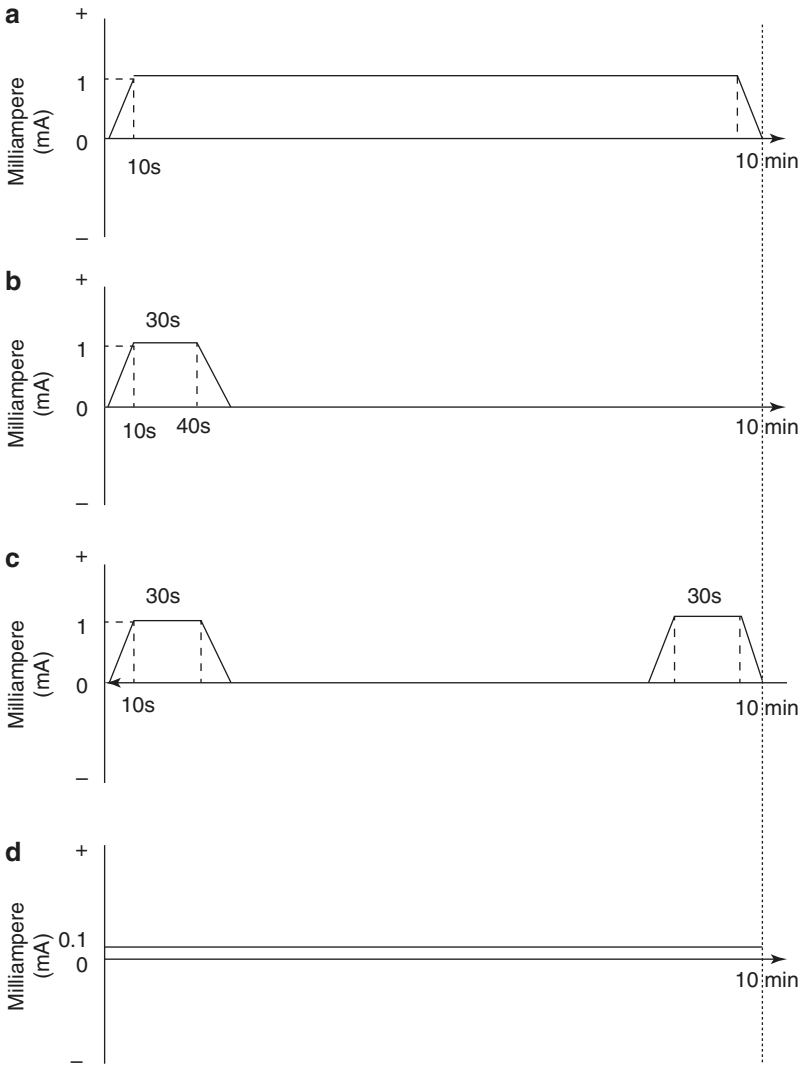

Fig. 7.3 Schematic diagram to simplify the techniques for application of sham tDCS (**a**) Active tDCS for 10 minutes with 10s fade in and 10s fade out at the beginning and end of the stimulation period. (**b**) The fade in, short stimulation, fade out (FISSFO) approach. (**c**) FISSFO at the beginning and FISSFO at the end of application time. (**d**) Low dose current (0.1mA) constant stimulation

maintained for the whole treatment time (e.g., between 10 and 20 min), while in sham tDCS it is ramped down after 30 s. The 30 s stimulation for sham tDCS was chosen based on previous reports that the perceived tingling sensations on the skin, usually fades during the start of tDCS (Nitsche et al. 2003). This method has been employed from the earliest tDCS studies. Gandiga et al. described similar rates of discomfort and adverse effects between active and sham tDCS (Gandiga et al. 2006). They also reported that none of the participants or investigators were able to distinguish between stimulation groups. This group concluded that tDCS can be used in double-blind sham controlled RCTs. In line with the findings in this study, other studies have also reported non-significant difference between the rate of common discomfort and adverse effects between the active vs. sham groups (Brunoni et al. 2011; Poreisz et al. 2007).

