Cerebellar Transcranial Direct Current Stimulation: Technique's Overview and Clinical Applications

The cerebellum has been considered for a long time to play a role in motor function (in the control of balance and intentional voluntary movement). However, neuroimaging [1], clinical/lesional [2], and neuromodulation [3] studies have shown that the cerebellum also plays a key role in many motor, cognitive, and emotional processes. In addition, studies have also shown that the cerebellum is implicated in many psychiatric disorders including attention-deficit hyperactivity disorder, autism spectrum disorders, schizophrenia, bipolar disorder, major depressive disorder, and anxiety disorders [4].

The cortico-ponto-cerebellar and cerebello-thalamo-cortical pathways allow the cerebellum to affect information processing in cortical areas responsible for cognitive and emotional processes [4]. These intricate connections between the cerebellum and other structures can explain why cerebellar damage can lead to various psychiatric disorders.

A recent possible way of gathering insights into the functional role of the human cerebellum in psychiatric and neurological disorders may be provided by transcranial direct current stimulation (tDCS) [5].

The need for a noninvasive tool to influence cerebellar function in normal and pathological conditions led researchers to develop cerebellar tDCS [3]. Cerebellar tDCS depends on the principle that weak direct currents delivered at around 2 mA for minutes over the cerebellum through surface electrodes induce prolonged changes in cerebellar function [6]. Usually, the stimulating electrode is placed over one or two cerebellar hemispheres and the other (return electrode) over the buccinator muscle, over the scalp or the right shoulders [6].

Though current evidence leaves open possible (transynaptic or antidromic) changes in other brain or brainstem structures, the physiological effects elicited by cerebellar tDCS arise mainly from functional changes in the cerebellum itself. Cerebellar tDCS could interfere with membrane polarization in Purkinje cells and in other neurons, fibers (mossy fibers and climbing fibers), and glial cells. DC stimulation applied to the cerebellar cortex in the decerebrated cat influences Purkinje and granular cell activity in a polarity-specific manner; while anodal DC flowing in the dendrite–axonal direction increases tonic neuronal activity, cathodal DC decreases it [7].

Cerebellar tDCS modulates several cerebellar skills in humans including motor control, learning, and emotional processing [3]. Several studies suggest that tDCS may be a valuable tool for the treatment of neuropsychiatric conditions such as depression, schizophrenia, addiction, and chronic pain [8, 9]. Research has also demonstrated cognitive improvement in some patients undergoing tDCS [10].

For instance, tDCS treatments for depression have used bifrontal montages with anodal (excitatory) stimulation targeting the left dorsolateral prefrontal cortex (DLPFC) [11]. There is limited research examining the effects of alternative electrode montages.

The first study aimed to examine the feasibility, tolerability, safety, and efficacy of two alternative electrode montages were conducted by Ho and colleagues [12]. They studied two different montages, fronto-occipital (F-O) and fronto-cerebellar (F-C), to target respectively midline brain structures and the cerebellum in 14 depressed participants. For F-O montage, the anode electrode was placed over the left supra orbital area and the cathode over the occipital area, for F-C montage the anode electrode was placed over the cerebellum and the cathode over the occipital area. The intensity of stimulation was set at 2 mA and delivered for 20 min/die for 3 consecutive weeks. Mood and neuropsychological functions (memory and frontal lobe functions) were assessed at baseline and after 4 weeks of tDCS. Using a computational modeling based on one healthy participant, they demonstrated that the novel montages resulted in greater activation in the anterior cingulated cortices and cerebellum than the bifrontal montage. They also showed that after 4 weeks of tDCS, overall mood improvement was observed under the F-O and F-C conditions and no significant

neuropsychological changes were found. Results of this open-label pilot study found both montages safe and feasible. The small sample size and the absence of a sham control group are major limitations of the study.

Successively, Minichino and colleagues [13] aimed to improve sleep quality of 25 euthymic outpatients with a diagnosis of bipolar disorder (BD) type I or II through the administration of prefronto-cerebellar tDCS. They placed the cathode electrode over the right cerebellar cortex and anode over the left dorsolateral prefrontal cortex (DLPFC); the intensity of stimulation was set at 2 mA and delivered for 20 min/die for 3 consecutive weeks. The sleep quality was assessed at baseline and after the tDCS treatment using Pittsburgh Sleep Quality Index (PSQI). They demonstrated that PSQI total score and all PSQI subdomains significantly improved after treatment.

Furthermore, Minichino and colleagues [14] using the same previous protocols [13] studied the effects of tDCS applied to cerebellar and prefrontal cortices on neuropsychological functioning of 25 euthymic patients with BD. All participants were assessed through the Rey Complex Figure Test delay and copy and the Neurological Examination Scale at baseline and after therapy with tDCS. The results of the present research suggest that concomitant prefrontal-excitatory and cerebellar-inhibitory tDCS might have a positive effect on visuospatial memory and executive functioning in euthymic BD patients, quantified through neuropsychological and neurological measures. The small sample size and the absence of a sham control group are major limitations of these two studies.

More recently, Bation and colleagues [15] in an open-label pilot study assessed the efficacy and the safety of orbitofrontal cortex (OFC) cathodal tDCS coupled with cerebellum anodal-tDCS in eight patients with treatment-resistant obsessive–compulsive disorder (OCD). Cathode electrode was placed over the left OFC and the anode over the right cerebellum for 10 sessions (twice a day) of 2 mA. Patients were assessed four times, once before tDCS and three times after: immediately after the ten sessions of tDCS, 1 and 3 months later. The effect of tDCS on the severity of obsessive and compulsive symptoms was assessed using the Yale–Brown Obsessive and Compulsive Scale score (Y-BOCS) and a self-reporting OCD Visual Analog Scale (OCD-VAS) given to the participant. The effect of tDCS on the severity of depressive symptoms was assessed using the Montgomery and Asberg Depression Rating Scale (MADRS).

They reported a significant 26.4 % decrease of Y-BOCS score, and the beneficial effect lasted during the 3-month follow-up. No effect of tDCS was observed on depressive symptoms. This open-label pilot study demonstrates for the first time the clinical interest of orbitofrontal and cerebellar tDCS in combination with SSRI in patients with treatment-resistant OCD. These promising results should be confirmed in large placebo-controlled trials.

The few cerebellar tDCS studies in psychiatric patients we reviewed here taken together, despite their heterogeneities, show that cerebellar tDCS is safe, feasible, and might improve psychiatric symptoms. Cerebellar tDCS probably could influence psychiatric symptoms through highly complex mechanisms, it could induce neuroplasticity throughout a distributed cortico-subcortical network. Premised that the clinical efficacy of cerebellar tDCS in patients with psychiatric disorders remains to be ultimately established by large, controlled clinical studies, future research work should systematically assess the clinical patient features predicting the optimal response: type and site of stimulation, time since the pathology occurred, age, gender, concurrent drug treatments, and comorbidities can all influence the tDCS effect.

Future research directions should include studies to clarify whether cerebellar tDCS could be combined with behavioral therapy, and whether these noninvasive techniques could be used to stimulate multiple brain sites. A study in a larger homogeneous population is needed to further investigate the possible therapeutic benefit of cerebellar tDCS.

Transcutaneous Spinal Direct Current Stimulation: Technique's Overview

As for the cerebellum, a new and fascinating target for noninvasive current stimulation has emerged in the recent years. Spinal cord is a critical, yet less understood, final pathway for motor control, but also acts a "highway" for modifying brain and brainstem function. Transcutaneous spinal direct current stimulation (tsDCS) is a noninvasive technique for modulating spinal cord activity in animals and humans [16–20]. DC stimulation intensity ranges from 1.5 to 2.5 mA, with effects lasting for minutes to hours [21]. After the first reports [19], this technique has come into increasingly widespread use, especially for modulating conduction along lemniscal pathways and nociceptive spinal system [22–24]. The device is the same used for transcranial direct current stimulation, but no conclusive remark has been reached so far regarding the position of electrodes over the spinal cord, ultimately influencing current density and distribution in biological tissues [25]. This remains a critical issue, together with inter-individual variability due to genetic polymorphisms, thus modifying neurophysiological and psychophysical response in an unpredictable way [26].

For lumbar spinal cord stimulation, the active electrode is commonly placed over the spinous process of the tenth thoracic vertebra and the reference above the right shoulder [19, 20], while for cervical modulation the active electrode is positioned on the seventh cervical vertebra and the reference either on the right shoulder [27] or on the anterior neck [28]. By analogy with the tDCS, placing the return electrode over the shoulder is the preferred montage, as it reduces interference between anodal and cathodal effects.

Mechanisms of Action

Putative Mechanisms of Action at a Spinal Level

Recent modeling studies have proved that, despite some inter-individual differences due to age and anatomical variability, the electrical field induced by tsDCS is longitudinally directed along all the vertebral column, especially when the return electrode is placed over the right arm or over Cz [25], confirming that both ventral (motor) and dorsal (sensitive) spinal tracts undergo identical electric field strength. Different from transcranial direct current stimulation (tDCS), anodal tsDCS has probably an overall inhibitory effect on spinal cord activity [19, 20, 28, 29]. Particularly, while anodal polarization could act directly on corticospinal descending pathways, without changes in postsynaptic motor neuronal excitability, the cathodal one seems to interfere with interneuronal networks [17, 27, 30]. By analogy with the effects of direct currents on peripheral nerves, it has been hypostasized that anodal tsDCS leads to a hyperpolarizing "anodal block" [31]. Conversely, there is an extensive debate whether cathodal tsDCS has or not polarity-specific effects on segmental activity [28]. Overall, as suggested for tDCS [32], rather than be simply specular, anodal and cathodal tsDCS may have quite similar effects on different targets. That widens the field of therapeutic applications, raising at the same time the possibility of a combined use of transcranial and spinal polarization in a number of clinical conditions, as proved in chronic stroke [33]. From a practical point of view, the same DC device could be used to simultaneously stimulate the cerebellum spinal cord and cerebral cortex, thus enhancing the tDCS after-effects.

Putative Mechanisms of Action at a Supra-Spinal Level

Many studies have proved possible supra-spinal mechanisms of action of spinal direct current stimulation, both in animal [34] and human models [30, 35], possibly synchronizing the activity among different cortical areas and inducing neuroplasticity [36]. That is not surprising also considering the literature about invasive current stimulation (SCS), suggesting a possible modulation of glutamatergic cortical interneurons in patients with neuropathic pain [37]. Moreover, it is known that alternating currents epidurally delivered to the posterior columns of the spinal

cord are able to modify sensory processing at thalamic relays and cortical levels [38]. Recently, studies from our laboratories have explored two main no-spinal targets, the (a) GABA(a) cortical interneurons, mediating the so-called short intracortical inhibition (SICI) [30], and the (b) interhemispheric processing [35]. Other groups did not confirm data about GABA(a); nonetheless, they studied a different anatomical region, with different recording montage and stimulation intensity [39].

Perspective on Clinical Studies

Different from cerebellar tDCS, only few studies have been published to date about the application of tsDCS in human disorders and little is known about its spinal and long-range (supra-spinal) effects both in health and disease. Although elusive, the possibility to interfere with cognitive processes by using spinal polarization is intriguing. First studies showed that tsDCS modulates somatosensory potentials evoked by stimulation of posterior tibial nerve, the post-activation H-reflex dynamics [23, 24] and the flexion reflex in the human lower limb [40]. In this view, Truini and colleagues [29] have proved that anodal spinal polarization leads to a significant decrease of the amplitudes of laser-evoked potentials (LEPs) derived from lower limb, thus modulating both the sensory-discriminative and affective-emotional dimension of pain. More recently, tsDCS has been successfully used both for interfering with maladaptive phenomena taking place in spinal cord injured patients [22] and improving symptoms in patients with restless legs syndrome [41]. Mechanisms of action of tsDCS have only partly been elucidated, but likely rely both on local (spinal) and supra-spinal effects. The later aspect is particularly attracting; in spinal cord injury (SCI) tsDCS may interfere with the maladaptive reorganization of cortical sensorimotor maps, thus improving motor output and preventing central pain sensitization [36]. That implies that tsDCS could be useful also as an early rehabilitation strategy in patients with acute brain lesions, such as stroke, when other NIBS tools are not indicated due to safety concerns.

