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REVIEW

Considering the influence of stimulation parameters on the effect of conventional and high-definition transcranial direct current stimulation

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ABSTRACT

Recently, techniques to non-invasively modulate specific brain areas gained popularity in the form of transcranial direct current stimulation (tDCS) and high-definition transcranial direct current stimulation. These non-invasive techniques have already shown promising outcomes in various studies with healthy subjects as well as patient populations. Despite widespread dissemination of tDCS, there remain significant unknowns about the influence of a diverse number of tDCS parameters (e.g. polarity, size, position of electrodes & duration of stimulation) in inducing neurophysiological and behavioral effects. This article explores both techniques starting with the history of tDCS, to the differences between conventional tDCS and high-definition transcranial direct current stimulation, the underlying physiological mechanism, the (in)direct effects, the applications of tDCS with varying parameters, the efficacy, the safety issues and the opportunities for future research.

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Introduction

Delivering direct electric current over the scalp has been reported since the distant past. The first records of electrical therapy date from 43 to 48 A.D., when Scribonius Largus (the physician of Roman Emperor Claudius) reported on the treatment of pain by placing a live torpedo fish – delivering a strong direct current – over the scalp [1]. Similar findings were found by Claudius Galen and Pliny the Elder [2]. In the eleventh century, Ibn-Sidah, suggested the placement of a live electrical catfish on the frontal bone for the treatment of patients suffering from epilepsy [2]. In the eighteenth century, with the introduction of the electrical battery, the science of electrophysiology was started by Walsh [3], Galvani [4,5], and Volta [6], who recognized that electrical stimuli of varying duration can evoke different physiological effects [7]. Research using non-invasive low current application to the brain has more or less sustained throughout the nineteenth and twentieth century (for a review see [8]), with a recent reappraisal of transcranial direct current stimulation (tDCS) as a non-invasive brain stimulation method at the turn of this century [9,10]. The studies of Priori and his colleagues [11] followed by Nitsche and Paulus [12,13] have demonstrated that low direct electrical currents, using tDCS, applied over the scalp are capable of influencing brain excitability [11] and can produce substantial aftereffects on cortical excitability that last for minutes to hours after termination of the stimulation [12]. In the past 15 years, tDCS has been investigated in a wide range of disorders (e.g. chronic pain, stroke, aphasia, tinnitus, depression, schizophrenia, craving, migraine, fibromyalgia,

Parkinson's disease, etc.) with promising outcomes and potential for future treatments (e.g. [14–28]).

In this article, we will focus on the technical parameters of conventional tDCS, which uses a direct current (i.e. uninterrupted unidirectional current flow [8],) to influence brain regions as well as the more recent and focalized form of tDCS, namely High-Definition tDCS (HD-tDCS) using an array of smaller 'high-definition' electrodes to target specific brain areas and brain networks. The article explores the mechanisms of action of tDCS, the applications with varying parameters, the efficacy, the safety and adverse effects of tDCS and the opportunities for future research.

Conventional tDCS

Conventional tDCS procedures use a pair of large surface electrodes (typically 25–35 cm²) connected to a stimulator delivering constant electrical direct current (typically 1–2 mA) to stimulate relatively broad brain areas located between the electrodes (see Figure 1). The most commonly used equipment for tDCS involves two saline-soaked sponges, electrodes (typically conductive rubber), non-conductive elastic straps, cables, and a battery powered direct current delivering device [29,30]. The two saline-soaked sponges contain slits in which the electrodes (an anode and a cathode) can be placed to form an electrode-sponge unit [30]. Another possibility is the use of rubber electrodes with conductive gel [29]. In conventional tDCS, usually one anode electrode and one cathode electrode are applied over the scalp to modulate a particular brain area by inducing polarity-dependent changes in the

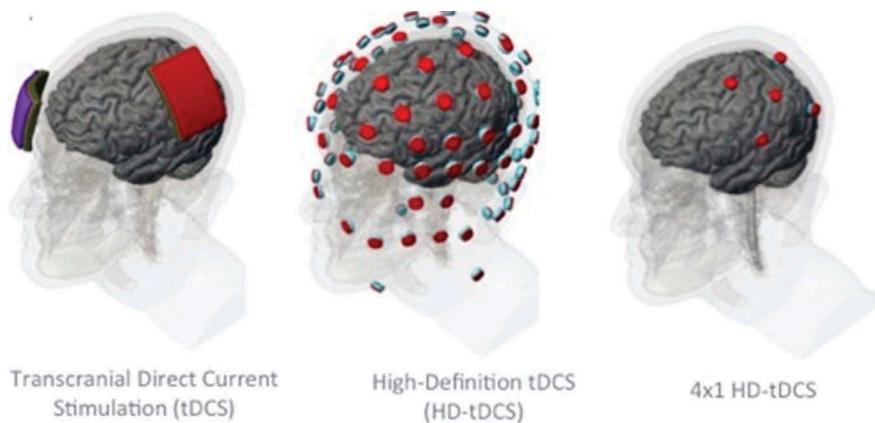


Figure 1. Example set-up of conventional tDCS, HD-tDCS and the 4x1 HD-tDCS montage. (Figure provided courtesy of Professor. Bikson and the Neural Engineering Group, The City College of New York).

brain, inducing a controlled electrical current at the anode while drawing an equivalent return current at the cathode [30], in other words, the current flows from the anode to the cathode. Due to the high electrical resistance of the skull [31], only 50% of the transcranially applied direct current reaches the brain, the rest being shunted through the extracranial soft tissues, as demonstrated by calculations on realistic head models, validated both in animal [32] and human [33] experiments.

TDCS devices on the market include Soletrix Medical 1 × 1 (U.S.A., <http://soterixmedical.com/t�cs>), NeuroElectronics Starstim (Spain, <http://www.neuroelectrics.com/products/starstim/starstim-tcs/>), magstim tDCS (U.K., <http://www.magstim.com/products/t�cs-stimulators>), Schneider Electronic (Germany), Rogue Resolution neuroConn tDCS (Germany, <http://www.rogue-resolutions.com/system/dc-stimulator-t�cs/>), Electro_Diagnostic & Therapeutic Systems GmbH (Germany), Foc.us v2 (U.S.A., <http://www.foc.us/v2/>), and the brain stimulator (U.S.A., <https://thebrainstimulator.net/>) among others.