2. FISSFO at the beginning and FISSFO at the end of application time (Fig. 7.3c) (Caparelli-Daquer et al. 2012). In this approach, the current is ramped up and down at the beginning and end of the treatment time.
3. Maintaining a very low-dose current (e.g., 0.1 mA) during the stimulation session (Coffman et al. 2012; Fig. 7.3d).
4. For HD-tDCS, as the electrodes are smaller, a scalp-shunt sham is possible where electrodes are placed in close proximity (Richardson et al. 2014). The full current dose is provided (e.g. 2 mA for 20 min) even in the sham arm, but the proximity minimizes brain stimulation.

The tolerability (sensations) during any tDCS active or sham protocol is highly dependent on the electrodes use and preparation. Therefore, the internal validity of sham in any trial and the rationale for comparing sham reliability across trials is entirely depending on the reporting and controlled of electrode selection and preparation techniques (Woods et al. 2016).

It should be noted that the third sham technique (Fig. 7.3d), maintaining a very low-dose current during the stimulation session, is not used broadly by researchers. This may be partly due to the fact that lower intensities are also capable of inducing corticospinal changes (Bastani and Jaberzadeh 2013a, b), therefore this method is not a true 'sham' and it may confound interpretation of 'active' and 'sham' outcomes.

While the FISSFO procedure at 1 mA validated by Gandiga and colleagues (Gandiga et al. 2006) is followed in the majority of tDCS studies, results from a series of more recent studies questioned the reliability of this method. Ambrus and colleagues (Ambrus et al. 2010, 2012) have shown that experienced investigators were able to correctly distinguish between active and sham tDCS. Using higher current intensities (i.e. 2 mA instead of 1 mA) is considered as a key factor that is associated with detection of active tDCS (Ambrus et al. 2010; Dundas et al. 2007; O'Connell et al. 2012; Palm et al. 2013). Aforementioned examinations refer mainly to single-session studies. Integrity of blinding becomes more problematic in multiple-session tDCS studies, which refers to daily tDCS sessions for several days or weeks. This process may help participants to become more aware of the difference between their feelings during active and sham stimulation sessions, which may

adversely affect the blinding process. In conclusion, compared to 2 mA, lower intensities (i.e. 1 mA) in single or multiple session tDCS studies represent a better approach to keep integrity of blinding. However, this is not in all cases the best functional solution and use of an "active" control (e.g., use of a behavioural task expected to not be influenced by stimulation of a given brain region) may provide greater clarity on tDCS specific effects.

tDCS as a Therapeutic Intervention

tDCS has been investigated as a therapeutic intervention for a large number of neurological and psychiatric conditions. In particular, tDCS has attracted a great deal of research attention in the areas of pain management, stroke rehabilitation, cognitive rehabilitation, and depression. There are a number of methodological considerations for selecting and designing tDCS protocols that should be taken into account depending on the method of intervention (i.e., as a stand-alone or adjunctive treatment). Considerations for both types of intervention are outlined below.

tDCS as a Stand-Alone Technique

Stand-alone tDCS, that is in the absence of a concomitant intervention, has promising therapeutic potential particularly for pain management and as a treatment for major depression. Additionally, it has been investigated for reducing symptoms in multiple other neurological and psychiatric conditions. These interventions typically involve the administration of repeated tDCS sessions over consecutive days, ranging from one to several weeks. The rationale is that the effects of tDCS on cortical excitability are cumulative when administered over repeated sessions (Alonzo et al. 2012; Galvez et al. 2013). There are several methodological considerations when designing a protocol for using tDCS as a stand-alone therapeutic technique.

First, both the number and spacing of treatments is potentially important for treatment outcomes. For example, for treatment of depression, greater number of sessions has been associated with increased treatment response (Brunoni et al. 2016). For management of neuropathic pain after spinal cord injury, however, shorter duration of treatment (i.e., <1 week) compared to longer duration of treatment (i.e., >1 week) was associated with better treatment effects (Mehta et al. 2015). The spacing of treatments also can affect physiological outcomes, with cumulative effects found with daily sessions, but not when sessions were spaced 1 day apart over a 5 day period (Alonzo et al. 2012). Choosing the optimal number and spacing of tDCS sessions therefore may be dependent on both the clinical condition and treatment outcome in question. Similar considerations should also be given to the duration of stimulation, current intensity and montage, as these factors may similarly affect outcomes differently for different clinical populations. This is the case

as therapeutic outcomes for a particular clinical condition may depend on stimulation of different targeted regions. When investigating the therapeutic effects of tDCS in a new clinical condition, titration of stimulus parameters is therefore recommended, for example, in a clinical pilot.