Theoretically, spinal DC may be also used to improve the effects of tDCS in a number of neuropsychiatric disorders likely characterized by impaired interhemispheric balance, ranging from schizophrenia and obsessive–compulsive disorder [42, 43] to major depression [44].

Putative ways to nonspinal targets are to date only speculative, but evidence in animals showed that supra-spinal effects of invasive spinal polarization could be induced by the modulation of indirect spinal projections to noradrenergic locus coeruleus (LC) neurons, which has widespread projections to the neocortical brain [45–47]. Alternatively, a critical role in brain plasticity after a SCI seems to be played by a reorganization of the serotonergic ascending pathways [48–51]; serotonergic system interferes also with bottom-up and top-down modulation of motor responses, especially through parallel and partially overlapping projections arising from the median and dorsal raphe nuclei [52–54]. As the serotonergic projections seem to participate in the regulation of different functional systems (motor, somatosensory, limbic), tsDCS may ultimately modulate this connectivity.

tsDCS could be of particular interest as a noninvasive, safe promising therapeutic tool in managing a number of human diseases. This technique could be useful also as a rehabilitation strategy in patients with brain lesions or even in the treatment of neurological disorders characterized by abnormal interhemispheric processing. In addition, the possibility to modulate supraspinal and intracortical processing of motor inputs makes tsDCS a useful approach, complementary to either SCS or noninvasive brain stimulation techniques, to modify spinal drive through nonspinal mechanisms.

Why Should Psychiatrists Be Interested in Cerebellar/Spinal DC Stimulation?

Despite the uncertainties, cerebellar and spinal tDCS for its simplicity, low cost, and possibility of online use has a great potential in the field of restorative psychiatry symptoms. This potential must however be developed through strictly

controlled and methodologically sound experimental and clinical research work [55].

Delivering DC currents for few minutes over the cerebellum or spinal cord can induce persistent, polarity-dependent excitability changes persisting several minutes after the current offset. Cerebellar DC stimulation can elicit neurophysiological and behavioral changes both in the motor functions and in cognitive-behavioral domain. Spinal cord DC stimulation elicits neurophysiological and behavioral changes related to spinal cord functions, but, interestingly, also changes in the brain functions that may arise from the activation of tonic afferent systems to the brain.

Future studies should endeavor to assess whether experimental data translate into benefits in real life, lengthen behavioral benefits, investigate how changing stimulation variables influences tDCS-induced effects, determine possible interactions with other treatments and improve patients' selection.

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Part II

Applications of tDCS in Neuropsychiatric Disorders

Mood Disorders

13

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Abstract

Major depressive disorder (MDD) is an incapacitating condition associated with significant personal, social, and economic impairment. Nearly 30 % of patients present drug refractoriness, reinforcing the need to develop novel therapeutic strategies for MDD. TDCS might be an alternative for these patients considering its tolerability, portability and ease of use. In this chapter, we reviewed putative tDCS antidepressant mechanisms as well as clinical evidence based on open and controlled studies and meta-analyses. Present evidence indicates that tDCS may be an effective treatment strategy for MDD. Finally, there are no studies specifically examining the efficacy of tDCS in bipolar depression and mania, which are urgently needed in order to address tDCS effectiveness for bipolar disorder.

Keywords

Major depressive disorder • Bipolar disorder • Depression • Transcranial direct current stimulation • Noninvasive brain stimulation • Clinical trial • Meta-analysis • Systematic review

Major Depressive Disorder

Introduction

Major depressive disorder (MDD) is an incapacitating condition associated with significant personal, social, and economic impairment. Patients with MDD present a "double burden," characterized by a lower quality of life associated with a higher prevalence of medical comorbidities [1]. The main symptoms of MDD include persistent low mood, anhedonia (i.e., diminished pleasure

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in previous significant activities), impairment in sleep, psychomotor retardation, weight changes, and negative thoughts that range from pessimism to guilt and suicidal ideation. Moreover, although only the most severe spectrum of depression is associated with suicide, its chronic, incapacitating symptoms make depression one of the most incapacitating conditions worldwide—in fact, MDD is projected to be the second most disabling condition by 2020 [2].

In addition, depression is a chronic, recurrent disorder, as nearly 80 % of patients relapse after the treatment of an episode [3]. Finally, about one-third of patients have treatment-resistant depression (TRD)—i.e., the failure to achieve adequate response of symptoms after adequate antidepressant treatment trials [4, 5]. In fact, the high prevalence of failure to respond to antidepressants is an important concern when managing major depression. In this context, the National Institute of Mental Health-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial confirmed that cumulative response and remission rates after two antidepressant treatments are 63 % and 56 %, respectively [6, 7]. After three failed treatments, response and remission rates decay to 16 and 13 % [6]. After four trials of treatment, including antidepressant medications and cognitive behavioral therapy, nearly 30 % of patients fail to achieve remission, i.e., have ongoing depressive symptoms despite appropriate psychological and pharmacological treatment [6]. These data reinforce the need to develop novel therapeutic strategies for MDD in order to offer alternatives to patients who fail to respond to antidepressants or who have intolerance or contraindication to these drugs.

The dorsolateral prefrontal cortex (DLPFC) is as an important site of dysfunction in depression mainly due to left hypo-function and right hyperfunction [8]. Neuroimaging studies also show structural alterations in fronto-cingulo-striatal (FCS) circuits—for instance, a recent meta-analysis found volumetric reductions in these circuits in depressed vs. healthy volunteers [9]. Current treatment approaches provide further support for abnormalities in discrete neural networks in MDD. For instance, volumetric analysis of MDD patients taking sertraline revealed an increment in gray matter volume over the left DLPFC [10], while high-frequency rTMS increased fractional anisotropy in the left middle frontal gyrus [11].

The imbalance between cortical and subcortical brain activities might also be involved in MDD pathophysiology. Response to fluoxetine was associated with a marked reduction in local cerebral blood flow as well as changes in downstream limbic and cortical sites as measured with positron emission tomography [8]. The effects of chronic deep brain stimulation for patients with refractory depression have also been investigated—for instance, the DBS protocol targeting the subgenual cingulate region, which is known to be metabolically overactive in treatment-resistant depression, showed clinically relevant outcomes [12].

Other brain areas, such as the amygdala and the hippocampus, have a lower volume in depressed patients when compared to controls [13, 14]. In addition, functional studies suggest a high level of activity in the ventro-medial prefrontal cortex (vmPFC) and a low level of activity in the DLPFC. In addition, patients with major depression have lower excitability in the left motor cortex [15], in the left hemisphere [16] and a higher brain activity in the right cortex [17]. These findings suggest a “differential activity” in certain brain areas in patients with MDD, which may explain some symptoms of depression: for instance, psychomotor retardation and executive function impairment (related to the DLPFC), feelings of guilt and hopelessness (related to hippocampus and amygdala dysfunction), anhedonia (related to nucleus accumbens) and negative emotional judgment (related to left-right imbalance) [18–20]. In fact, two major pathways can be determined here: the cognitive-executive pathway, in which a hypoactive DLPFC fails to regulate areas related to executive functioning and the affective-somatic pathway, in which a hyperactive vmPFC modulates erratically areas related to feelings of negative affect and self-awareness [21]. The rationale in using different brain stimulation therapies, including tDCS, is based on their mechanisms of inhibiting or enhancing activity of these pathways.

Technical Aspects of Using tDCS in Major Depression

Based on the rationale that the left DLPFC is a key brain area involved in MDD pathophysiology and that its stimulation is associated with depression improvement [22], the main target for anodal tDCS has been the left (hypoactive) DLPFC (F3 on the 10–20 EEG system)—in fact, virtually all tDCS studies in MDD placed the anode over this region (see the section "Clinical Evidence"). The cathode position varies among studies—most of them used the cathode over the right supraorbital area that is considered neutral in terms of the influence of cathodal stimulation effects on the treatment. Other studies have chosen to place the cathode over the right DLPFC [23, 24] or lateral frontal area [25] according to the theory of prefrontal asymmetry that this brain area is hyperactive in MDD and therefore applying the inhibitory effects of cathodal stimulation over this area would help to improve depressive symptoms. Alternative tDCS montages have also been tested [26], aiming to stimulate other deeper, key brain areas in MDD, such as the anterior cingulate cortex, nucleus accumbens, and basal ganglia (fronto-extracephalic, fronto-occipital, and bitemporal montages), and the cerebellum (fronto-cerebellar montage) [27, 28].

The "dose" of tDCS might also influence its efficacy. In fact, there is no standard definition of how to measure the "dose" of tDCS delivered in a clinical study: factors that determine the amount of current injected are the size and position of electrodes, the electric current intensity, the duration of the tDCS session and the total number of sessions. Therefore, the tDCS "dose" can be expressed in terms of current intensity (usually 1–2 mA), current density (intensity divided by the square area of the electrodes, usually from 0.28 to 0.8 A/m^2) and charge density delivered per session (intensity multiplied by session duration, usually from 336 to 1440 C/m^2). In a recent individual patient data meta-analysis, tDCS dose was associated with greater depression improvement across six randomized clinical trials [29]. The interval between sessions (e.g., every other day, once daily, twice daily) might also influence the clinical effects. For instance, daily tDCS (compared to every other day) led to greater increases in cortical excitability over a 5-day period [30].

Finally, tDCS effects in depression seem to be influenced by other concomitant interventions. Regarding pharmacotherapy, tDCS had greater antidepressant effects when started simultaneously with sertraline [24], and showed lower antidepressant effects in patients on concurrent benzodiazepine medication [24, 31]. TDCS combined simultaneously with cognitive control training presented superior efficacy in one randomized clinical trial [32] but not in other [33].

Mechanisms of Action

Although the antidepressant mechanisms of action are still elusive, it is supposed that tDCS acts by increasing cortical excitability and neuroplasticity of the DLPFC, hypoactive in depression, and, by restoring this brain area to normal activity, tDCS ameliorates depressive symptoms. For example, tDCS has been shown to improve affective and cognitive processing in depressed patients [34–36]—since the DLPFC is involved in such processing in depression, these findings suggest that tDCS modulates DLPFC activity. There is also evidence that tDCS increases neuroplasticity. For example, depressed patients receiving frontal tDCS showed increased neuroplasticity, tested over the adjacent motor cortical area (which also received some stimulation, given the diffuse nature of tDCS) [37];. Nonetheless, neuroimaging or quantitative EEG studies are still needed to identify regional changes in functional activation, which correlate with the antidepressant effects of tDCS.

One study found that the serotonin transporter genetic polymorphism (SLC6A4), which codifies the pre-synaptic serotonin reuptake transporter (SERT), predicts antidepressant tDCS efficacy, with long/long homozygotes displaying a larger improvement comparing active vs. sham tDCS, but not short-allele carriers [38]. In fact, antidepressant effects of tDCS seem to involve the serotonergic system, as shown in the pharmacological

study of Nitsche et al. [39], which found that the excitability-enhancing effects of anodal tDCS were boosted with citalopram whereas the excitability-decreasing cathodal effects were reversed—leading to, in fact, excitability-enhancing effects. This proof of concept was subsequently demonstrated in the SELECT clinical trial, which showed the antidepressant effects of tDCS were enhanced by sertraline [24]. Nitsche and colleagues suggested that citalopram administration might activate serotonin-sensitive potassium channels that decrease outward potassium current, therefore extending calcium influx into the synaptic cleft [40]. The net result would be, ultimately, increased LTP after anodal tDCS and conversion of inhibition into facilitation for cathodal tDCS. Sertraline is also involved in cortical/amygdala regulation. Acute and chronic stress, which may form the pathophysiological basis of at least some forms of depression [41], are associated with cortical hypoactivity and subcortical hyperactivity [42]—i.e., a "bottom-up" pattern that is more prone to occur in *s*-carriers, as such patients have increased amygdala response to anxiogenic stimuli [43]. Possibly, such modulation is implicated in tDCS antidepressant effects, which would be impaired in individuals with an overactive amygdala (such as *s*-carriers).