Behavioral studies have revealed potential therapeutic applications of tDCS for a wide array of disorders including chronic pain, stroke, aphasia, tinnitus, depression, schizophrenia, craving, migraine, fibromyalgia, Parkinson's disease (e.g. [14–23,34]). It has also been shown to improve cognitive functions, such as memory and learning in healthy individuals (see [35]), in contrast to mood, which seems uninfluenced in healthy volunteers [36]. However, focal stimulation of target cortical regions not involving stimulation of neighboring anatomical areas is difficult to achieve with conventional tDCS [37]. Modeling and imaging studies suggest diffuse brain stimulation [38–40]. Low focality is not always a problem for each application of tDCS [41,42]. In some clinical disorders, modulation of pathologically altered excitability of larger regions might be preferable [41,42]. However, if efficacy and safety are to be systematically optimized, it is paramount to identify the precise site of action of electrical stimulation paradigms [42]. Also for research purposes, a more focal stimulation is important, to gain a better understanding of the specific brain regions involved in the studied symptom or disease, which is difficult to dissect with diffuse electrical stimulation [41].

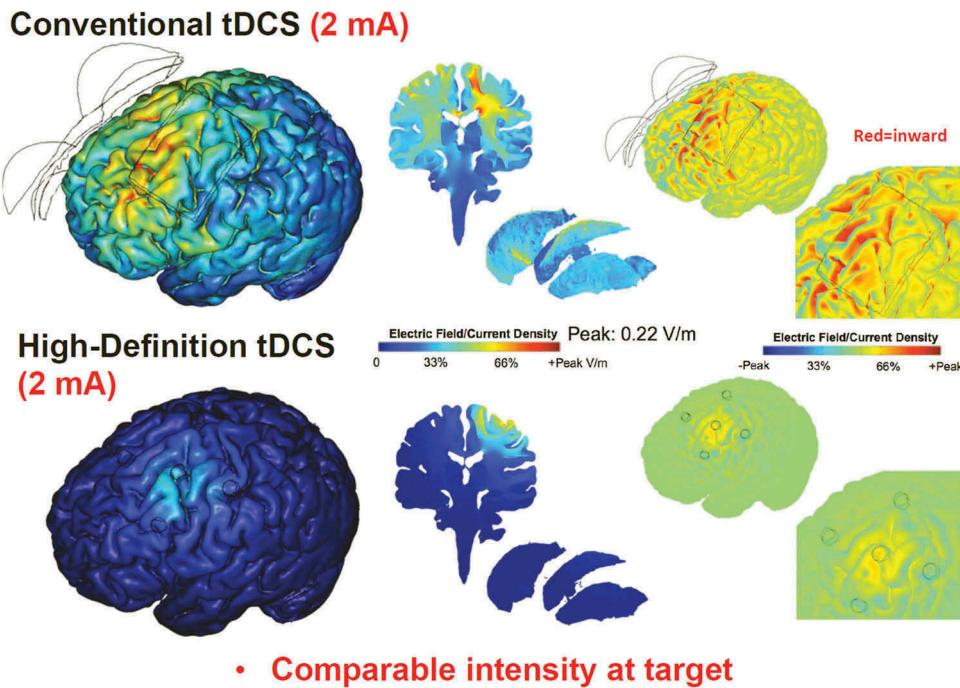
HD-tDCS

High-Definition transcranial Direct Current Stimulation (HD-tDCS) has been recently introduced to improve the spatial accuracy of conventional, by using arrays of smaller 'high-definition' electrodes, instead of the two large pad electrodes [8,27,37,39,42,43] (see Figures 1 and 2). A diminished electrode size has been shown to reduce affected cortical area size and therefore increase focality [44]. Targeting a brain area using HD-tDCS is achieved by placing the electrodes in a predetermined configuration to rationally guide current flow [37,42]. HD-tDCS can be provided using a variation of montages having different positions and different number of electrodes (see Figure 1) [42]. Some of the devices that can deliver HD-tDCS are NeuroElectronics Starstim (Spain-<http://www.neuroelectrics.com/products/starstim/starstim-tcs/>), Rogue Resolution neuroConn HD-tDCS (Germany-<http://www.rogue-resolutions.com/system/hd-t�cs/>), and Soletrix Medical (US-<http://soterixmedical.com/hd-t�cs>) among others.

Although relatively few studies have been published on HD-tDCS so far, it has been shown to reliably target specific brain areas and has shown to produce plastic changes that may outlast conventional tDCS [45]. Studies have been performed investigating motor cortex excitability [45,46], conscious movement intention [47], fibromyalgia [25], pain [26,28], tinnitus [27], verbal learning and memory functioning [48], and pre-attentive spectro-temporal feature processing in auditory system [43]. Different types of smaller 'high-definition' electrodes have been used in studies, such as silver pellet, silver/silver chloride pellet, rubber pellet, silver/silver chloride ring, and silver/silver chloride disc [49]. A study comparing conventional tDCS with a HD-tDCS design using a set of small electrodes approximating the conventional set-up (covering the large pad-electrodes) found that the HD-tDCS approach achieved electrical fields with greater focality (80% improvement) and higher target intensity (98% improvement) at cortical targets using the same total current applied [42].

Mechanism of action

Although the exact mechanisms involved in the effect of tDCS are not fully understood [34,50], tDCS is known to use surface



- Comparable intensity at target

Figure 2. Focality of conventional tDCS and HD-tDCS using comparable intensity (2 mA) and target (dorsal lateral prefrontal cortex). (Figure provided courtesy of Professor Bikson and the Neural Engineering Group, The City College of New York).

electrodes over the scalp resulting in some shunting of current at the scalp as well as cerebrospinal fluid (CSF) with a portion of the current eventually penetrating the brain [30]. The current used in tDCS is subthreshold which means that tDCS, unlike Transcranial Magnetic Stimulation (TMS), does not induce action potentials [51]. Indeed, when applying tDCS on the motor cortex, in contrast to TMS, no muscle contractions can be noted. Instead tDCS modulates membrane potential facilitating or inhibiting spontaneous neuronal activity [30,52]. Anodal stimulation will produce inward current flow, which is expected due to somatic depolarization of pyramidal cortical neurons and apical dendrite hyperpolarization, while cathodal stimulation will typically produce outward current flow and is expected to result in somatic hyperpolarization of pyramidal cortical neurons and apical dendrite depolarization [53,54].