A further consideration is standardization of subject's activity during the tDCS stimulation. This is potentially important as the relative activity levels within stimulated regions can interact with treatment outcomes. For example, the post stimulation physiological effects of tDCS have been shown to be dependent 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 (Antal et al. 2007; Fig. 7.4). The relative level of task-related activity may also affect treatment outcomes. Whilst performance of a slow motor task during stimulation of the motor cortex improved learning and increased cortical excitability, poorer learning and decreased cortical excitability occurred when subjects performed a fast motor task (Bortoletto et al. 2014). Due to these potential interactions dependent on

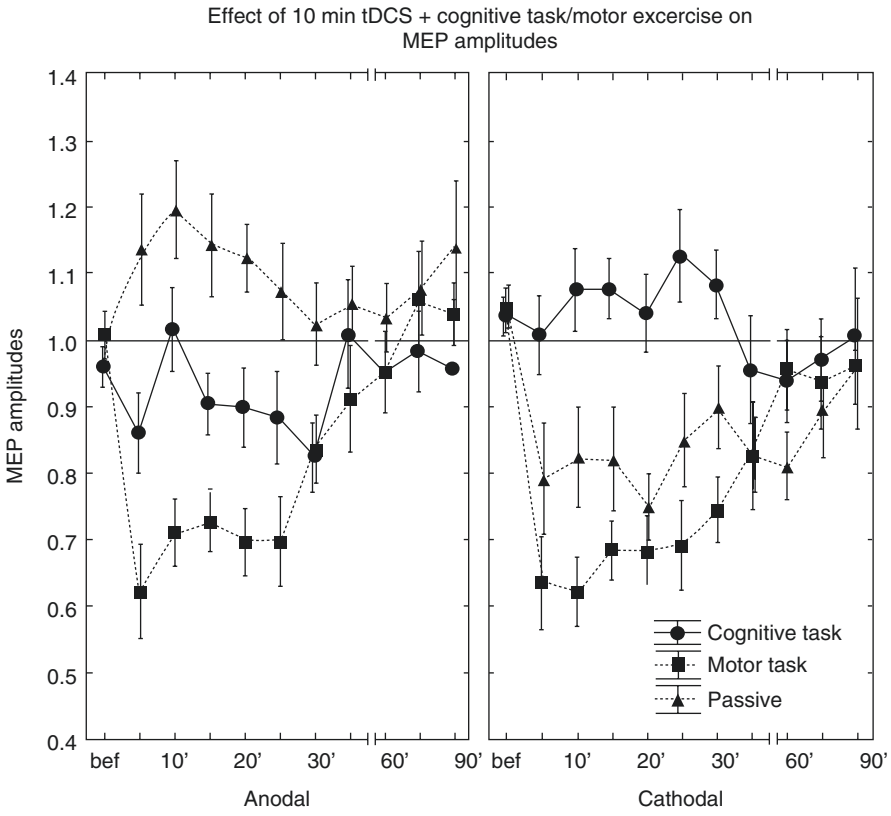

Fig. 7.4 Task related modulation of tDCS induced changes in cortical excitability within the motor cortex. (Reproduced with permission from Antal et al. (2007))

task activity during tDCS, attempts should be made to control for potential brain state effects during administration of tDCS as a stand-alone treatment. Implementing methods to either standardize or restrict behavioural activity, such as movement and talking, prior to, during and following stimulation is therefore recommended. Finally considering the interaction of placebo-related brain state changes with tDCS (Schambra et al. 2014), the patient experience (clinical ritual) including interaction with staff should be defined and controlled – especially in trials without concomitant intervention (explicit matched behavioural/cognitive therapy) as the case for most depression and pain trials.