Dopamine might also be involved in the antidepressant mechanisms of tDCS, considering that the use of dopamine agonists and antagonists modify tDCS-induced cortical excitability [44, 45]. Moreover, it was shown that genetic polymorphisms of catechol-*o*-methyltransferase (COMT, an enzyme that degrades cathecolamines such as dopamine) influence tDCS effects on executive functions and response inhibition in healthy volunteers [46, 47]. However, COMT polymorphisms have not been evaluated in depressed patients receiving tDCS.

Conversely, there is no evidence to date that tDCS induces any specific changes in peripheral biomarkers that have been associated to MDD pathophysiology. For instance, decreased heart rate variability (HRV) is observed in depression, which reflects autonomic dysfunction (decreased vagal tone) [48], although HRV levels do not change after tDCS treatment [49]. Moreover, decreased brain-derived neurotrophic factor (BDNF) levels have been found in depression, suggesting that depression is associated with decreased neuroplasticity (the "neurotrophin hypothesis of depression"), and BDNF levels increase after treatment with pharmacotherapy [50], but not after tDCS—this was also observed for non-BDNF neurotrophins [51, 52]. Finally, the "inflammatory hypothesis of depression" postulates that MDD incorporates an increased production of pro-inflammatory cytokines, which leads to an over-activation of the hypothalamic-pituitary-adrenal axis as well as monoaminergic disturbances and inflammatory cytokines. Nonetheless, tDCS does not specifically decrease cytokine levels after treatment [53]. One possibility for these negative findings is that the effects of tDCS are restricted to the brain, exerting no or minimal influence on peripheral activity. Nonetheless, to date there is no peripheral biomarker associated with tDCS efficacy in MDD.

Clinical Evidence

It should be acknowledged that the investigation on the effects of tDCS as an antidepressant therapy dates from the 1960s. However, the lack of methodological rigor on some parameters such as the target area, current strength, electrode size, reference electrode position, number of sessions, and duration of each session might explain some contradictory findings between the studies. For instance, Arfai et al. [54] did not find significant effects on depression in a randomized, double-blinded, sham controlled study where tDCS ($i = 0.25$ mA) was applied on frontal cortex with the reference on the thigh; on the other hand, Redfearn et al. [55], in an open pilot study, found a reduction of depressive symptoms after tDCS ($i = 0.02$–0.25 mA) over frontal areas with the reference electrode on the knee (for extended reviews see [56–58). This scenario only began to change in the last 15 years with new tDCS protocols in which the parameters of stimulation were better defined and further developed. Also, the emergence of other techniques of brain stimulation, such as TMS, allowed a better understanding of

Table 13.1 Summary of open-label tDCS trials in major depression

Author	Sample (*n*)	Anode	Cathode	Intensity (A/m^2)	Number of sessions	Depression improvement (%)
Rigonatti et al. [59]	42	F3	RSO	0.57	10 (1×/day)	36.20
Ferrucci et al. [60]	14	F3	F4	0.57	10 (2×/day)	32.1
Ferrucci et al. [61]	32	F3	F4	0.57	10 (2×/day)	27.70
Brunoni et al. [62]	31	F3	F4	0.57	10 (2×/day)	45.2
Martin et al. [27]	11	F3	R arm	0.57	20 (1×/day)	42.80
Dell'Osso et al. [63]	23	F3	F4	0.57	10 (2×/day)	31.30
Brunoni et al. [31]	82	F3	F4	0.57	10 (2×/day)	18
Ho et al. [28]	14	F3	Occ/Cer	0.57	20 (1×/day)	44/16

RSO right supraorbital area, *F4* right dorsolateral prefrontal cortex, *R arm* right arm, *Occ/cer* occipital/cerebellar

the effects of tDCS effects on cortical excitability. In the past decade, some open-label and randomized, double-blinded, sham-controlled clinical trials on the effects of tDCS on depression have been conducted, as we discuss below.

Open-Label Studies

Rigonatti et al. [59] compared the clinical effects of active prefrontal tDCS vs. a 6-week treatment protocol with 20 mg/day fluoxetine, finding that the effects of both therapies were similar. Ferrucci and colleagues [60] used tDCS in 14 patients with severe depression using 2 mA per day, twice a day for 5 consecutive days, demonstrating an improvement of about 30 % on depressive symptoms. In another study, Ferrucci et al. [61] evaluated 32 patients, finding that tDCS improvement was greater in severe depression (50 %) than those in mild/moderate depression (10 %). Brunoni et al. [62] used anodal tDCS over the left DLPFC in 31 patients (14 with bipolar and 17 with unipolar depression). Depressive symptoms in both study groups improved immediately after the fifth session. The beneficial effect persisted after 1 week and 1 month. Another recent open study [63] demonstrated the efficacy of tDCS in 23 patients with refractory depression, with a mean reduction in symptoms of 25 %. Martin et al. [27] performed tDCS sessions consecutively for 20 days, with 2 mA for 20 min, in 11 patients with depression. In this open study, which placed the cathode on the right deltoid muscle, there was also a significant reduction in symptoms of about 44 %.

Brunoni et al. [64] in a open-label study of 82 patients with unipolar and bipolar depression, found that 5 days of twice-daily tDCS significantly improved depression symptoms. This study also showed that the effects of tDCS are enhanced when associated with antidepressants and decreased with benzodiazepines. Finally, a pilot study tested two novel tDCS montages, recruiting seven patients to receive fronto-occipital (F-O) and seven patients to receive fronto-cerebellar (F-C) tDCS. All patients received 20 sessions of tDCS (2 mA, 20 min per session). Patients receiving F-O tDCS presented a significant reduction of 44 % of depressive symptoms; whereas patients receiving F-C tDCS had a nonsignificant reduction of symptoms. The study suggested that F-O montage is a promising antidepressant treatment [28] (Table 13.1).

Randomized, Sham-Controlled Trials

Fregni et al. [65], in the first modern, sham-controlled, randomized clinical trial, found a significant decrease in the Hamilton Depression Rating Scale and Beck Depression Inventory after 5 days of active stimulation with 1 mA for 20 min once daily in ten patients, with a mean reduction in depression scores of 60–70 % for active tDCS group relative to baseline. Similar results were demonstrated in a further study in antidepressant-free patients with recurrent major depressive episodes after 5 days of active tDCS stimulation [66] with 18 patients. Boggio et al. [67] recruited 40 patients with moderate to severe

depression, evaluating depression improvement immediately after 10 consecutive weekdays of stimulation and 30 days later. Only prefrontal tDCS reduced depressive symptoms significantly, with effects sustained at 30-day follow-up.

After these positive results, three other studies reported negative findings. Loo et al. [68] recruited 40 patients to receive active vs. sham tDCS and did not find significant differences between these groups. However, treatment was provided for only five treatment sessions, 3 days per week (same parameters as the initial Fregni et al. [65] study). This study also did not exclude patients with personality disorders. Palm et al. [69] recruited 22 patients with depression and randomized them to receive 1 mA stimulation, 2 mA stimulation or sham tDCS in a crossover design. Active and placebo tDCS was applied for 2 weeks, but no differences in depression improvement were found. Finally, Blumberger et al. [23] did not find significant differences between active vs. sham tDCS in a tertiary sample of 24 highly refractory patients. All these studies acknowledged methodological limitations (notably small sample sizes) that could have undermined the efficacy of tDCS.

In fact, the two largest tDCS trials observed that tDCS was an effective treatment for depression. Loo et al. [25] randomized 64 patients to receive active or sham tDCS (2 mA, 15 sessions over 3 weeks), followed by a 3-week open-label active treatment phase. Mood and neuropsychological effects were assessed. There was significantly greater improvement in mood after active than sham treatment. Attention and working memory improved after a single session of active but not sham tDCS. There was no decline in neuropsychological functioning after 3–6 weeks of active stimulation. Brunoni et al. [24] enrolled 120 antidepressant-free patients with moderate and severe depression who were randomized in four arms (2×2 design): sham tDCS and placebo pill, sham tDCS and sertraline, active tDCS and placebo pill, and active tDCS and sertraline (the study name was Sertraline vs. Electric Current Therapy to Treat Depression Clinical Trial—SELECT-TDCS; its design is described in [70]). The tDCS parameters were 2 mA per 30 min/day, for 2 weeks and two extra tDCS sessions every other week until week 6 (study endpoint); the dose of sertraline was fixed (50 mg/day). The main findings were that: (1) combined tDCS/sertraline was significantly more effective than the other treatment groups in reducing depressive symptoms; (2) tDCS and sertraline efficacy did not differ; (3) active tDCS as a monotherapy was also more effective than the placebo group. Of note, it was also found that (1) there was no decline in cognitive improvement after tDCS or sertraline treatment; (2) there were five cases of hypomanic/manic episodes in the combined treatment group vs. one case in tDCS-only, one case in sertraline-only and no cases in the placebo arm (although this difference was not statistically significant); (3) use of benzodiazepines and treatment-resistant depression were both predictors of lower response; and (4) treatment was well tolerated with mild adverse effects, which were of similar frequency in both arms, except for skin redness that was more prevalent in the active group. Biological markers were also evaluated.

In 2014, two randomized, sham-controlled trials evaluated the efficacy of tDCS combined with cognitive control therapy (CCT), an intervention that aims to increase prefrontal cortical activity through working memory tasks (in both cases, an adapted version of the Paced Serial Addition Task, PASAT). Segrave et al. [32] enrolled 27 patients to receive tDCS and CCT, sham tDCS and CCT, and sham CCT and tDCS (2 mA, five sessions). All treatments led to a reduction in depression severity after five tDCS sessions, but only the combined tDCS/CCT treatment resulted in sustained antidepressant response at week 4. The study suggested that CCT enhances antidepressant outcomes of tDCS. In contrast, Brunoni et al. [33] randomized 37 participants to receive sham tDCS and CCT or active tDCS and CCT (2 mA, ten sessions) and found similar antidepressant improvement in both groups. However, further analysis showed that in older patients, those with greater improvement in CCT task performance also had greater antidepressant improvement with active tDCS.

The last RCT published hitherto was a phase-II trial in which 24 escitalopram-resistant depressed patients were randomized to receive

Table 13.2 Summary of controlled tDCS trials in major depression

Author	Sample (*n*)	Anode	Cathode	Intensity (A/m^2)	Number of sessions	Results
Fregni et al.2006 [65]	10	F3	RSO	0.28	5 (every other day)	Positive
Fregni et al.2006 [66]	18	F3	RSO	0.28	5 (every other day)	Positive
Boggio et al. 2008 [67]	40	F3	F4	0.28	10 (1×/day)	Positive
Loo et al.2010 [68]	40	F3	RSO	0.28	5 (every other day)	Negative
Palm et al. 2011 [69]	22	F3	RSO	0.28/0.57	10 (1×/day)	Negative
Blumberger et al. 2012 [23]	24	F3	F4	0.57	15 (1×/day)	Negative
Loo et al.2012 [25]	64	F3	RSO	0.57	15 (1×/day)	Positive
Brunoni et al.2013 [24]	120	F3	F4	0.8	10 (1×/day)	Positive
Segrave et al. 2014 (Segrave cct)	27	F3	RSO	0.57	5 (1×/day)	Mixed
Brunoni et al. 2014 [33]	37	F3	F4	0.8	10 (1×/day)	Mixed
Bennabi et al. 2015 [71]	23	F3	RSO	0.57	10 (2×/day)	Negative

RSO right supraorbital area, *F4* right dorsolateral prefrontal cortex, *R arm* right arm, *Occ/cer* occipital/cerebellar

two daily sessions of tDCS for 5 days (2 mA, ten sessions over 1 week) (Table 13.2). In this study, tDCS did not induce clinically relevant antidepressant effects in active and sham stimulation groups [71].