However, tDCS often results in a delayed clinical effect [55,56], which cannot be explained by pyramidal or interneuron cell firing. Therefore, two other mechanisms have been proposed to be involved in tDCS: glial and stem cell modulation. Based on cable theory one type of glial cell, namely astrocytes, are possible targets [57]. Astrocytes control the formation, maturation, function (and elimination) of synapses through various secreted and contact-mediated signals [58] and can thereby regulate neural circuit development and function [58]. This could potentially explain the delayed effect of tDCS. Furthermore, another type of glial cell, microglia, who prune synapses, might also be involved. It has indeed been shown that tDCS activates microglia both under anode and cathode [59]. Thus, glial cells might be modulated by tDCS resulting in synapse formation and/or elimination.

But apart from modulating neurons, both pyramidal and interneurons, and glial cells, both astrocytes and microglia,

tDCS could exert its delayed effects via stem cell activation. Indeed, tDCS seems to recruit proliferating neural stem cells under the cathode [59] thereby opening the possibility of regenerative capacities for tDCS.

The mechanisms of action of tDCS regarding neuromodulation and neuroplasticity have also been investigated using a pharmacological approach. Pharmacological studies enhance the knowledge about the mechanism of tDCS using diverse drugs to block and/or enhances the activity of neurotransmitters and its receptors to observe how and whether tDCS-induced cortical excitability is modified [9]. Table 1 gives an overview of studies regarding the impact of central nervous system (CNS) active drugs that interact with tDCS effects. Studies have demonstrated that changes induced by tDCS involved regulation of a broad range of neurotransmitters including dopamine, acetylcholine and serotonin [60–62] and also affected different neuronal membrane channels, such as voltage-gated sodium and calcium channels [63].

Excitability changes during anodal and cathodal tDCS are due to the modulation of membrane potential, thus modulating the conductance of sodium and calcium channels [41,63]. The increase in cortical excitability induced by anodal tDCS [13] is reduced by calcium channel blocker flunarizine, and abolished by the sodium channel blocker carbamazepine [64,65]. However, in cathodal tDCS, unlike anodal stimulation, blockade of neither voltage-dependent calcium nor sodium channels had an effect on excitability shifts [64,65]. In contrast to the effects of tDCS during stimulation, the aftereffects of tDCS appear to be driven by changes in synaptic strength. TDCS modulates synaptic activity via neurotransmitters and neuromodulator activity. More specifically, glutamatergic N-methyl-D-aspartate (NMDA)-receptor modulation seems to be involved in the aftereffects of tDCS in humans [64].

Table 1. CNS active drugs that interact with tDCS effects.

Substance	Study	Results
<i>Voltage-gated ion channels</i>		
Carbamazepine	[64]	Abolishment of the depolarizing effect of anodal tDCS
	[65]	
Flunarizine	[65]	Abolishment of the depolarizing effect of anodal tDCS
<i>Glutamatergic system</i>		
Dextromethorphan	[64]	Abolishment of the aftereffect of anodal and cathodal tDCS
	[65]	
D-cycloserine	[66]	Enhancement of the duration of anodal tDCS; no effects on cathodal tDCS
<i>GABAergic system</i>		
Lorazepam	[67]	Promoted a delayed, enhanced and prolonged effect of anodal tDCS
<i>Dopaminergic system</i>		
Sulpiride	[68]	Abolishment of the aftereffect of anodal and cathodal tDCS and promoted a delay in the increase of excitability after anodal tDCS
Pergolide	[68]	Prolonged the aftereffects of cathodal tDCS
L-dopa	[70]	Low (25 mg) and high (200 mg) dosages of L-dopa abolished anodal and cathodal tDCS; medium (100 mg) dosage turned facilitatory plasticity caused by anodal tDCS into inhibition and prolonged effect of cathodal tDCS
	[71]	
Ropinirole	[61]	Produced an inverted U-shaped dose-response curve on plasticity for anodal and cathodal tDCS
<i>Cholinergic system</i>		
Rivastigmine	[60]	Abolishment of the depolarizing effect of anodal tDCS; Stabilized the aftereffects of cathodal tDCS
<i>Serotonergic system</i>		
Citalopram	[65]	Enhanced and prolonged effect of anodal tDCS; turned cathodal-induced inhibition into facilitation
<i>Catecholaminergic system</i>		
Amphetamine	[72]	Enhanced and prolonged effect of anodal tDCS

Blocking NMDA-receptors abolishes the aftereffects of tDCS, whereas enhancement of NMDA-receptor efficacy by D-cycloserine (a partial NMDA agonist) enhances selective, facilitatory plasticity [66]. The NMDA-antagonist dextromethorphan suppressed the aftereffects of both anodal and cathodal tDCS [64]. Beyond modulation of the glutamatergic system, anodal and cathodal tDCS have also been found to reduce free gamma-amino-butyric acid (GABA) in the cortical areas under the electrodes [73]. Administration of the GABA receptor agonist lorazepam increased and prolonged cortical facilitation with anodal stimulation after an initial transient depression [67].

Taken together, the voltage-gated sodium and calcium channels, the glutamatergic system and the GABAergic system could be seen as the drivers of plasticity [74]. However, other neuromodulating neurotransmitter systems can modulate plasticity [74]. TDCS can be modified, abolished, prolonged and even reversed by co-application of drugs acting on the central nervous system [75]. Amphetamine and citalopram were found to increase and prolong anodal tDCS-induced excitability [65,72], whereas citalopram also reverses the cathodal tDCS effect [65]. Another drug for boosting the tDCS aftereffects is rivastigmine, which stabilized the aftereffects of cathodal tDCS [60]. Dopamine has a nonlinear effect on tDCS-induced plasticity which depends on dosage and sub-receptor activity [61,68–70].