For study design, the inclusion of a control condition that uses a different tDCS montage (e.g., actively stimulating an alternative target region) can also be considered. This could have potential utility for elucidating whether treatment effects are associated with neuromodulatory effects in particular brain regions. For example, Boggio et al. (2008) investigated the effects of stand-alone tDCS as a treatment for depression and randomized participants to receive either 10 sessions of active tDCS with the anode positioned either over the left dorsolateral prefrontal cortex (LDLPFC), or occipital cortex with the cathode positioned over the right supraorbital area, or sham. Results showed therapeutic effects only in the LDLPFC condition. This research thus formed the rationale for tDCS montages used in subsequent RCTs investigating tDCS for depression. Given limits on tDCS focality, computational models of current flow may be consulted in selecting the targeted intervention montage and active control montages (Truong et al. 2014).

tDCS as an Adjunctive Technique

Recently, there has been increased attention given to the investigation of tDCS as an adjunctive technique, through combining tDCS with other therapeutic interventions. These other therapeutic interventions could potentially be pharmacological, another form of brain stimulation, or behavioral. The rationale for using tDCS as an adjunct to pharmacological interventions is based on evidence that particular medications either potentiate or diminish tDCS neuromodulatory effects (Nitsche et al. 2012; Stagg and Nitsche 2011). tDCS may be used in combination with other forms of brain stimulation to prime, or precondition prior to administration of the second form of brain stimulation (Loo et al. 2009). Regarding combining tDCS with behavioral interventions, studies using animal models show that the presence of ongoing background activity is necessary for inducing lasting neuroplastic changes (i.e., Hebbian plasticity; Fritsch et al. 2010). In this regard, tDCS has been investigated as an adjunctive intervention to rehabilitative strategies in patients following stroke (Elsner et al. 2016), cognitive rehabilitation (Elmasry et al. 2015) and other interventions (e.g., cognitive behavioral therapy; D'Urso, Mantovani et al. 2013).

A potentially important methodological consideration for using tDCS as an adjunctive method with behavioral interventions is the timing of tDCS administration relative to intervention/task execution. Both behavioral and physiological

outcomes have been shown to differ depending on whether tDCS is administered 'online' (i.e., during tDCS administration) or 'offline' (i.e., either immediately prior to or following stimulation). For example, while improvement in motor learning was found with 'online' tDCS, decreased learning occurred when the same task was performed 'offline' following tDCS stimulation (Stagg et al. 2011). Similarly, better performance on a cognitive training task was found during 'online' compared to 'offline' tDCS administration, with maintenance of performance benefits the following day (Martin et al. 2014). These effects could at least be partly attributed to relative differences in the effects of tDCS on regional blood flow (i.e., as an index of neuronal activity) between the two conditions, with widespread increased activity during 'online' stimulation, and decreased activity in the period immediately following stimulation (Stagg et al. 2013). Given that therapeutic outcomes are likely dependent on the nature of the intervention (e.g., the effect of cognitive behavioral therapy on tDCS neuromodulatory effects), careful consideration should therefore be given to the timing of tDCS administration.

A further consideration is study design. It is ideal to include stand-alone tDCS as a control condition when it is unclear whether there is a therapeutic, additive or synergistic effect of tDCS as a stand-alone treatment or when combined with a particular intervention. The SELECT DCS trial was conducted in patients with major depression (Brunoni et al. 2013). This study used a 2 × 2 factorial design which included the following conditions: sham tDCS + placebo, tDCS + placebo, sertraline + sham tDCS, and sertraline + tDCS conditions. Such a design thus enabled the investigation of whether tDCS as an adjunctive intervention combined with sertraline had additive or synergistic effects on treatment outcomes.

Selection of an appropriate tDCS protocol depends upon the nine parameters outlined in Fig. 7.5.