Follow-Up Studies

Two studies evaluated the efficacy of tDCS in the maintenance phase of the depressive episode. One of them [70] recruited 42 patients who were tDCS responders from the SELECT-TDCS trial and performed tDCS sessions every other week for 3 months and then every month for 3 additional months (tDCS sessions were interrupted earlier in case of relapse, characterizing failure treatment). In this follow-up study, treatment-resistant depression was significantly associated with an increased relapse rate (over 80 % in 6 months). On the other hand, >80 % non-refractory patients sustained clinical response for at least 6 months. In this trial, the overall relapse rate in 6 months was around 50 %, with most relapses occurring in the first 3 months. The other study [72] also followed responders previously treated in a randomized clinical trial ($n=26$) and performed weekly tDCS sessions for 3 months, followed by tDCS sessions every other week in the remaining 3 months. Similarly, a relapse rate around 50 % in 6 months was observed. However, most relapses occurred after the 3 initial months, when tDCS sessions were further spaced. Therefore, although the evidence is very preliminary, these trials suggest that intensive continuation treatment during early follow-up might be recommended to sustain clinical improvement.

Meta-Analyses

The first two published meta-analyses for tDCS in depression showed disparate results—interestingly, these meta-analyses evaluated the same randomized clinical trials, although using different outcome measures—i.e., Kalu et al. [73] employed continuous outcomes (depression improvement), finding positive results, and Berlim et al. [74] dichotomous measures (response and remission) for estimating the effect size of the intervention, finding nonsignificant results regarding tDCS efficacy. In an updated meta-analysis including data from SELECT-TDCS, not included in the previous meta-analyses, active vs. sham tDCS was more effective using both continuous and categorical outcomes, with the effect being small to moderate [75].

Finally, one individual patient data meta-analysis was recently performed in order to further assess efficacy and to identify predictors of response. Data were extracted on an individual patient basis and pooled from six randomized sham-controlled trials, enrolling 289 patients. Active tDCS was significantly superior to sham for response (34 % vs. 19 %, respectively; OR = 2.44, 95 % CI = 1.38–4.32, NNT = 7),

remission (23.1 % vs. 12.7 %, respectively; OR = 2.38, 95 % CI = 1.22–4.64, NNT = 9) and depression improvement (B coefficient = 0.35, 95 % CI = 0.12–0.57). Treatment-resistant depression and higher tDCS "doses" were, respectively, negatively and positively associated with tDCS efficacy. In this study, the effect size of tDCS treatment was comparable to those reported for repetitive transcranial magnetic stimulation and antidepressant drug treatment in primary care [29].

Bipolar Disorder

The use of tDCS in bipolar depression has not been as yet sufficiently investigated, with only one open-label study comparing the efficacy of tDCS in unipolar vs. bipolar depressed patients and showing efficacy in both conditions [62]. Another open study evaluated a sample of unipolar and bipolar patients for 3 months, but did not report results separately for the unipolar and bipolar groups [63]. Finally, Pereira-Junior et al. reported on pilot results from a double-blinded study in progress, in which five patients with bipolar depression received active tDCS. Response and remission rates were, respectively, 40% and 20 % [76]. Regarding efficacy in mania, the evidence is limited to one single case report showing improvement of manic symptoms after five sessions of tDCS that was applied with the anode over the right and the cathode over the left DLPFC [77].

There are four stand-alone case reports in literature [78–81] and some reports in randomized clinical trials of mania or hypomania induction after tDCS treatment. Some of these occurred in patients with unipolar depression, i.e., with no prior history of mania or hypomania. Most of these episodes resolved spontaneously, with tDCS withheld for a few days, or with small dose adjustments/introduction of a new pharmacotherapy, although one of them was a full-blown episode of mania with psychotic features [81].

It is difficult to estimate the precise frequency of this adverse effect or, even, if it is directly caused by tDCS or if the case reports represent events that occurred coincidently with the repeated tDCS sessions. It is also unclear if having a diagnosis of bipolar disorder places a patient at higher risk of a manic switch with tDCS, as has been suggested for other brain stimulation therapies. Therefore, the same recommendations of care for depressed patients are also valid when using tDCS as an antidepressant treatment—i.e., careful observation of the patients' clinical outcomes while on a clinical treatment. Further, patients should be carefully assessed for history of bipolar disorder and history of switching into mania with past antidepressant treatments, as these factors may indicate a higher risk of manic switch with tDCS. In these patients, concurrent treatment with mood stabilizer medications during the tDCS treatment course should be considered.

Discussion

The response rate of tDCS ranged from 20 to 40 %, with open-label trials showing discretely better results than the active arms of sham-controlled trials. Such improvement is in the same range of antidepressant drug treatment [82] and, in fact, two studies that directly compared tDCS vs. fluoxetine [59] and sertraline [24] found similar improvement rates in the pharmacological and non-pharmacological arms. This could suggest that tDCS might be a *substitute* for pharmacotherapy when its use is hindered, for instance, due to medical conditions [83]. The advantages of substituting tDCS for medicines is that tDCS does not cause systemic effects, has no serious adverse effects, and the problem of pharmacological interactions is avoided. One the other hand, the necessity of daily tDCS sessions requires patients to be in daily attendance, which may be difficult for outpatients. In this context, the development of portable, remotely supervised "home-use" tDCS devices could help in this issue, as the number of visits to the clinical center would be dramatically reduced [84].

Moreover, other reviewed studies evaluated the role of tDCS as an *augmentation* strategy for pharmacotherapy, showing that the combined

therapy of tDCS with antidepressant drugs, particularly SSRIs, was associated with superior improvement. On the other hand, tDCS combined with CCT showed mixed results; therefore, this association should be evaluated further in future trials.

Another critical and unclear point is the optimal treatment protocol during the maintenance phase. Only two follow-up studies were carried out hitherto [70, 72] with relatively poor results, with a relapse rate of around 50 % in 6 months. We propose that the same strategies under research for rTMS could be employed here, namely more frequent stimulation sessions and use of antidepressant drugs during the maintenance phase. Preliminary data in a few patients suggests that repeated course of tDCS in those who relapse may be safe and effective but this needs further evaluation [85].

Finally, though results to date are promising, it should be underscored that not all clinical trials yielded positive results and one meta-analysis failed to show superiority from active tDCS to sham treatment. Some reasons for these mixed findings include relatively small sample sizes, disparate treatment modalities (including number of sessions, cathode positioning, duration and intensity of the sessions) and different depression characteristics (regarding refractoriness, severity, mean age, unipolar vs. bipolar depression, and concomitant use of pharmacotherapy). In our individual patient data meta-analysis we found that tDCS efficacy in treatment-resistant depression is lower. Nonetheless, further randomized clinical trials are necessary and, in fact, several trials are currently being performed worldwide. Although we cannot presently conclude that tDCS is *definitively* effective in depression, in the next few years a definite answer regarding tDCS clinical efficacy is expected.

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Schizophrenia

14

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Abstract

This chapter proposes an overview of current evidence and future directions for using tDCS in schizophrenia. To date, the effects of tDCS have been investigated in three main outcomes: (1) to alleviate auditory verbal hallucinations using a frontotemporal tDCS montage (the anode placed over the left dorsolateral prefrontal cortex coupled with the cathode placed over the left temporoparietal junction); (2) to alleviate negative symptoms using a frontal montage (the anode placed over the left dorsolateral prefrontal cortex coupled with the cathode placed over the right dorsolateral prefrontal cortex, the right supraorbital region or extra-cephalically); and (3) to enhance cognitive functions, using different tDCS montages. Promising results have been reported for these three outcomes. tDCS can decrease the severity of symptoms such as auditory verbal hallucinations and negative symptoms by about 30 % and enhance a wide range of cognitive functions (e.g., working memory, self-monitoring, facial emotion recognition). However, most studies to date are case-reports and open labeled studies with small samples. Thus, large randomized controlled studies are needed to confirm the usefulness of tDCS in schizophrenia.

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Introduction

Schizophrenia is a frequent and debilitating psychiatric condition occurring in about 1 % of the general population. The clinical expression of schizophrenia is heterogeneous, and symptoms are usually classified into five main dimensions: positive (e.g., hallucinations, delusions), negative (e.g., flat expression, avolition), depression, disorganization, and grandiosity/excitement. Symptoms of schizophrenia are usually alleviated by psychopharmacological medications. However, up to 30 % of treated patients still report disabling symptoms such as auditory verbal hallucinations, negative symptoms, and cognitive deficits [1, 2]. These treatment-resistant symptoms are associated with a higher risk of relapse and worse prognosis, justifying the need for developing novel alternative approaches.

Over the last decade, various nonpharmacological approaches such as noninvasive brain stimulation (NIBS) techniques have been developed in order to alleviate treatment-resistant symptoms in patients with schizophrenia. NIBS techniques are safe tools to modulate brain activity and connectivity in living humans. These approaches were based on neuroimaging studies that have highlighted some brain correlates of schizophrenia symptoms: auditory verbal hallucinations were associated with hyperactivity in the left temporoparietal region [3] and frontotemporal dysconnectivity [4]; negative symptoms and cognitive deficits were associated with structural and functional abnormalities in the prefrontal cortices [5]. According to their neuromodulatory effects, NIBS techniques were thus proposed to reduce treatment-resistant symptoms in patients with schizophrenia by targeting the brain regions that showed abnormal activities. One of the NIBS techniques recently used in these patients is transcranial direct current stimulation (tDCS).

The first studies investigating the use of tDCS to improve symptoms of schizophrenia have been published in 2011. Since then, a rapid increase in the number of published articles in the field was observed (Fig. 14.1)—in fact, 20 studies investigating the clinical interest of tDCS in schizophrenia were indicated as "ongoing" on clinicaltrials.gov database in September 2015 (ten in North America, four in Europe, two in Middle East, one in Australia, one in South America, one in Africa, and one in East Asia) suggesting the international growing interest of tDCS for schizophrenia.

Two tDCS montages for schizophrenia have been mostly used. The first one, a frontotemporal electrode montage, is proposed to reduce treatment-resistant auditory verbal hallucinations. In this montage, the anode (presumably excitatory) was placed over the left prefrontal cortex and the cathode (presumably inhibitory) was placed over the left temporoparietal junction [6, 7]. The second one is proposed to reduce treatment-resistant negative symptoms and to improve cognitive functions by targeting the left prefrontal region. In this montage, the anode was placed over the left dorsolateral prefrontal cortex (DLPFC) and the cathode over the right supraorbital region, the right DLPFC or extra-cephalically [8, 9].

The aim of this chapter was to investigate whether tDCS can alleviate symptoms and improve cognitive functions in patients with schizophrenia. Hence, we reviewed studies investigating the clinical effects of tDCS on auditory verbal hallucinations, negative symptoms and other symptoms of schizophrenia. We also reviewed studies focusing on the effects of tDCS on cognitive functions in patients with schizophrenia. After a description of current evidence regarding the interest of using tDCS in patients with schizophrenia and the brain correlates of clinical and cognitive improvements, we also discussed the safety of this approach and how tDCS parameters can be optimized to improve efficacy.