Direct regional and indirect network effects of tDCS

The effect of tDCS has mostly been investigated on the motor cortex physiology [9]. However, there is evidence for similar functional or physiological impact of tDCS targeting other cortical regions including the visual cortex [76], the somatosensory cortex [77,78], and the auditory cortex [79] although the effects of stimulation might differ slightly [41,80]. Beyond the regional effects of tDCS under the stimulation electrodes, more remote effects on topographically distant cortical and subcortical areas have been found [40] (see Figure 3). Combining tDCS with non-invasive brain imaging techniques such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) allow for a better understanding of the effect of tDCS on large-scale brain connectivity and network alterations. Recent studies have shown that tDCS affects brain connectivity patterns during rest and task performance [81–92], suggesting that this is not influencing only the target area, but a brain network [93]. Resting-state studies examined the effect of tDCS in healthy subjects (for review see [93]) as well as in patients (e.g. tinnitus patients [91]) using resting-state fMRI (for review see [93]) or resting-state EEG [91,94] before and after stimulation. Thus, the effects of tDCS are not only restricted to the areas under the electrodes. TDCS also induces specific modifications of functional connectivity of networks linked to those areas [41,80]. So far, our understanding of the precise electrophysiological mechanisms of tDCS and how the effect spreads across functionally connected networks is still far from being complete [95].

tDCS parameters

The effects of tDCS depend on a lot of factors, tDCS parameters as well as uncontrollable factors including the resistance of several cephalic structures such as skin, skull, blood vessels, and brain tissue [9,30,50,63]. In this part, we will only focus on controllable tDCS parameters. These factors include (1) polarity of the electrodes, (2) size of the electrodes, (3) the position of the electrodes, (4) the intensity of stimulation or the amount of current delivered (in mA), and (5) the duration of the stimulation (varies between 20 and 40 min in most studies) [9,30,50,80]. By varying these tDCS parameters, stimulation protocols can be customized to a certain extent to achieve the desired direction, strength, focality, and duration of effects on cortical activity and excitability [9,80].

The effect of polarity on stimulation

The effect of tDCS depends on the polarity of the stimulation. The most simple design schemes for tDCS assume a region of 'increased excitability' in the cortex directly under the anodal electrode, and a region of 'decreased excitability' under the cathode [38] (see Figure 4). For example, in tDCS for a current of 1 mA and a duration less than 20 min, anodal stimulation over the motor cortex increases motor evoked potential (MEP) and results in an opposite effect when the polarity is changed to cathodal stimulation [75]. Such polarity-dependent modulations have been found in motor processing, visual processing, attention, working memory and language [96]. However,

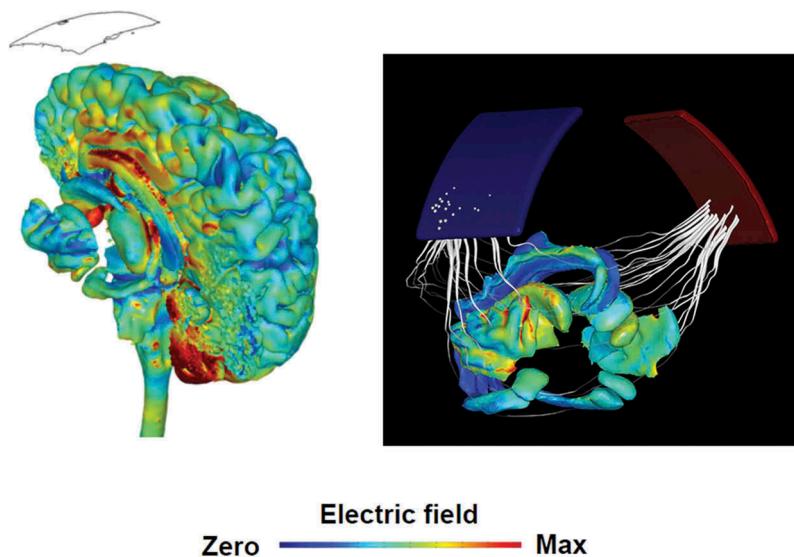


Figure 3. Regional effects of tDCS under the stimulation electrodes and more remote effects on topographically distant cortical and subcortical areas. (Figure provided courtesy of Professor. Bikson and the Neural Engineering Group, The City College of New York).

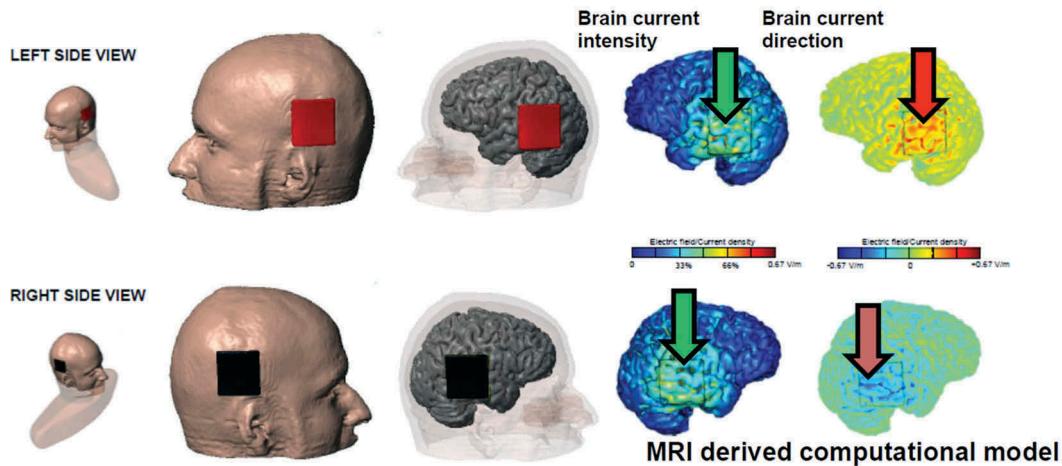


Figure 4. Polarity of the stimulation. TDCS assumes a region of 'increased excitability' in the cortex directly under the anode electrode, and a region of 'decreased excitability' under the cathode electrode. (Figure provided courtesy of Professor. Bikson and the Neural Engineering Group, The City College of New York).

changing dose, including increasing duration and/or intensity, or alteration in ongoing brain activity, can change and even invert the direction of excitability modulation [96,97]. For HD-tDCS, using more complex electrode configurations, a recent study has suggested that an accurate description of the direction of the electrical field (electrical field orientation) is more relevant than the polarity of the electrodes themselves [98]. The authors recommend that tDCS as well as HD-tDCS studies must not be constrained by the anodal/cathodal dichotomy.