Physiologic/Therapeutic Goals

Physiologic Effects

Physiologic effects of tDCS can be polarity dependent (Priori et al. 1998; Rowny and Lisanby 2008; Wagner et al. 2007). Typically, it is considered in the literature that application of the positive polarity electrode (Anode) over the target brain area (a-tDCS), increases resting membrane potential (depolarization of soma of cortical neurons) which leads to increased cortical excitability (Nitsche and Paulus 2000). Instead, application of the negatively polarity electrode (cathode) over the target brain area (c-tDCS), decreases resting membrane potential (hyperpolarization of cortical neurons soma), and causes decreased cortical excitability. However, new literature indicates that the polarity dependent effect of tDCS on cortical excitability is protocol

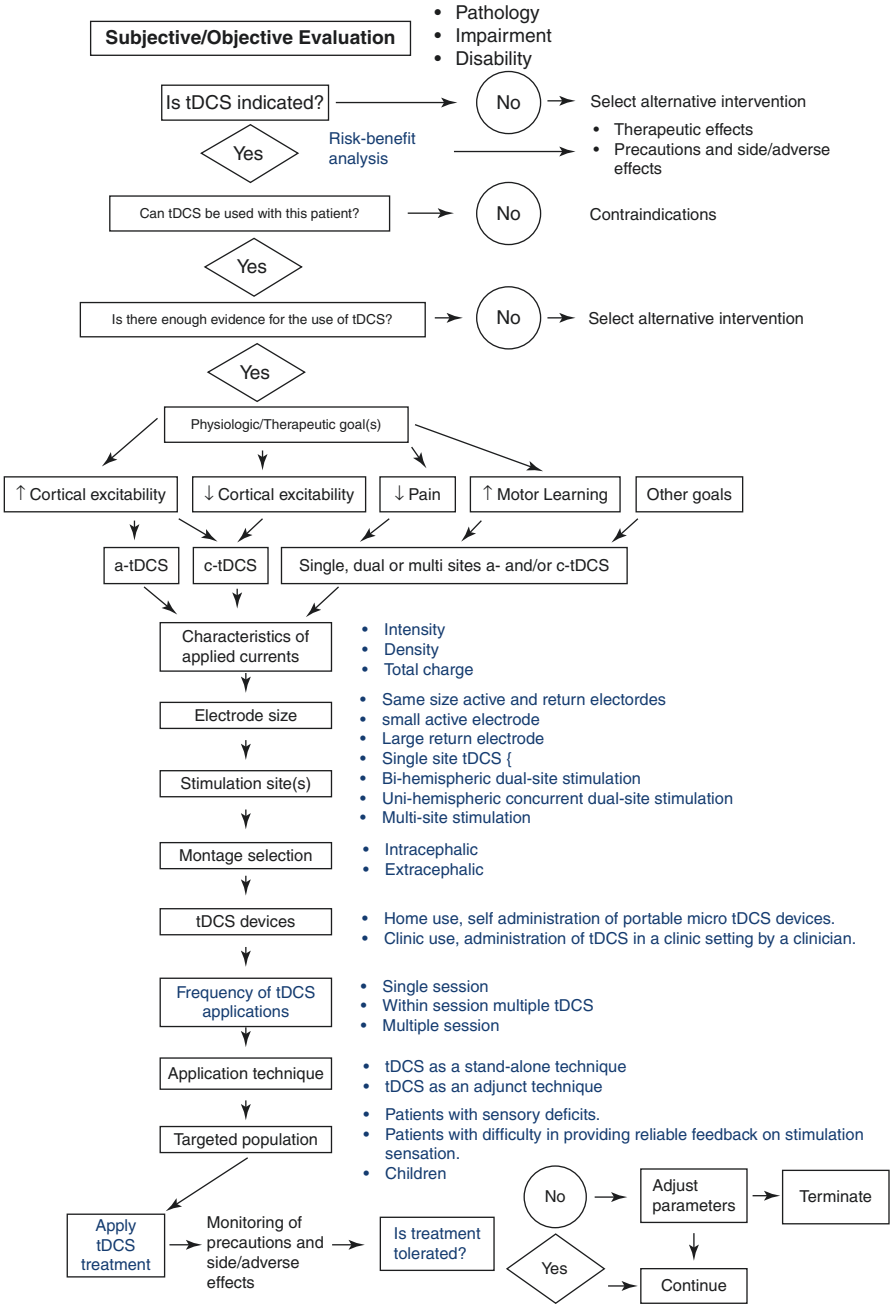

Fig. 7.5 Decision tree for selection of tDCS protocols

specific. This indicates that c-tDCS parameters, such as current intensity, duration of application, and site of stimulation, may determine its effects on corticospinal excitability (Batsikadze et al. 2013; Boros et al. 2008; Monte-Silva et al. 2010). Batsikadze et al. (2013) described a non-linear relationship between stimulation intensity and modulation of corticospinal excitability (Batsikadze et al. 2013). For example, one study showed that 20 min c-tDCS with intensity of 1 mA significantly *diminished* corticospinal excitability, while 20 min c-tDCS with intensity of 2 mA *increased* corticospinal excitability (Batsikadze et al. 2013). Recently, Vaseghi et al. showed that concurrent c-tDCS of M1 and DLPFC increased the corticospinal excitability, unlike separate stimulation of these two cortical centers (Vaseghi et al. 2016). These finding supports the notion that the effects of c-tDCS is protocol specific.

Therapeutic Effects

tDCS is a non-invasive technique that is considered to produce only transient and mild adverse effects (Aparício et al. 2016; Bikson et al. 2016, 2017; Russo et al. 2017). Its use in clinical research has significantly increased, particularly for neuropsychiatric disorders such as major depressive disorder, schizophrenia, rehabilitation after stroke, Parkinson's disease, drug addiction and other neurological and psychiatric conditions (Fregni and Pascual-Leone 2007; George and Aston-Jones 2010; Nitsche et al. 2009). In spite of heterogeneous results in some studies, typically due to differences in the methodological procedures and differing inclusion/exclusion criteria used in a given study, the findings are generally promising and further well controlled clinical studies are required to better address the therapeutic effects of tDCS.