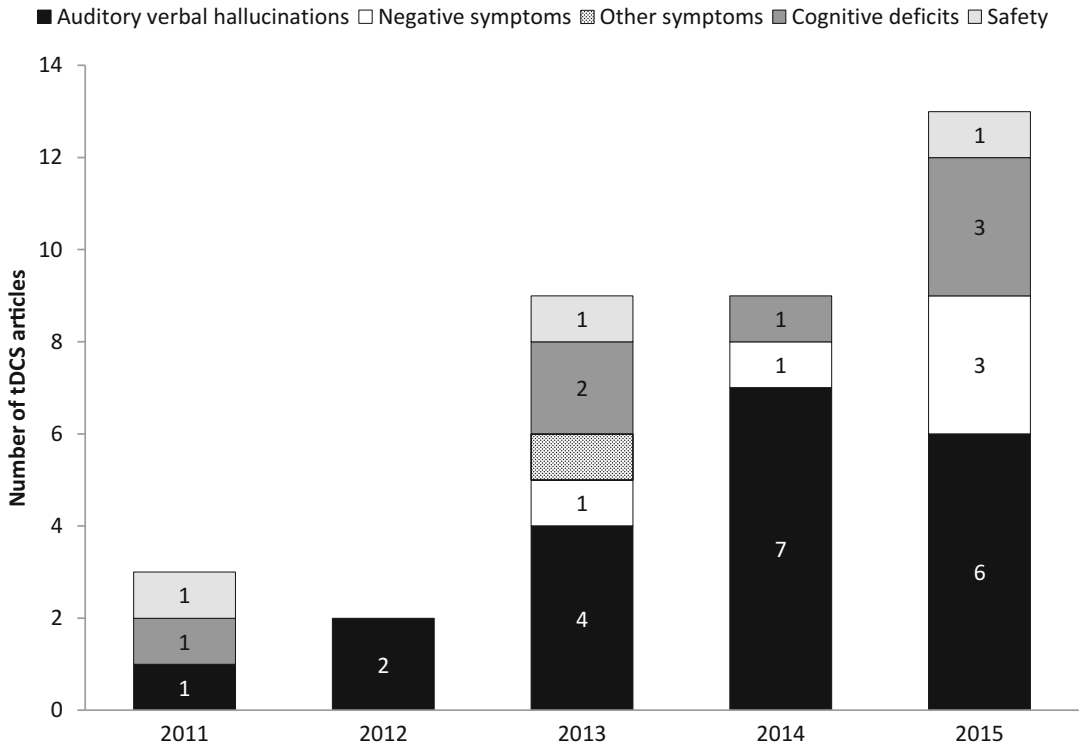

Fig. 14.1 Number of published articles per year examining the effects of transcranial direct current stimulation (tDCS) in patients with schizophrenia. Articles investigating the effects on auditory verbal hallucinations, negative symptoms, other symptoms, cognitive deficits, and safety have been listed (*Source*: PubMed/Medline)

Effects of Frontotemporal tDCS on Auditory Verbal Hallucinations

Twenty-one studies investigated whether tDCS targeting the frontotemporal network can improve the symptoms of treatment-resistant auditory verbal hallucinations in patients with schizophrenia (see Table 14.1). Among them, three randomized sham-controlled studies have reported a significant effect of active tDCS on auditory verbal hallucinations as compared to sham [6, 26, 27]. In the first one [6], 30 patients with schizophrenia received ten sessions of 20 min of either active (2 mA) or sham tDCS delivered twice daily on 5 consecutive days. Electrodes were placed on the scalp based on the 10/20 international EEG system, with the center of the anode placed between F3 and FP1 (assuming to correspond to the left prefrontal cortex) and the center of the cathode placed between T3 and P3 (assuming to correspond to the left temporoparietal junction). Auditory verbal hallucinations were assessed using the Auditory Hallucination Rating Scale (AHRS). Patients receiving active tDCS reported a significant 31 % decrease of their treatment-resistant auditory verbal hallucinations whereas patients receiving sham tDCS reported a nonsignificant 8 % decrease [6]. Remarkably, the effect of tDCS on auditory verbal hallucinations was still significant at 1 and 3-month follow-up [6].

Similar results were reported using the same tDCS protocol in two randomized controlled studies published in 2015 [26, 27]. It is important to stress that samples enrolled in these studies partially overlapped with the study sample of Brunelin et al. [6]. In the first study, Mondino et al. [26] reported a significant 46 % reduction in the frequency of auditory verbal hallucinations assessed by the first item of the AHRS after 10 sessions of

active tDCS, whereas a nonsignificant 10% decrease was reported in the sham group. In the second one, a significant 28% decrease in auditory verbal hallucinations measured by the AHRS was reported after the ten sessions of active tDCS, whereas a nonsignificant 10% decrease was reported in patients receiving sham tDCS [27].

Using the same electrodes montage, promising effects of tDCS for reducing auditory verbal hallucinations were also reported in 4 open labeled studies including 23 [25], 21 [17], 16 [28], and 6 [18] patients with schizophrenia. All studies included patients with schizophrenia receiving ten sessions of 20 min of active 2 mA tDCS delivered twice daily on 5 consecutive days. In the first one, Shivakumar et al. [25] recruited 23 patients and assessed their auditory verbal hallucinations using the "auditory hallucination" subscale of the Psychotic Symptom Rating Scale (PSYRATS). Patients showed a nearly 30% significant decrease of their treatment-resistant auditory verbal hallucinations after tDCS. Bose et al. [17] recruited 21 patients and assessed the auditory verbal hallucinations, also using the "auditory hallucination" subscale of the PSYRATS. After tDCS, patients showed a significant decrease (32.7%) in auditory verbal hallucinations. Brunelin et al. [28] recruited 16 patients and assessed their auditory verbal hallucinations using the AHRS. After tDCS, patients showed a significant 20% decrease in auditory hallucinations. In Ferrucci et al. [18], six patients were included and assessed using the Cardiff Anomalous Perceptions Scale (CAPS). After tDCS, patients showed a 33% decrease in frequency and a 40% decrease in distress of auditory verbal hallucinations.

Thirteen case-reports also investigated the effects of frontotemporal tDCS on auditory verbal hallucinations in patients with schizophrenia. Of note, three of them observed a complete remission of auditory verbal hallucinations after tDCS [11, 12, 19]. Indeed, Rakesh et al. [11] and Shivakumar et al. [12] assessing auditory verbal hallucinations with AHRS, reported that ten sessions of 20 min of active 2 mA tDCS delivered twice daily on 5 consecutive days allowed complete remission of auditory verbal hallucinations. Shivakumar et al. [19], assessing auditory verbal hallucinations with the "auditory hallucinations" subscale of the PSYRATS, reported a complete remission of auditory verbal hallucinations for at least 3 months after ten sessions of tDCS delivered twice daily for 20 min at 2 mA. Two case studies also highlighted the efficacy and safety of maintenance tDCS sessions for 1 and 3 years [14, 19]. Shivakumar et al. [19] reported a complete remission of auditory verbal hallucinations assessed with the PSYRATS "auditory hallucinations" subscale during 1 year after ten sessions of tDCS delivered twice daily for 20 min at 2 mA. In fact, the patient presented three relapses within 1 year, which were successfully managed with only two sessions of tDCS (in 1 day). Andrade [14] reported a decrease in auditory verbal hallucinations assessed with clinical scales during 3 years of tDCS delivered domiciliary once then twice daily, for 20 then 30 min at 1–3 mA intensity. Within 2 months, the patient self reported a 90% improvement.

Finally, a randomized sham controlled study failed to replicate the beneficial clinical effect of tDCS on auditory verbal hallucinations assessed by a single item on the Positive and Negative Syndrome Scale (PANSS) measuring hallucinations severity [20]. In this study, 15 sessions of tDCS (2 mA, 20 min) were delivered once a day during 3 consecutive weeks using either a left frontotemporal montage (with the anode over F3 and the cathode over the T3-P3) in 11 patients with schizophrenia or an original bilateral montage with four electrodes (two anodes over F3 and F4 and two cathodes over T3-P3 and T4-P4) in 13 patients with schizophrenia. In a recent case-report study, Bose et al. [24] reported that 18 sessions of left frontotemporal tDCS (with the anode placed midway between F3 and FP1 and the cathode over the T3-P3) had no effect on auditory verbal hallucinations as assessed by the "auditory hallucination" subscale of the PSYRATS. However, when switching the electrode montage to the right side of the brain with the anode placed over the right DLPFC (between F4 and FP2) coupled with the cathode over the right temporoparietal junction (between T4 and

Table 14.1 Summary of studies investigating the effects of frontotemporal tDCS on auditory verbal hallucinations in patients with schizophrenia

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (*n*/day)	*I* (mA)	Duration (min)	Outcomes and main results
Homan et al. 2011 [10]	Case	1	44	M	FP2/T3P3	10 (1/day)	1	15	1. Decrease in HCS score (−60 %) 2. Decrease in PANSS score (−20 %) 3. Decrease in PSYRATS score (−16 %) 4. Decrease of rCBF in Wernicke's area (BA22), left Heschl's gyrus (BA41/42), and Broca's area (BA44/45) Sustained effect on symptoms at 6-month follow-up
Brunelin et al. 2012a [7]	RCT	30 15A 15S	37.7	22M/8F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHRS score (−31 %) Sustained effect at 1 and 3-month follow-up 2. Decrease in PANSS score (−13 %)
Brunelin et al. 2012 [6]	Case	2	37.5	M	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHRS score (patient 1: −77 %; patient 2: −48 %) 2. Decrease in PANSS score (patient 1: −20 %; patient 2: −49 %) Sustained effects at 3-month follow-up
Rakesh et al. 2013 [11]	Case	1	24	M	F3FP1/T3P3	10 (2/day)	2	20	1. Complete cessation of AH measured by AHRS 2. Improvement in measured by an increase in IRS from 1 to 5
Shivakumar et al. 2013 [12]	Case	1	28	F	F3FP1/T3P3	10 (2/day)	2	20	1. Complete cessation of AH measured by AHRS 2. Improvement in insight measured by an increase in IRS from 0 to 5
Shiozawa et al. 2013 [13]	Case	1	31	M	F3/Oz F3/T3P3	10 (1/day) 10 (1/day)	2	20	1. Decrease in AHRS score (−20 %) 2. Decrease in visual hallucinations measured by LSHS score (−20 %) 3. Decrease in general (−29 %), positive (−38 %) and negative symptoms (−27 %) assessed by PANSS
Andrade 2013 [14]	Case	1	24	F	F3/T3P3	1–2/day at home during 3 years	1–3	20–30	1. Decrease in AH and general symptoms measured by clinical ratings
Nawani et al. 2014 [15]	Case	1	31	M	F3/T3P3	10 (2/day)	2	20	1. Decrease in AHRS score (−30 %) 2. Increased changes in amplitudes of N100 induced by tetanic blocks. These changes were reported only for the frontal electrodes

(continued)

Table 14.1 (continued)

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (*n*/day)	*I* (mA)	Duration (min)	Outcomes and main results
Nawani et al. 2014 [16]	Case	5	33.2	2M/3F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHRS score (−30 %) 2. Modulation of N100 amplitude in the auditory cortex during "talk" and "listen" conditions: before tDCS, no differences between N100 amplitudes in talk and listen conditions After tDCS, smaller N100 amplitude during "talk" as compared to "listen"
Bose et al. 2014 [17]	Open	21	33.1	9M/12F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in PSYRATS AHS scores (−32.7 %) 2. Improvement in insight measured by an increase in SAI scores from 7.8 ± 4.4 to 12.2 ± 4.2 Correlation between the both
Ferrucci et al. 2014 [18]	Open	6	41–66	ND	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in frequency (−33 %) and distress (−40 %) of AH measured by the CAPS. The effects lasted up to 1 month 2. Decrease in PANSS negative symptoms scores (−24 %)
Shivakumar et al. 2014 [19]	Case	1	42	F	F3FP1/T3P3	10 (2/day)	2	20	1. Complete cessation of AH measured by the AHS of PSYRATS during 1 year. 2 sessions at relapse allow maintenance of beneficial effect
Fitzgerald et al. 2014 [20]	RCT	11 13	39.3	15M/9F	F3/T3P3 F3 + F4/ T3P3 + T4P4	15 (1/day)	2	20	1. No significant decrease in PANSS AH score (unilateral: −17 %; bilateral: −14 %) compared to sham (−7 %; −3 %). No effects in total PANSS scores, PANSS positive symptoms and PANSS negative symptoms 2. No effect on SANS
Narayanaswamy et al. 2014 [21]	Case	1	22	F	F3FP1/T3P3	10 (2/day)	2	20	After the ten sessions of tDCS: 1. No changes in AHRS scores 2. No changes in SANS scores During the subsequent 2 weeks: 1. No changes in AHRS scores 2. Decrease in SANS scores (−30 %) At 6-month follow-up: 1. Decrease in AHRS scores (−37 %) 2. Decrease in SANS scores (−60 %)