The effect of the size of the electrodes

The size of the electrode is of importance, as the electrode size (for a fixed applied electrical current) influences the current density (i.e. is defined as a function of current intensity (mA) and electrode size (cm^2) (mA/cm^2)) as well as the focality of brain stimulation [44]. There are a variety of electrode sizes (e.g. $5 \text{ cm} \times 5 \text{ cm}$, $5 \text{ cm} \times 7 \text{ cm}$, $8 \text{ cm} \times 8 \text{ cm}$, and $10 \text{ cm} \times 10 \text{ cm}$;

see [29]). For conventional tDCS, the size of the two electrodes (i.e. 'anode' and 'cathode') typically varies between 25 and 35 cm^2 with one 'active' electrode over the target area and a 'return' (or 'reference') electrode on another scalp location or other body part. A larger electrode (e.g. 64 and 100 cm^2) can be used as the return electrode, since this electrode (when also positioned on the scalp) is not physiologically inert and can produce unwanted excitability changes under the electrode [9,44]. Enhancing the size of the return electrode can reduce the current density under the return electrode while keeping the current strength constant [44]. Instead of using one large return electrode, the use of multiple small return electrodes has also been suggested [99]. For the target electrode, studies have suggested that the smaller the electrode size, the larger the current density [39,100], but modelling studies have suggested that the relationship between the electrode size and the area of modulation to be more complex [101]. Computational models suggest that the

resulting current density under the electrodes is lower for smaller electrodes compared to larger electrodes with the same current intensity-to-electrode size ratio [99,101]. Similarly, a study showed that larger target electrodes (35 cm^2) resulted in greater increase in cortical excitability compared to smaller electrodes (16 cm^2) [102]. Superior levels of shunting of current on the scalp have been found for smaller electrode compared to larger electrodes [50]. One study even suggested that small electrodes might require a greater injection of current to result in the same current density within the brain [103]. Regarding focality, it has been found that smaller HD-tDCS electrodes, typically of 8-mm diameter (e.g. [49]) enhanced the focality compared to conventional tDCS electro-pads [37].

The placement of electrodes

The correct placement of the electrodes is crucial for achieving the intended effects [9,13]. Electrode positioning is of significance for the spatial distribution and direction of the flow of the current which together determines the effectiveness of the stimulation [34]. These electrodes induce effects right beneath the underlying cortex, as well as at remote areas [39–41,44,80]

(see Figure 3). There is evidence that beyond the local effects of stimulation, tDCS induces specific modifications of functional connectivity of the targeted networks [80,89]. The placement of the electrodes on the scalp is usually determined according to the international EEG 10–20 system [9,30].

For conventional tDCS, two electrodes are used with one electrode positioned over the region of interest and the other electrode (the ‘return’ or ‘reference’ electrode) elsewhere on the scalp (often the contra-lateral supraorbital region or an uninvolved head region) (known as ‘bipolar’ or ‘bicephalic’ montage, i.e. montage with two electrodes on the head; see Figure 5A) or elsewhere on the body in an extracephalic location (known as a ‘unipolar’ or ‘monocephalic’ montage – i.e. when the return electrode is placed below the neck) (see Figure 5B) usually on the shoulder or upper arm [9,30,75] or even the leg [104].

In bicephalic montages, it is possible that any effects of tDCS on behavior are due to modulation at the return electrode, or an interaction between the target and the reference site [96,105]. This can only be ruled out by conducting control experiments with alternative reference locations [96] or by using a larger reference electrode [44,96]. Thus, depending on the aim of the study it may be more advisable to place

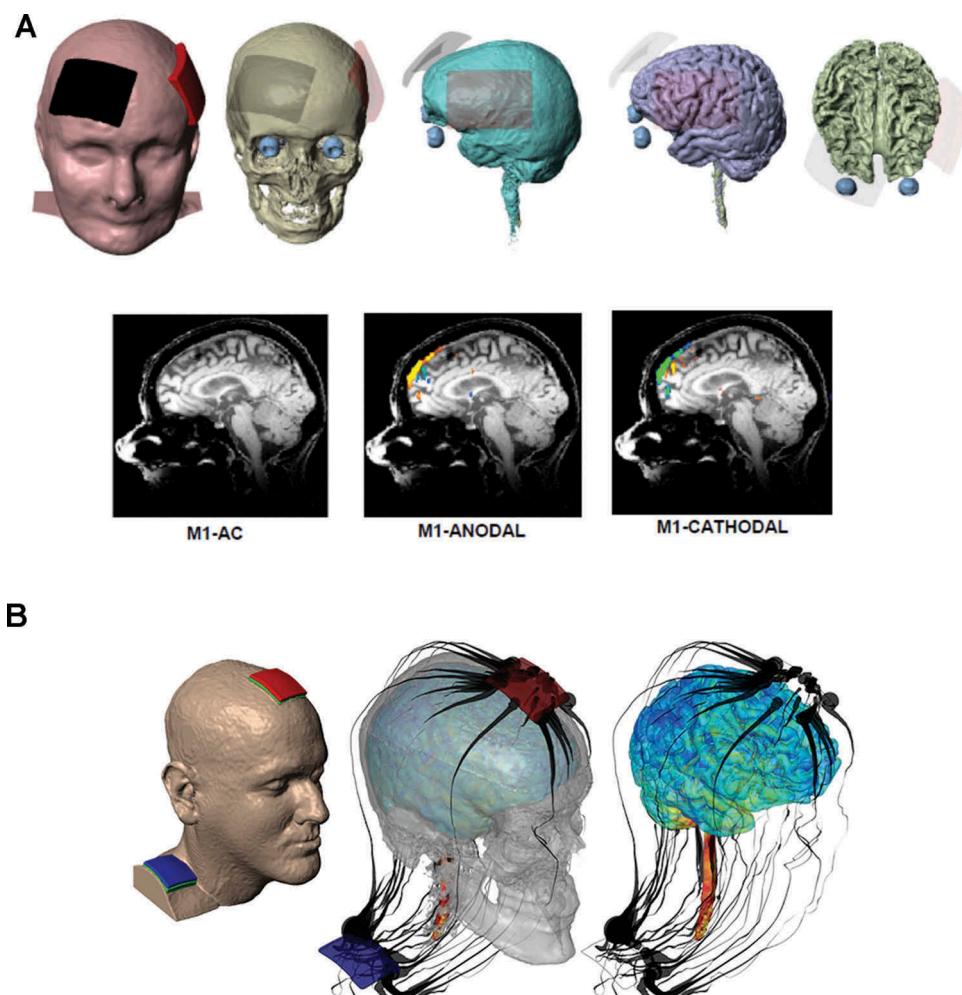


Figure 5. (A) “bipolar” or “bicephalic” montage: two electrodes are used with one electrode positioned over the region of interest and the other electrode elsewhere on the scalp (B) unipolar” or “monocephalic” montage: two electrodes are used with one electrode positioned over the region of interest and the other elsewhere on the body in an extracephalic location (Figure provided courtesy of Professor Bikson and the Neural Engineering Group, The City College of New York).