Characteristics of Applied Currents

The extent of tDCS-induced corticospinal excitability changes depend on the current intensity/density (Nitsche and Paulus 2000) and duration of current application (Furubayashi et al. 2008; Nitsche et al. 2008; Nitsche and Paulus 2000; Nitsche and Paulus 2001). As reported in a systematic review (Bastani and Jaberzadeh 2012), tDCS with higher current densities induces larger corticospinal excitability changes. Nitsche and Paulus (2000) compared five current intensities between 0.2 and 1 mA (CDs between 0.006 and 0.029 mA/cm^2). They found that a stimulus intensity of at least 0.6 mA (electrode size 35 cm^2; CD: 0.017 mA/cm^2) for 5 min is required to induce a significant increase in corticospinal excitability (Nitsche and Paulus 2000).

Even though, literature indicates success in the use of 1–2 mA (10–20 min) for induction of different cortical and behavioral changes (Furubayashi et al. 2008; Nitsche and Paulus 2000; 2001; Nitsche et al. 2008), Bastani and Jaberzadeh (2013a, b)

showed that lower intensities (i.e. 0.3 mA) induces larger corticospinal excitability changes than 0.7 mA or 1.4 mA. This indicates that effects of intensity may be non-linear. Thus, future research is required to further evaluate the modulatory effects of lower current intensities on the induction of corticospinal changes. Compared to higher intensities (1–2 mA), the 0.3 mA induces less side/adverse effects and therefore it is tolerated better by participants and could be safely used in protocols with multiple tDCS applications. However, the majority of current evidence in tDCS exists for stimulation intensities between 1 and 2 mA.

Electrode Size

Electrode size is a key factor in determination of current density and total charge density during application of tDCS, which also influences the relative spatial distribution of the applied current in the brain. Using smaller electrode sizes tends to increase the relative spatial focality, as measured by neurophysiological outcomes, of the induced cortical electric field during application of tDCS (Nitsche et al. 2007) though physical computational models (Datta et al. 2009; Dmochowski et al. 2011) and measurments (Antal et al. 2014; Huang et al. 2017; Jog et al. 2016) predict current must always flow in the brain regions between electrodes. Due to close proximity of cortical sites within the brain, larger electrodes can directly affect a number cortical sites affected by stimulation.