Shenoy et al. 2015 [22]	Case	1	25	F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHS of PSYRATS (−25 % immediately after the ten sessions and −95 % 4 months after tDCS sessions) 2. Safety and tolerability during pregnancy assessed using sonography
Praharaj et al. 2015 [23]	Case	1	49	M	F3/T3P3	5 (1/day)	2	20	1. More than 90 % decrease in frequency and duration of AH after the 1st session 2. Decrease in PSYRATS AHS score 3. No effect on PSYRATS delusion score 4. Subjective report of reduction in distress associated with AH Symptoms return to baseline 6 days after the last tDCS session
Bose et al. 2015 [24]	Case	1	37	F	F3FP1/T3P3 F4FP2/T4P4	18 (1/day) 20 (1/day)	2	20	After 18 sessions of F3FP1/T3P3 tDCS: 1. No effects on AHS of PSYRATS 2. No effects on "attentional salience" item of the AHRS After 20 sessions of F4FP2/T4P4 tDCS: 1. Decrease in AHS of PSYRATS (−31.4 %) 2. Decrease in "attentional salience" item of the AHRS (from 6 to 4)
Shivakumar et al. 2015 [25]	Open	23	33.4	10M/13F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in PSYRATS AHS after tDCS. Greater decrease in the COMT val/val group ($n=11$) than in the met group (val/met or met/met; $n=12$)
Mondino et al. 2015 [26]	RCT	28 15A 13S	Active: 36.5 Sham: 39.2	9F/6M 7F/6M	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in "frequency" item of the AHRS (−46 %) 2. Improvement in internal source monitoring performances (decrease of externalization bias) Correlation between both

(continued)

Table 14.1 (continued)

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (*n*/day)	*I* (mA)	Duration (min)	Outcomes and main results
Mondino et al. 2015b [27]	RCT	23 11A 12S	Active: 36.7 Sham: 37.3	8M/3F 7M/5F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHRS scores (−28 %) 2. Decrease in PANSS negative score (−17 %). No effects on PANSS positive symptoms and general psychopathology 3. Effects on rs-FC of the left TPJ measured by fMRI: decreased rs-FC of the left TPJ with the left anterior insula and the right inferior frontal gyrus. Increased rs-FC of the left TPJ with the left angular gyrus, the left dorsolateral prefrontal cortex and the precuneus Correlation between the reduction of AHRS scores and the reduction of the rs-FC between the left TPJ and the left anterior insula
Brunelin et al. 2015 [28]	Open	16	41	6M/10F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHRS scores (−20 %) Greater decrease in nonsmokers (−46 %) than in smokers (−6 %)

tDCS electrodes placement was described according to 10/20 EEG system: F3: Left dorsolateral prefrontal cortex; F4: Right dorsolateral prefrontal cortex; FP2: Right supraorbital region; FP1: Left supraorbital region; Oz: Occipital region; T3P3: Left temporoparietal junction; T4P4: Right temporoparietal junction; T3: Left temporal region; T4: Right temporal region

A active, AH auditory hallucinations, *AHRS* auditory hallucination rating scale, *AHS* auditory hallucinations subscale, *BA* Brodmann's area, *CAPS* Cardiff anomalous perceptions scale, *F* female, *fMRI* functional magnetic resonance imaging, *HCS* hallucination change score, *I* intensity, *IRS* insight rating scale, LSHS, Launay–Slade hallucination scale, *M* male, *n* number of subjects, *PANSS* positive and negative syndrome scale, *PSYRATS* psychotic symptom rating scale, *rCBF* regional cerebral blood flow, *RCT* randomized controlled trial, *rs-FC* resting-state functional connectivity, *S* sham, SAI schedule for assessment of insight, *SANS* scale for the assessment of negative symptoms, *tDCS* transcranial direct current stimulation, *TPJ* temporoparietal junction

P4), 20 sessions of tDCS induced a 31.4 % reduction of auditory verbal hallucinations.

In sum, among the studies investigating the effects of frontotemporal tDCS on auditory verbal hallucinations, the intensity of stimulation varied from 1 to 3 mA for a 15- to 30-min duration. The size of the electrodes was mostly 35 cm^2 (7 × 5 cm), but some studies used 25 cm^2 electrodes (5 × 5 cm; [14, 23]). tDCS regimen consisted in 5–20 sessions of tDCS delivered either once or twice daily. Auditory verbal hallucinations were assessed using various standardized multidimensional scales such as the PSYRATS or the AHRS, but also using single item assessments such as the "auditory hallucinations" item of the PANSS [20] or the "frequency" item of the AHRS [26]. These assessments and outcomes may not have the same sensitivity to capture changes in auditory verbal hallucinations. Further studies are needed to confirm promising effects observed on auditory verbal hallucinations following frontotemporal tDCS in patients with schizophrenia.

Effects of Frontotemporal tDCS on Other Symptoms

Remarkably, among studies reporting a reduction of auditory verbal hallucinations in patients with schizophrenia following tDCS, some also observed a decrease in general symptoms of schizophrenia [6, 7, 10, 14], positive symptoms [13], negative symptoms [13, 18, 21, 27], and insight into the illness [11, 12, 17]. In addition, Shiozawa et al. [13] investigated the effect of ten sessions of tDCS with the anode over F3 and the cathode over the occipital region (Oz) followed by ten sessions with the anode over F3 and the cathode over the temporoparietal cortex (T3-P3) on visual and auditory verbal hallucinations in a patient with schizophrenia. They reported that ten sessions of each electrode montage lead to a reduction of hallucinations in both visual and auditory modalities.

Predictive Markers of Response to Frontotemporal tDCS on Auditory Verbal Hallucinations

Two open labeled studies investigated potential predictive markers of response to tDCS [25, 28]. Shivakumar et al. [25] investigated the effects of frontotemporal tDCS in 23 patients with treatment-resistant auditory verbal hallucinations divided into two groups depending on their COMT Val158Met polymorphism. A significant reduction of auditory verbal hallucinations was observed in both groups. However, patients with the val/val COMT polymorphism ($n = 11$) showed a greater reduction in auditory verbal hallucinations than met-allele carriers (val/met or met/met polymorphism; $n = 12$). The COMT Val158Met polymorphism may thus modulate response to tDCS. An excessive dopamine transmission has been implicated in the clinical expression of positive symptoms. The Val variant catabolizes frontal dopamine at up to four times the rate of its methionine counterpart, suggesting that lower extracellular dopamine rates in the frontal region predicts beneficial clinical outcome in patients with AVH.

Brunelin et al. [28] reported a mean 20 % decrease of auditory verbal hallucinations following 10 sessions of frontotemporal tDCS in 16 patients with treatment-resistant auditory verbal hallucinations. In this sample, patients with a comorbid tobacco use disorder showed a nonsignificant 6 % reduction in auditory verbal hallucinations, whereas nonsmokers displayed a significant 46 % reduction in auditory verbal hallucinations. Thus, smoking may prevent the effect of repeated sessions of frontotemporal tDCS in patients with treatment-resistant auditory verbal hallucinations. It has been hypothesized that interactions between antipsychotic medication and nicotine may influence dopamine transmission and in turn modulate tDCS effects on neural plasticity.

Furthermore, one case study suggested that some clinical characteristics such as attentional salience of auditory verbal hallucinations could

influence site-specific response to tDCS. Namely, Bose et al. [24] described the case of a patient with high attentional salience auditory verbal hallucinations that failed to respond to left-sided frontotemporal tDCS but that decreased after right-sided frontotemporal tDCS.

Brain Correlates of the Effects of Frontotemporal tDCS on Auditory Verbal Hallucinations

Several studies used fMRI and EEG to investigate how tDCS modulates the brain when reducing auditory verbal hallucinations in patients with schizophrenia.

In a first single case study, Homan et al. [10], reported that tDCS decreased the regional cerebral blood flow in Wernicke's area (BA22), left Heschl's gyrus (BA41/42), and Broca's area (BA44/45), as well as auditory verbal hallucinations. This work supports the hypothesis that tDCS applied over the left temporoparietal junction reduces auditory hallucinations by normalizing brain activity, specifically by suppressing the hyperactivity observed in the language-related network during auditory verbal hallucinations [3].

In a randomized sham controlled study including 23 patients with schizophrenia, Mondino et al. [27] reported that active tDCS decreased resting state functional connectivity of the left temporoparietal junction with the left anterior insula and the right inferior frontal gyrus and increased resting state functional connectivity of the left temporoparietal junction with the left angular gyrus, the left dorsolateral prefrontal cortex and the precuneus as compared to sham tDCS. These changes in functional connectivity were accompanied by a reduction of auditory verbal hallucinations. Moreover, there was a correlation between the reduction of auditory verbal hallucinations and the reduction of the resting state functional connectivity between the left temporoparietal junction and the left anterior insula. These results also suggest that the reduction of auditory verbal hallucinations induced by tDCS was associated with a modulation of the brain activity within an auditory verbal hallucinations -related brain network, including brain areas involved in inner speech production and monitoring.

Using EEG, Nawani et al. [16] investigated the effects of ten sessions of left frontotemporal tDCS on auditory verbal hallucinations and on the amplitude of the auditory evoked potential N100 in five patients with schizophrenia. The N100 amplitude was measured when patients were listening to speech stimuli and when they were asked to produce speech. The authors reported that patients with schizophrenia showed no difference at baseline between N100 amplitudes generated in talk and listen conditions. This absence of N100 modulation during talking as compared to listening is suggested to reflect abnormalities in the corollary discharge. After tDCS, the amplitude of N100 was significantly smaller during talking than listening. Thus, tDCS seems to restore the N100 amplitude modulation when reducing auditory verbal hallucinations.

In a case study, Nawani et al. [15] tested whether the same protocol of left frontotemporal tDCS had an effect on cortical plasticity measured by EEG. Namely, they measured the N100 amplitude evoked by an auditory oddball task before and after a tetanic block before and after tDCS. The authors reported that ten sessions of frontotemporal tDCS reduced auditory hallucinations and increased the modulation of the N100 amplitude induced by the tetanic block. This effect was measured in the frontal region only. Since a change in N100 amplitude after tetanic block is considered as an indicator of neuroplasticity, these results suggested that tDCS modulates cortical neuroplasticity in patients with schizophrenia.

Effects of Frontal tDCS on Negative Symptoms and Other Symptoms of Schizophrenia

Five studies investigated the clinical effect of tDCS on treatment-resistant negative symptoms of schizophrenia (see Table 14.2). In these studies, the targeted brain region was the DLPFC, mainly its left part. This brain region was targeted with tDCS by placing the anode over the left DLPFC (F3) and the cathode either over the supra orbital region (FP2), the right DLPFC (F4) or the right

Table 14.2 Summary of studies investigating the effects of frontal tDCS on negative symptoms and other symptoms in patients with schizophrenia

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (n/day)	*I* (mA)	Duration (min)	Outcomes and main results
Palm et al. 2013 [8]	Case	1	19	M	F3/FP2	10 (1/day)	2	20	1. Decrease in PANSS total scores (−29 %), negative (−25 %) and positive (−37 %) subscores 2. Decrease in SANS scores (−28 %) 3. Decrease in depression assessed by CDSS (−82 %) Effects on FC measured using fMRI: reduced FC in the subgenual cortex, the anterior cingulate, the medial frontal gyrus, the and superior frontal gyrus 4. Increase in TMT performances 5. Decrease in the number of errors at the SOPT
Palm et al. 2014 [9]	RCT	20	ND	ND	F3/FP2	10 (1/day)	2	20	1. Decrease in SANS scores 2. Decrease in PANSS total scores 3. Effects on FC measured using fMRI: Deactivated cluster in the nucleus accumbens, subgenual cortex and striatum
Kurimori et al. 2015 [29]	Open	9	40.3	3F/6M	F3/Right deltoid	10 (1/day)	2	20	1. Decrease in PANSS negative symptoms scores (−24 %). Decrease in total PANSS scores (−8 %). No change in PANSS positive and general symptoms
Gomes et al. 2015 [30]	RCT	15 7A 8S	A: 43.3 S:34.2	5M/2F 6M/2F	F3/F4	10 (1/day)	2	10	1. Decrease in PANSS negative symptoms scores (−20 %) in the active group (versus −0.5 % in the sham group). Decrease in general and total PANSS scores (−15 % and −12 %) in the active group (0 % in the sham group). No effect on PANSS positive symptoms scores 2. No effect on depression assessed by CDSS 3. No effect on global functioning assessed by GAF
Shiozawa et al. 2013 [31]	Case	1	65	F	F3/F4	10 (1/day)	2	20	1. Decrease of catatonic symptoms assessed by BFS scores until complete remission (4 months after tDCS sessions)

tDCS electrodes placement was described according to 10/20 EEG system: F3: Left dorsolateral prefrontal cortex; F4: Right dorsolateral prefrontal cortex; FP2: Right supraorbital region

A active, *BFS* Bush–Francis scale, *CDSS* Calgary depression scale, *F* female, *FC* functional connectivity, *fMRI* functional magnetic resonance imaging, *GAF* global assessment of functioning, *I* intensity, *M* male, *n* number of subjects, *PANSS* positive and negative syndrome scale, *RCT* randomized controlled trial, *rs-FC* resting-state functional connectivity, *S* sham, *SANS* scale for the assessment of negative symptoms, *SOPT* self ordered pointing task, *tDCS* transcranial direct current stimulation, *TMT* trail making test

deltoid. In the first study, Palm et al. [8] reported that 10 sessions of tDCS delivered once a day with the anode placed over the left DLPFC (F3) and the cathode electrode placed over the right supra orbital region (FP2) reduced treatment-resistant negative and positive symptoms in a patient with schizophrenia. In a further randomized sham controlled trial with 20 patients with negative symptoms, Palm et al. [9] reported that ten daily sessions of active tDCS as compared to sham tDCS decreased negative symptoms as measured by the Scale for the Assessment of Negative Symptoms (SANS) and general symptoms as assessed by the PANSS. These beneficial clinical effects were maintained at the 2-week follow-up assessment.