the return electrode on an extracephalic position to resolve the ambiguity in the interpretation of the tDCS effects with two cephalic electrodes [9,34] or to have two cephalic electrodes when increasing and decreasing activity in different brain areas simultaneously may be advantageous [9]. Generally, in bicephalic configurations increasing the distance between the electrodes decreases the current shunted through the scalp, increases the current into the brain and increases the current density in depth [38,106,107]. Some authors suggest that the strongest stimulation might not only occur in the brain region directly underneath the electrodes, but also in the areas in between the electrodes [107,108]. A study investigating the influence of inter-electrode distance on long-lasting effects of tDCS found that when the distance between the electrodes is increased by changing the return electrode from the forehead ('bicephalic') to the upper arms ('monocephalic' montage), higher stimulation intensity is needed to achieve similar after-effects of tDCS distance [109]. Thus, when using an extracephalic reference electrode with tDCS the stimulation intensity should to be adapted to the inter-electrode distance [109].

In HD-tDCS, many different positions and number of electrodes can be used to deliver the electrical current with each montage adjusted for a specific clinical or experimental aim. The montages tested include the 4 × 1 ring configuration (e.g. [25–27,39,43,45,110]), as well as individually optimized arrays (e.g. [28,42]).

The most commonly used HD-tDCS configuration is the 4 × 1 ring configuration where the center ring electrode (anode or cathode) overlies the targeted brain area and is surrounded by four reference electrodes at 3–7.5 cm radius [26,27,37,39,43,45,98,110], such that decreasing ring radius increased the focality of the stimulation [24] (see Figure 6). This configuration enables more restricted cortical neuromodulation [24,26,45,111] and leads to higher electrical fields in comparison to the larger electro-pads [111]. Even using this strict configuration, the focality and intensity of the stimulation can be altered by changing the ring diameter [24,106,110]. A wider ring leads to a wider, intense and deeper region of induced cortical current flow, whereas decreasing

the ring diameter is suggested to lead to increased focality at the cost of current shunting across the scalp [24]. In a recent computational modelling study comparing conventional tDCS montages with HD-tDCS montages, the authors found that HD-tDCS montages (i.e. 4 × 1 ring configuration and 2 × 2 montage) enhanced the focality, but stimulated less deep than tDCS montages [24]. The peak of electrical field using the 4 × 1 HD-tDCS was further found to be under the center electrode, whereas using the conventional tDCS the electrical field peaked midway between the two electrodes instead of underneath one of them [39,111]. A study focusing on the inter-individual variation during tDCS demonstrated that the HD-tDCS 4 × 1 ring configuration is more compelling than the conventional tDCS, because this configuration led to current flow restricted within the ring perimeter across all subject, minimizing variability in current flow pattern [111]. Furthermore, the 4 × 1 montage has been found to be a suitable design for radially oriented currents, but is unlikely to be appropriate for tangential fields [42]. An advantage of 4 × 1 montage is that the diffusion of return current along the four electrodes forming a ring results in a more unidirectional modulation such that the polarity of the center electrode (anode or cathode) determines the primary change in excitation; this is compared with conventional tDCS where both anodal and cathodal effects must be considered [25,27,39,110]. The effects of the 4 × 1 HD-tDCS montage is not only more focal compared to conventional tDCS, but also longer lasting [45]. The effect of 4 × 1 HD-tDCS may be time-dependent reaching its peak several minutes (30 min) after the end of the stimulation and not immediately after [25,37,45]. Therefore, sequential assessments over different time points following the intervention may be needed in order to obtain accurate results [37].

Recently, new electrode montages have been reported in research such as 2 × 2 HD-tDCS montages [28]. In this montage, four electrodes are arranged at the corners of a 4 × 4 cm² area, centered over the targeted brain region. Two anode electrodes were positioned anterior to the target area and two cathode electrodes were positioned anterior to the

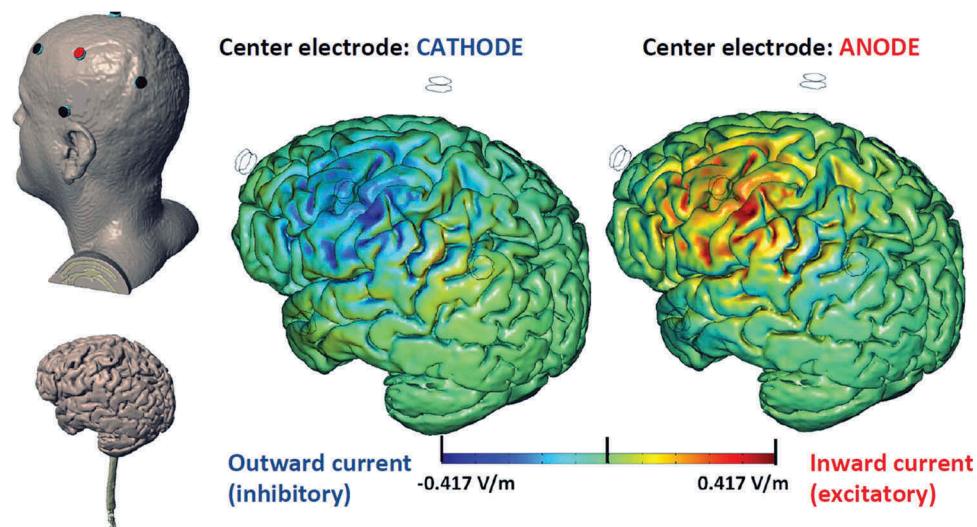


Figure 6. The 4x1 ring configuration. (Figure provided courtesy of Professor. Bikson and the Neural Engineering Group, The City College of New York).

target area, at the corner of a $4 \times 4 \text{ cm}^2$ to focally target the selected brain area on a postero-anterior direction [28].