Nitsche et al. (2007) have manipulated the size of conventional pad electrodes and assessed its effects on modulation of corticospinal excitability. They found that a small (3.5 cm^2) anode placed over the abductor digiti minimi representation over M1 did not affect the excitability of the neighbouring representation of the first dorsal interosseus muscle, which located just outside the boundaries of the anode. Furthermore, computer modelling studies showed that larger electrodes resulted in more diffuse current flow between the electrodes (Datta et al. 2009; Wagner et al. 2007). Additionally, Bastani and Jaberzadeh (2013a, b) compared the effects of different electrode sizes over M1 and showed that using smaller electrodes with same current density induces larger corticospinal excitability changes. They concluded that the larger electrodes may also stimulate nearby cortical functional areas, which may have inhibitory effects on the M1. The relationship between electrode current density and resultant current density (electric field) in the brain is not simple, depending also in the position of the "return" electrode, and can be informed by computational current flow models (Bikson et al. 2010; Faria et al. 2011) (also see Chap. 9).

However, even the smallest brain regions can be functionally connected to other distal brain regions. Thus, it is not correct to assume that even more focal stimulation of a brain region, or even truly focal stimulation of a single gyrus (the latter of which is currently not possible with currently available methods – such as what we see during high definition tDCS), remains locally. Indeed, it may have downstream effects on the function of anatomically connected distal

brain regions (Polanía et al. 2012). This fact highlights the critical importance for *not* over-interpreting the focality of tDCS results, even when using smaller electrodes such as 3.5 cm^2 or even 1 cm diameter high definition electrodes.

Stimulation Site(s)

The stimulation site should be selected carefully based on the desired effects of tDCS interventions. As discussed above, no brain region operates in true isolation. Different neural processes are carried out by a dynamic network of interacting brain regions (Baudewig et al. 2001; Lang et al. 2004, 2005). In addition, many behavioral indicators of neurological and psychiatric diseases are not merely the result of abnormality in one isolated brain region but represent alterations in different brain sites within brain networks. As a result, simultaneous or consecutive stimulation of different superficial sites in the brain networks may be central to optimizing tDCS outcomes.

Montage Selection

Traditional application of tDCS involves, placement of one electrode where current is delivered to the head over a cortical site of interest and one return electrode where that current is taken back up, over another area. This electrode arrangement is called a cephalic montage and is the most utilised montage for application of tDCS. If the return electrode is positioned over another region of the body (not over the cranium) the technique is called extracephalic. It should be noted that the size and the place of the return electrode determine the path of the penetrating current, which appears to influence the final effects of stimulation (Bikson et al. 2010; Kabakov et al. 2012). A common misconception in the literature is that the return electrode is passive (or inert). However, studies have shown that the return electrodes are not physiologically passive/inert and actively contribute (whether antagonistic or additive) based on return electrode position (Accornero et al. 2007; Antal et al. 2004).

tDCS Devices

Currently a limited set of certified tDCS-stimulators are available. All certified devices deliver constant current (Agnew and Mccreery 1987; Bronstein et al. 2015), are battery operated and can be broadly classified as either laboratory/clinic-based (DaSilva et al. 2011; Schestatsky et al. 2013; Villamar et al. 2013) or

home-based (Kasschau et al. 2015) devices. Stimulators differ for specific features, such as suitability for other stimulation protocols (e.g., transcranial alternating current stimulation, transcranial random noise stimulation, etc.), programming capabilities, number of channels, size, weight, portability, suitability for magnetic resonance imaging (MRI), ramp features, and blinding options. All certified tDCS-stimulators provide the basic features required for tDCS. These basic features include the ability to produce constant current, the ability to ramp current up and down over a period of time (rather than on/off), a method for evaluating electrode contact quality (e.g., impedance), a method for setting stimulation intensity (e.g., 1 vs. 2 mA), and a method for setting stimulation duration (e.g., 10, 15, 20 min, etc.). As such, stimulator choice depends on planned application (e.g., need for blinding protocols, desired intensity level, number of electrodes, portability, wear-ability, home-use, lab/clinic-use, etc.). In contrast to lab/clinic stimulation devices, home-based devices are designed to simplify self- (or proxy-) administration to patients at home. In these home-based devices the stimulation parameters are usually set by the clinicians or researchers, and to avoid any un-authorized use, they are fitted with locking mechanisms (e.g., coded activation of device for single use, remote activation by clinician, etc.) (Charvet et al. 2015). In addition, exactness of delivered current delivered is of crucial importance, and should be tested (e.g., by aid of an oscilloscope), since minor deviances can result in prominent alterations of experimental or clinical outcomes.