These beneficial effects of tDCS on negative symptoms were also reported more recently in an open-label study including nine patients with schizophrenia [29] and in a randomized sham-controlled study including 15 patients with schizophrenia [30]. In the first study, patients received ten daily sessions of tDCS with the anode placed over the left DLPFC (F3) and the cathode placed over the right deltoid muscle [29]. After tDCS, patients showed a significant 24 % reduction in negative symptoms assessed by the PANSS negative subscale as compared to baseline. In the second study, patients received ten daily sessions of either active or tDCS with the anode placed over the left DLPFC (F3) and the cathode placed over the right DLPFC (F4) [30]. After tDCS, patients receiving active tDCS showed a significant 20 % reduction in negative symptoms as measured by the PANSS negative subscale whereas patients receiving sham tDCS showed no significant difference. Patients receiving active tDCS also reported a significant 15 % reduction in PANSS general symptoms as compared to patients receiving sham tDCS.

Brain Correlates of the Effects of Frontal tDCS on Negative Symptoms

Only one case study and one randomized controlled study investigated how tDCS modulates the brain when reducing negative symptoms in patients with schizophrenia. In the case study, Palm et al. [8] used fMRI to measure the effects of ten sessions of tDCS with the anode placed over the left DLPFC and the cathode placed over the right supraorbital region (FP2) on resting-state functional connectivity. Following tDCS, the patient showed a reduction in positive and negative symptoms and a reduced functional connectivity in the anterior part of the default mode network including the subgenual cortex, the anterior cingulate, the medial frontal gyrus and superior frontal gyrus. In a larger sample including 20 patients with schizophrenia, the same group of authors reported that the clinical improvement in negative symptoms observed after patients received tDCS was accompanied by a significant reduced functional connectivity within the nucleus accumbens, the subgenual cortex and the striatum [9].

Effects of Frontal tDCS on Other Symptoms

In a case study, Shiozawa et al. [31] reported a reduction in severity of catatonic symptoms in a patient suffering from treatment- and electroconvulsive therapy-resistant catatonic schizophrenia following ten sessions of tDCS delivered once a day with the anode over F3 and the cathode over F4. After 1 month, the remission of symptoms was complete and lasted for at least 4 months.

Effects of TDCS on Cognitive Functions

Cognitive deficits are a key feature in patients with schizophrenia. Several studies explored whether tDCS could improve cognitive functions in patients with schizophrenia (Table 14.3).

In the first study, Vercammen et al. [32] reported that a single session of active tDCS had a facilitating effect on probabilistic association learning measured by the weather prediction test in patients who displayed the best learning abilities before stimulation. In this study the anode was placed over the left DLPFC (F3) and the cathode over the right supraorbital region (FP2).

Table 14.3 Summary of studies investigating the effects of tDCS on cognitive functions in patients with schizophrenia

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (*n*/day)	*I* (mA)	Duration (min)	Outcomes and main results
Vercammen et al. 2011 [32]	Cross-over	20	37.6	10F/10M	F3/FP2	1	2	20	1. No effects on probabilistic learning assessed by the WPT in the whole sample. Significant improvement of performances in participants showing adequate performances at baseline
Ribolsi et al. 2013 [33]	Cross-over	15	34.3	4F/11M	P3/Right shoulder P4/Left shoulder	1	1	10	1. Anodal stimulation applied over P4 partially corrected the lack of leftward bias described using a line bisection task
Hoy et al. 2014 [34]	Cross-over	18	42.2	6F/12M	F3/FP2	1	0; 1 and 2	20	After stimulation at 2 mA intensity: 1. Increase in working memory performances assessed by the n-back task until 40 min after tDCS session After stimulation at 1 mA intensity: 1. No effect of 1 mA stimulation on working memory
Rassovsky et al. 2015 [35]	RCT	Anode 12 Cathode 12 12S	45.8 47.8 41.6	2F/10M 6F/6M 4F/8M	FP1/FP2	1	2	20	1. Anodal tDCS increases the identification of facial expressions assessed by the FEIT 2. No effect on social cognition assessed by the MSCEIT 3. No effect on social perception assessed by the PONS 4. No effect on theory of mind assessed by the ASIT 5. No effect on cognitive functions assessed by the MCCB composite score
Smith et al. 2015 [36]	RCT	30 14A 16S	A: 46.7 S: 44.8	14M/3F 10M/6F	F3/FP2	5 (1/day)	2	20	1. Increase in the MCCB composite score, the MCCB working memory score and in attention-vigilance domain scores in the active group as compared to sham 2. No effect on PANSS scores 3. No effect on smoking assessed by self report of cigarettes smoked and breathalyzer CO levels 4. No effect on cigarette dependence assessed with the cigarette dependence scale 4. No effect on craving assessed by the QSU

(continued)

Table 14.3 (continued)

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (*n*/day)	*I* (mA)	Duration (min)	Outcomes and main results
Schretlen et al. 2015 [37]	Cross-over no sham	5 patients 6 first degree relatives	50	6F/5M	F3/F4 F4/F3	1	1.5	30	1. No effect on motor speed assessed by the GPT and the FTT 2. No effect on processing speed assessed by the PCT 3. Increase in novel design production with no changes in world fluency productivity assessed by the CIFA 4. No effect on WMS-III spatial span and WAIS-III digit span forward (assessing attention) 5. Increase in overall backward span test performance (assessing working memory) during anodal versus cathodal tDCS
Hoy et al. 2015 [38]	Cross over	18	42.2	6F/12M	F3/FP2	1	0, 1 and 2 mA	20	After stimulation at 2 mA intensity: 1. Increase in working memory performance measured by the 2-back task at 20 and 40 min post-stimulation 2. Increase in gamma event-related synchronization measured by EEG at 40 min post-stimulation After stimulation at 1 mA intensity: 1. No effect on working memory 2. No effect on gamma event-related synchronization

tDCS electrodes placement was described according to 10/20 EEG system: F3: Left dorsolateral prefrontal cortex; F4: Right dorsolateral prefrontal cortex; FP2: Right supraorbital region; FP1: Left supraorbital region; P3: Left parietal region; P4: Right parietal region

A active, ASIT, awareness of social inference test, *CIFA* calibrated ideational fluency assessment, *CO* carbon monoxide, *EEG* electroencephalography, *F* female, *FEIT* facial emotion identification test, *FTT* finger tapping test, *GPT* grooved pegboard test, *I* intensity, *M* male, *MCCB* MATRICS consensus cognitive battery, *MSCEIT* Mayer–Salovey–Caruso emotional intelligence test; *n* number of subjects, *PANSS* positive and negative syndrome scale, *PCT* perceptual comparison test, *PONS* profile of nonverbal sensitivity, *QSU* questionnaire of smoking urges, *RCT* randomized controlled trial, *S* sham, *tDCS* transcranial direct current stimulation, *WAIS III* Wechsler adult intelligence scale, 3rd ed, *WMS-III* Wechsler memory scale, 3rd ed, *WPT* weather prediction test

In another study, Hoy et al. [34] observed beneficial effects of the same electrode montage on working memory performances measured using the n-back task. These beneficial effects lasted up to 40 min after the end of the stimulation period and were associated with an increase in frontal gamma event related synchronization [38]. Ribolsi et al. [33] reported a reduction of visuospatial attention deficit in patients with schizophrenia after a single session of tDCS where the anode electrode was placed over the right parietal (P4) and cathode over the left shoulder.

Several studies investigated the effects of anodal tDCS applied over the left DLPFC on cognitive functioning of patients with schizophrenia using a standardized battery of cognitive tests. In one of them, Rassovsky et al. [35] tested the effect of a single session of either anodal or cathodal tDCS applied over FP1 or FP2 (with the reference electrode placed over the upper right arm) on social cognition and cognitive functions in 36 patients with schizophrenia. Social cognition was measured using the Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT) that assesses four components of emotional processing, the Facial Emotion Identification Test (FEIT) that assesses the identification of facial emotion, the Profile of Nonverbal Sensitivity that assesses social perception, and the Awareness of Social Inference Test that assesses theory of mind. Cognitive functions were assessed using the MATRICS Consensus Cognitive Battery (MCCB) composite score. Following anodal tDCS, patients showed a significant improvement in the FEIT only, indicating that a single session of anodal tDCS over the prefrontal cortex might enhance identification of facial emotion in patients with schizophrenia.

In another study, Schretlen et al. [37] compared the effects of two 30-min sessions of tDCS, applied either with the anode over the left and cathode over the right DLPFC or with the reverse montage, on working memory and on a brief battery of cognitive measures in five outpatients with schizophrenia and six first-degree relatives of patients with schizophrenia. No differences were reported between tDCS conditions on motor speed assessed by the Grooved Pegboard Test and the Finger Tapping Test and on processing speed assessed by the Perceptual Comparison Test. No effects of tDCS condition were observed on attention assessed by the Wechsler Adult Intelligence Scale, 3rd Ed. Digit Span and Wechsler Memory Scale, 3rd Ed. Spatial Span. Working memory performances assessed by backward digit and spatial span were shown to be improved during anodal stimulation of the left DLPFC relative to cathodal stimulation. In addition, patients showed an increase in novel design production without alteration of overall productivity at the calibrated ideational fluency assessment during anodal versus cathodal tDCS.

Finally, only few studies investigated the effects of repeated sessions of tDCS on cognition in patients with schizophrenia. For instance, in a randomized double-blind, sham-controlled study, Smith et al. [36] investigated the effects of five sessions of either active or sham tDCS on cognition assessed by the MCCB composite score, psychiatric symptoms assessed by the PANSS, and smoking and cigarette craving in 37 patients with schizophrenia or schizoaffective disorder who were current smokers. tDCS was delivered with the anode placed over F3 and the cathode electrode placed over the right supra orbital region (FP2). Patients receiving active tDCS, as compared to sham, showed a significant improvement in the MCCB composite score, in the MCCB working memory score and in attention-vigilance domain scores. However, no significant effects were observed on clinical symptoms assessed by the PANSS, hallucinations, cigarette craving, and cigarettes smoked.

In a double-blind sham controlled study, Mondino et al. [26] tested the effects of ten sessions of left frontotemporal tDCS on source monitoring performance and treatment-resistant auditory verbal hallucinations in 28 patients with schizophrenia. Source monitoring was defined as the ability to discriminate between internally generated words and externally produced words. After ten sessions of active tDCS, patients performed better at recognizing internally generated words as compared to sham tDCS. In addition, there was a negative correlation between the reduction in the frequency of treatment-resistant

auditory verbal hallucinations and the increased recognition of internally generated words.