The effect of the intensity of stimulation

TDCS uses a low-intensity constant current ranging from 0.2 to 2 mA to modulate specific brain areas [12,13,54]. The current intensity (mA) is an important factor in defining the tDCS electrical dose or the current density (mA/cm^2) (the current density is calculated as a function of current intensity (mA) and electrode size (cm^2)) [102]. Changing this parameter is thought to influence the magnitude of the stimulation outcome. The effect of current intensity between 0.2 and 1 mA on motor cortical excitability was investigated, while maintaining the electrode size of 35 cm^2 , and it was found that higher current intensity (1 mA) formed greater changes in cortical excitability than lower current intensity (0.2 mA). Since then, there is a trend for using higher current intensities (e.g. 2 mA) in studies to produce more robust effects on excitability, although it is still uncertain whether current intensity is the key factor [102]. Recently, more and more studies indicate that increasing the intensity of the stimulation does not necessarily increase the efficacy of the stimulation [41,97,112,113]. One study has suggested that anodal tDCS at low current intensities can in fact produce the same or even greater increase in cortical excitability compared to higher current intensities [112]. There is also evidence that there is no difference in the magnitude of changes in excitability for anodal tDCS between current intensities of 0.8 and 1.2 mA [113]. Moreover, there is an indication that high-intensity (2 mA) stimulation may shift the direction of excitability alterations. Whereas low-intensity (1 mA) stimulation causes conventional polarity specific modulation of neural excitability (i.e. anodal increased versus cathodal decreased excitability), higher-intensity (2 mA) stimulation can lead to increased excitability for both stimulation polarities (i.e. anodal and cathodal) [97]. For example, anodal as well as cathodal stimulation over the left primary motor cortex at 2 mA has been found to reduce perceived pain in fibromyalgia using HD-tDCS [25]. Furthermore, in contrast to low-intensity stimulation protocols, 2 mA stimulation has been found to induce aftereffects with a delay [97]. The effects of 2 mA emerge after 90 min [97]. Studies have been conducted to investigate possible altered intensity of current flow for diverse subpopulations, including pediatric [114,115] and obese populations [116] as well as persons with skull defects and skull plates [117]. In children and adolescents, the effect of tDCS is hypothesized to differ compared to adults because of increased conductivity of head tissue in children and adolescents, altered cortical excitability and pre-activation of the immature brain [118]. Stimulation intensities have to be adjusted for this specific group, as studies have found age-specific influences of tDCS on the cortical excitability [114]. Compared with sham, both 1 mA anodal and cathodal tDCS resulted in a significant increased excitability [114]. Interestingly, 0.5 mA cathodal tDCS decreased excitability, whereas 0.5 mA anodal stimulation did not result in any effect [114]. In obese subjects, tDCS effects were hypothesized to be altered because of a thick, low-conductivity layer of subcutaneous fat around the head,

however the study of Truong and colleagues [116] suggest that current density variation is a result of multiple factors and not only the Body Mass Index. They argue that head fat contributes to current density distribution only in conjunction with other anatomical differences. Regarding persons with skull defects and skull plates it is hypothesized that this would alter the intensity and location of current flow through the brain [117]. Here too, Datta and his colleagues [117] suggested that this depend on a specific combination of factors. However, they found that the condition that led to the largest increase in peak cortical electric field was when one electrode was placed directly over a moderate-sized skull defect. In contrast, small defects midway between electrodes did not significantly change cortical currents.

The effect of stimulation duration

The duration of the stimulation mostly ranges between 20 and 40 min [9,75]. For a single session of tDCS, the duration of the aftereffects is restricted. In order to even achieve aftereffects, it is necessary to stimulate for at least 3 min with an intensity of at least 0.6 mA. Options to prolong the effects of tDCS are increasing the duration of tDCS or repetition of tDCS. Similar to stimulation intensity, increasing the stimulation duration does not seem to be a successful approach to increase the efficacy of tDCS [41,97]. For example, the prolongation of anodal tDCS from 13 to 26 min resulted in reduced motor cortex excitability, most probably caused by intraneuronal calcium overflow [119]. Therefore, repeated stimulation protocols may be a better option to increase the efficacy of stimulation [80,119]. Studies have indicated that repetitive stimulation over days increases tDCS efficacy (e.g. [120]). Therefore, in treatment studies, stimulation protocols often exist of repeated sessions over consecutive days to enhance the clinical impact. Repeated tDCS in clinical studies mostly conduct tDCS daily in five or more consecutive days for effects that can last for 1 month or more after stimulation (e.g. [22,120,121]). Another option to prolong the aftereffect of tDCS is by co-application of drugs acting on the central nervous system as described earlier [75].

Behavioral effects of tDCS

Transcranial direct current stimulation (conventional and high-definition tDCS) has been found to be beneficial in health and disease. However, the understanding of how tDCS causes behavior changes is still scarce [122]. Predicting how neurophysiological changes caused by tDCS translate into behavioral changes does not seem to be that straightforward [122]. Typically, anodal tDCS is assumed to facilitate performance, whereas anodal tDCS leads to impaired performance [96,123]. This a priori assumption is often made where the neurophysiological tDCS effect is directly mapped on to behavioral effects [124]. However, several studies have reported paradoxical stimulation effects [96], such as enhancement from cathodal stimulation [79,125] and polarity non-specific effects in which both anodal and cathodal stimulation disrupt performance [125,126]. Several studies have also reported no cathodal effects on performance [78,127]. These findings



challenge the assumed polarization effect of tDCS and make it difficult to understand the true effect of anodal and cathodal stimulation on behavior. In a meta-analysis study of Jacobson and his colleagues [128], where they investigated the polarity effect in motor and cognitive domains, they found that the dual polarity effect was quite common in motor (or more neurophysiological) studies but rarely in cognitive (or neuropsychological studies). Cognitive studies mainly exhibited anodal effects (improved performance) whereas the cathodal effect (impaired performance) was less common. One possible explanation for the difference between motor and cognitive studies given was that motor effects of tDCS are usually tested with MEPs, which involves only the stimulated (motor) region [88], whereas the cognitive effect of tDCS are measured using a variety of behavioral measures (e.g. reaction time, accuracy, etc.), which is highly susceptible to external noise [128]. The lack of inhibitory cathodal cognitive effects might also reflect compensation processes as cognitive functions are typically supported by rich brain networks [123,128].

Safety and adverse effects

In general, no serious adverse events caused by tDCS have been reported in more than 10,000 subjects investigated in the contemporary tDCS literature (1998–2014) [129]. The safety of tDCS depends on the strength of the current, the size of the electrodes and the duration of the stimulation [127,130].