Frequency of tDCS Applications

Earlier literature reported a monotonic relationship between the duration of tDCS application and its induced effects (Jaberzadeh et al. 2012; Nitsche and Paulus 2000, 2001). However, this notion was challenged by Monte-Silva et al. (2013). They concluded that the observed direct relationship between the duration of tDCS application, size and duration of the effect of stimulation may not exist during longer applications of tDCS. Neuronal counter-regulation, which prevents over-excitation of the involved neurons, is a possible mechanism for explanation of this observation (Monte-Silva et al. 2013). This finding suggests that increasing the duration of tDCS application is not the best strategy for induction of larger and longer lasting corticospinal excitability (Monte-Silva et al. 2013), but may not generalize to other outcomes (e.g., cognition, etc.). Within session repetition of shorter tDCS applications, could be considered as an alternative approach for induction of larger and more lasting effects (Bastani and Jaberzadeh 2014; Monte-Silva et al. 2013). Monte-Silva et al. (2013) showed that single-session repetition of 13 min of a-tDCS within certain time intervals induces M1 excitability alterations which lasted for 24 h. This finding was supported by Bastani and Jaberzadeh (2014), concluding that within-session repeated tDCS induces larger corticospinal excitability with day-long lasting effects. Multiple sessions of tDCS application

appear to extend the size and duration of the effects (Goldsworthy et al. 2015; Meinzer et al. 2014).Stimulation repetition interval may also be relevant (Monte-Silva et al. 2013).

Application Technique

tDCS could be used as a stand-alone therapeutic intervention or as an adjunctive technique to prime the effects of other treatments (Hesse et al. 2007; Hummel and Cohen 2006). As a stand-alone therapeutic technique, tDCS has been used for modulation of pain (Mehta et al. 2015; Rostami et al. 2015), treatment of depression (Brunoni et al. 2016), and management of epileptic seizures (Assenza et al. 2014). As an adjunct technique it could be used to facilitate motor rehabilitation following stroke (Elsner et al. 2016), or to enhance learning with other interventions.

Targeted Population

tDCS can be used in both healthy and patient populations at different age levels. Differences in brain size and anatomy suggest that children and adult brains require different tDCS dosage (Kessler et al. 2013; Minhas, Bikson, Woods, Rosen, & Kessler, 2012). This is driven by a number of factors, including smaller overall head size, thinner cerebrospinal fluid space in children, thinner skulls in children, and a number of other physical factors. Likewise, compared to younger adults, the brain in elderly people, require special consideration for similar reasons (e.g., greater cerebrospinal space, etc.). This will be described further in Chap. 20. Population specific dosage calculations for these groups have not been established yet and should be considered as a priority for future tDCS research. Caution must be taken when selecting specific design criteria for populations yet unstudied or with limited prior study using tDCS. In addition, special consideration should be given to vulnerable populations or groups that may not clearly adhere to the study design considerations above (e.g., children). Ethical considerations regarding vulnerable populations and regarding protocol selection will be discussed in Chap. 14.

Conclusion

This chapter provided a framework for considering the factors relevant to make an informed choice about the appropriate tDCS approach, protocol and device for a given study or clinical trial. The necessary workspace that must be considered to reach an informed and appropriate decision is highly complex. Ranging from

electrode size, stimulation intensity, online vs. offline application, stand-alone vs. adjunctive approaches, duration of stimulation, location of stimulation, or the additional factors covered in this chapter, each must be considered carefully before study initiation or clinical application. Many of the topics in this list deserve careful and detailed consideration in their own right. Other chapters in this book will serve to provide the detailed information necessary for full consideration of tDCS approach, protocol, and device in the design phase of clinical and research applications of tDCS. While the literature provides a primary point of reference for study protocols used in past studies, it is very often the case that incomplete methodological reporting limits our ability to fully replicate prior studies. The information provided in the current chapter will help the reader to identify critical considerations that should be attended to not only in their own study or trial design, but also in their evaluation of studies presented in the literature.

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