For conventional tDCS, a stimulation intensity of up to 2 mA for the duration of about 20 min is considered to be safe [127,131]. The application of tDCS has presented minimal risk in various studies when it has been applied in research and clinical studies within standard parameters [129]. Standard parameters to date are (1) the current is less than 2.5 mA, (2) tDCS is applied through electrodes that are known to minimize skin burns at the specific current, (3) the current application duration is less than 20–60 min per session, and (4) sessions are not more frequent than twice per day [129]. TDCS administered according to safety guidelines [127,131] is associated with minor adverse effects [9,130,132] and the frequencies of adverse effects in studies is low [132]. The most frequent side effect include tingling sensation [130,132], itching sensation [130,132,133] right under the electrodes, headache [130,132], moderate fatigue [130] and burning sensation [130,132,133] (for an overview of reported adverse effects, see [130,132]). These effects have been found for tDCS on different cortical areas in healthy subjects as well as in patients with different neurological disorders [130,132]. On rare occasions, tDCS application has led to skin lesion, more likely when stimulating at higher intensities (e.g. 1.5 and 2 mA) for a longer period (e.g. repeated sessions) [134–136].

For High-Definition tDCS, studies using 4 × 1 ring configuration with intensities up to 2 mA for up to 20 min have demonstrated its tolerability in both healthy (e.g. [26,45,48]) and patient populations (e.g. [28,37]). Using HD-tDCS, the spatial focality is improved compared to conventional tDCS at the cost of increased electrode current density [137]. Especially for the 4 × 1 ring HD-tDCS configuration, increased scalp current could be expected as more shunting of the

current on the scalp has been found for smaller electrodes compared to larger electrodes [50] and a limited ring diameter is found to increase the current shunting across the scalp [24]. For skin safety, possible skin discomfort can be solved by increasing the distance between the stimulation electrodes but at the cost of stimulation focality [39,106].

To reduce the risk of adverse events using tDCS and HD-tDCS, contraindications for tDCS need to be investigated before stimulation [37]. These contraindications are similar to the general exclusion criteria for non-invasive brain stimulation [9]. For a screening list of considerations to be taken into account before stimulation, we refer to the publication of Villamar and his colleagues [37]. The most important contraindications include the presence of metallic implants and devices in the head, severe brain injuries or significant skin lesions [37].

The safety of tDCS has only been demonstrated for short-term use. The effects of long-term use are still unknown [129]. One longer treatment trial of 6 weeks of tDCS (15 sessions) did not show increased incidence of adverse events [121].

Expert commentary

Despite widespread dissemination of tDCS (conventional as well as high-definition transcranial direct current stimulation), there remain significant unknowns about the exact mechanisms of action and the influence of various tDCS parameters on the actual effect of stimulation and on behavior. This article provides general insights on the influence of different controllable tDCS parameters on the actual effect of the stimulation based on knowledge gained from previous studies. Since, more and more tDCS studies are conducted where some of the designs are based on over-simplified, deceptive rules (e.g. such as the trend to use higher current densities, such as 2 mA, to produce more robust effects on excitability), this article aims to give a review of the current knowledge of these parameters and its influence on the actual stimulation as a guide for future researchers and clinicians to design customized stimulation protocols.

Since the preference to choose certain tDCS parameters over others depend on the specific aims of the tDCS application, it is impossible to suggest the most optimal or the most efficient stimulation protocol in general. Depending on the subpopulation (e.g. specific disorders), and the specific stimulation purpose (e.g. research or treatment, focal, or deep stimulation) certain tDCS parameters will be more preferable. For instance, in some disorders modulation of larger brain regions using two cephalic pad electrodes to simultaneously increase and decrease activity in different brain regions might be more preferable than more focalized stimulations with smaller high-definition electrodes. Having the possibility to choose from different tDCS parameters (different electrodes, different montages, different intensities, and different stimulation duration) gives the user a great flexibility to customize stimulation protocols.

Besides the discussed controllable tDCS parameters in this article, there are more general factors (not covered in this article) that might be less tangible to control but need to be considered, for example the brain state before and during

stimulation, the combination of tDCS with medication or training etc. More research is being done to investigate the influences of these factors on the tDCS effect and efficacy. More research has also been conducted to investigate the influence of tDCS in alterations of connectivity within cortical and cortico-subcortical networks.

In general, tDCS is a promising tool that offers several advantages compared to other brain stimulation techniques. It is safer than invasive brain stimulation and compared to transcranial magnetic stimulation it is less uncomfortable, easier to conduct and it is less expensive. However, more controlled longitudinal large scale studies combined with neuroimaging is needed to enrich the knowledge in understanding the neurophysiological and behavioral mechanisms of tDCS that will lead to more efficient and safe stimulation protocols.

Five-year view

Stimulation of the brain is a rapidly growing field with an enormous potential for research and therapy. In the near future, more studies using tDCS (conventional and HD-tDCS) will be expected to better understand the underlying mechanisms followed by more efficient customized stimulations protocols. Meta-analysis and controlled large-scale clinical trials will fill in the need for more robust study findings regarding the effect of tDCS in various neurological and psychiatric disorders.

Research will focus on other methods of low-intensity transcranial electrical stimulations that have been less investigated, such as transcranial Alternating Current Stimulation, transcranial Random Noise Stimulation, and transcranial Pulsed Current Stimulation.

Modeling studies will be more accurate in estimating the electric field flow induced by tDCS in cortical as well as in

deeper subcortical brain areas. Furthermore, methods to fully automate current-flow modeling for individualized treatment with tDCS will be further investigated for clinical use. These simulation studies might require incorporation of individual structural and functional connectivity data to verify whether the current follows anatomical or functional connectivity pathways, once it reaches the cortex.

Future technical developments will focus on producing new designs of electrodes, stimulators, devices resulting in low-cost, light-weight, programmable, and portable tDCS devices. Development of new electrodes and new electrode montages will lead to new forms of tDCS protocols, such as simultaneous anodal stimulation on different brain regions. Recording of electrical brain activity from the same electrodes as used for stimulation will allow for more accurate understanding of activity and connectivity changes involved or induced by tDCS.

With the gained knowledge, it is very likely that the application of tDCS will increasingly develop in routine clinical practice for a variety of neurological and psychiatric conditions over the next 5 years.

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Key issues

- Conventional tDCS and HD-tDCS are considered safe with minimum risks when used within safety guidelines and for short-term use.
- HD-tDCS allows for more focal stimulation compared to conventional tDCS.
- By varying controllable tDCS parameters, stimulation protocols can be customized to a certain extent to achieve the desired direction, strength, focality, and duration of effects on cortical activity and excitability.
- The relationship between intensity and duration of stimulation and efficacy of tDCS is not linear under all conditions.
- tDCS exerts direct regional effects as well as indirect network effects.

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