Safety of Using tDCS for Treating Schizophrenia

The reviewed articles investigated the impact of at least one tDCS session on more than 300 patients with schizophrenia. The duration of the tDCS session lasted from 10 to 30 min, with the intensity of stimulation ranging from 1 to 3 mA. Among expected adverse events following a session of tDCS [39], patients with schizophrenia more commonly reported tingling or itching sensations under the electrodes as well as sleepiness. No study reported any serious adverse event. In addition, ten sessions of tDCS delivered once or twice daily were well tolerated by specific populations such as patients with childhood-onset schizophrenia (mean age 15 years old; range 10–17) [40], female patients during pregnancy [22], and patients with comorbid skin condition [41]. Importantly, these studies did not observe any worsening of symptoms. An important improvement for patients with severe handicaps would be to have the possibility of tDCS to be delivered at home. Indeed, this was suggested for one patient with schizophrenia [14]. However, to allow this practice, the national authorities should establish recommendations ([42], also discussed in Chap. 26 of this book).

Optimizing tDCS Efficacy on Symptoms of Schizophrenia

Optimizing tDCS Parameters

The use of tDCS in schizophrenia is just at its beginning. There are still numerous unanswered questions including optimal stimulation parameters such as intensity, duration, and the number of sessions. Concerning stimulation intensity, tDCS has been mostly delivered at 1, 1.5, and 2 mA. Some studies comparing 1–2 mA stimulation suggested that 2 mA is the cut off for an optimal efficiency in reducing clinical symptoms and improving cognitive functions in schizophrenia [14, 34]. In that line, an interesting case study reported the safety of a 3 mA stimulation [14]. Concerning the duration of a session, most studies used sessions of a 20-min duration each. However, few studies reported beneficial effects of different session durations. For instance, Homan et al. [10] reported reduced auditory verbal hallucinations following ten sessions of tDCS delivered once daily at 1 mA during 15 min in a patient with schizophrenia. In another single case study, Andrade [14] enhanced tDCS duration from 20 to 30 min without adverse effects. In a randomized controlled study, Gomes et al. [30] reported the effects of ten sessions of tDCS delivered once daily at 2 mA during 10 min on negative symptoms and general symptomatology in 15 patients with schizophrenia. Concerning the number of sessions to deliver, patients with schizophrenia showed improvement after ten sessions delivered once or twice per day. One study, delivering 15 sessions of tDCS once per day, did not show any significant effect on auditory hallucinations [20]. In one case study, delivering five sessions of tDCS once per day induced a substantial reduction of auditory hallucinations that lasted at least 6 days [23]. To sum up, even if there is still much to learn about the tDCS optimal parameters, gathered evidence suggests that ten sessions of tDCS of 20-min duration and at a 2 mA intensity delivered once or twice per day produce a positive outcome such as reducing symptoms and improving cognition in patients with schizophrenia.

Other Modalities of Transcranial Electric Stimulation in Schizophrenia

Other forms of transcranial electric stimulation besides tDCS, such as high frequency oscillatory unidirectional *transcranial random noise stimulation* (tRNS) [43], have been tested in schizophrenia. To date, two studies investigated the effects of unidirectional tRNS with high frequencies ranging from 100 to 640 Hz, in patients

with schizophrenia. Palm et al. [44] reported an improvement in negative symptoms after 20 sessions of tRNS with the anode applied over the left DLPFC cortex and the cathode over the right supraorbital cortex. Haesebaert et al. [45], using the left frontotemporal montage during ten sessions of tRNS, observed a reduced severity of auditory hallucinations and an improved insight into the illness. Moreover, one study investigated the effects of transcranial slow oscillatory direct stimulation applied at a frequency of 0.75 Hz during phase 2 of sleep in 14 patients with schizophrenia [46]. In this study, slow oscillatory tDCS was applied at an intensity of 0.3 mA through two spherical 8 mm diameter electrodes placed bilaterally over F3 and F4 and at the mastoids. Stimulation was delivered for five blocks of 5 min separated by 1-min intervals free of stimulation. The authors reported that patients displayed greater performances to retain verbal information following active as compared to sham stimulation. A significant elevated mood was also observed in the morning after stimulation as compared to the morning after sham stimulation.

Combining tDCS with Other Approaches

tDCS studies most often include patients with schizophrenia suffering from treatment-resistant symptoms, and thus, treated with several medication classes including typical, atypical antipsychotics and selective serotonin reuptake inhibitors. These treatments should be taken into account when studying the impact of tDCS sessions. Indeed, in studies involving healthy subjects, dopaminergic, serotonergic, and GABAergic agents/drugs have been shown to have an impact on motor cortex excitability after tDCS sessions [47, 48]. For example, tDCS aftereffects in healthy subjects are considerably reduced with sulpiride [48]. With this in mind, it seems important that the studies investigating the effect of tDCS in patients with schizophrenia should determine the optimal association between pharmacology and the tDCS protocol. For example, a major depression study showed that bifrontal tDCS efficacy was reduced with concomitant use of benzodiazepine drugs [49]. Such interactions might also occur in patients with schizophrenia. Future work is therefore needed to study the association between tDCS effects, medication, and even nicotine intake [28] with tDCS efficacy in schizophrenia.

Another interesting approach, with the aim to improve tDCS effects on symptoms, could involve combination with neurocognitive strategies such as cognitive remediation therapy [50, 51]. For example, tDCS has been shown to improve working memory [52], therefore it could work with cognitive training as to enhance both cognitive and clinical efficacy. Further studies are needed to determine the optimal associations with the aim of improving clinical outcomes.

Conclusion

In this chapter, we reviewed and discussed studies investigating the usefulness of tDCS to reduce symptoms and improve cognitive functions of patients with schizophrenia. To date, two electrode montages seem to stand out: one frontotemporal montage with the anode placed over the left prefrontal cortex and the cathode placed over the left temporoparietal junction, which may reduce auditory verbal hallucinations; and one frontal montage with the anode placed over the left DLPFC and the cathode placed over the right DLPFC or the right supraorbital region which may also have beneficial clinical outcomes, mainly on negative symptoms. However, as the use of tDCS is quite recent and since most studies reviewed here were case-reports and open labeled studies with small samples, further randomized controlled trials with large samples are needed to confirm the efficacy of tDCS in schizophrenia. Moreover, further investigations have to be conducted to determine biological correlates and the optimal stimulation parameters to use to better impact on the symptoms of schizophrenia.

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OCD, Anxiety Disorders, and PTSD

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Abstract

According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), obsessive-compulsive and related disorders, anxiety disorders, and trauma-related disorders are now categorized as separate psychiatric conditions. However, they share common clinical features for which similar treatment strategies are applied. Due to a high prevalence of these disorders and their high rate of treatment resistance, the investigation of new interventions to include in their treatment algorithms is paramount. In OCD, neuroimaging findings of cortical-striatal-thalamic-cortical circuit hyperactivity and the evidence of clinical effectiveness of low-frequency TMS suggest that the application of cathodal tDCS to the pre-supplementary motor area (pre-SMA) and the orbitofrontal cortex (OFC) could induce positive results, as pointed out by some preliminary results. In healthy subjects and in one patient with GAD, tDCS to the dorsolateral prefrontal cortex (DLPFC) has shown promising results in modulating attention to threat and symptoms of anxiety, respectively. In PTSD, the combination of a computerized working memory training with tDCS over DLPFC was reported to revert some cognitive,

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emotional and neurophysiological abnormalities; moreover, based upon fear extinction models, the combination of exposure therapy and tDCS might also be applied in this disorder. Ultimately, despite the intriguing rationale and some encouraging results, tDCS for OCD, GAD, and PTSD must be considered still in its infancy.

Keywords

Anxiety • Obsessive-compulsive disorder • OCD • General anxiety disorder • GAD • Post-traumatic stress disorder • PTSD • Transcranial direct current stimulation • tDCS

Introduction

Obsessive-compulsive and related disorders, anxiety disorders and trauma-related disorders are considered three different groups of psychiatric conditions, and are described in three different chapters of the last edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1]. However, these disorders share some important clinical features, including increased perception of thread, worry, harm avoidance, and neurovegetative hyperarousal. These similarities probably account for the shared response to treatments such as selective serotonin re-uptake inhibitors (SSRIs) and cognitive behavioral therapy (CBT). Taken together, they have a 12-month period prevalence of approximately 14 % and a lifetime prevalence of approximately 21 % in the general population, with very high costs for the community [2]. Moreover, these disorders can display high rates of partial or no response to first and second line treatments [3] and can lead to high levels of personal suffering, social dysfunction and family burden, which are comparable to those found in schizophrenia [4].

Therefore, the search for a better understanding of their etiology and for new treatment strategies is paramount. In this chapter we focus on the rationale of using tDCS for the treatment of obsessive-compulsive disorder (OCD), anxiety disorders, and post-traumatic stress disorder (PTSD), and we review the available clinical data and published scientific literature.

OCD

It has been proposed that OCD results from aberrant functioning of cortico-striato-thalamo-cortical circuitry including the medial prefrontal cortex (i.e., supplementary motor area-SMA and anterior cingulate cortex-ACC), the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), and basal ganglia [5, 6]. This model inspired the neurosurgical approaches to OCD, which turned out to be effective treatments, as evidenced by the FDA humanitarian use approval for high frequency deep brain stimulation (DBS) in treatment-resistant cases [7]. However, the need for noninvasive alternatives for patients who do not respond to standard treatments (e.g., serotonin reuptake inhibitors or CBT) remains.

While rTMS has shown promise when applied to the pre-SMA and to the OFC [8], tDCS has been less investigated for the treatment of OCD. Therefore, questions about which area(s) should be targeted by tDCS and which parameters should be used still need to be addressed.

DLPFC is a crucial area for the cognitive and emotional control as well as the most frequently targeted region in psychiatric applications of noninvasive brain stimulation (NIBS) techniques. However, in the very first clinical application of tDCS in OCD, cathodal tDCS resulted ineffective when applied to this cortical area [9].

Based upon the neuroimaging evidence of hyperactivity in the orbitofrontal cortex (OFC) of OCD patients, other studies targeted this region using cathodal inhibitory tDCS. In a case report, ten tDCS sessions (2 mA, 20 min) were delivered

twice a day with a 2-h interval, with the cathode (35 cm^2) placed over the left OFC and the anode (100 cm^2) placed over the contralateral occipital region. No adverse event was reported. At the end of the tDCS treatment no variation of symptoms severity was observed. One month after the completion of tDCS sessions, it was observed a 26 % reduction in severity of obsessive and compulsive symptoms measured using the Yale-Brown Obsessive Compulsive Scale scores [10]. These findings are consistent with a previous study reporting a similar reduction in obsessive and compulsive symptoms after low-frequency rTMS was applied to the left OFC [11].

Subsequently, the same group of researchers combined cathodal stimulation of the left OFC with anodal stimulation of the right cerebellum, using two active electrodes of 35 cm^2, to decrease OCD symptoms in patients with treatment-resistant OCD. In an open-label pilot study, eight patients with treatment-resistant OCD received ten sessions (twice a day) of 2 mA tDCS applied with this new montage. OCD (Y-BOCS and OCD-VAS) as well as depressive (MADRS) symptoms were measured before tDCS, immediately after the end of treatment, 1 and 3 months after the tenth tDCS session. The study reported a significant 26.4 % (±15.8) decrease of Y-BOCS score ($p = 0.002$). The beneficial effect lasted during the 3 month follow-up. No effect of tDCS was observed on depressive symptoms. At end point, five out of eight patients had a decrease of ≥25 %; and three out of eight patients had a decrease of ≥35 % in Y-BOCS score. The treatment was well tolerated [12].

Another suitable area of tDCS application in OCD is the pre-SMA, which has been found to be hyperactive in OCD patients during performance of cognitive tasks related to attentional aspects of action control [13, 14]. In fact, the evidence deriving from the clinical efficacy of inhibitory rTMS on this area [15] and from neurophysiological measures of altered motor cortex excitability in OCD [16], that normalized after 1-Hz rTMS to the pre-SMA [17], suggest that the premotor/motor system is abnormally hyperactive in OCD, and that there is a pathophysiological link between such hyperexcitability and OCD symptoms.

However, there is conflicting evidence about whether cathodal or anodal tDCS should be applied on pre-SMA to relieve OCD symptoms. While one study reported the successful treatment of two OCD patients using anodal tDCS over the left pre-SMA with the reference electrode placed on the contralateral SO region [18], another case study reported OCD symptoms worsening using anodal tDCS and improvement using cathodal tDCS over the bilateral pre-SMA with extracephalic reference electrode [19]. This last montage resulted effective also in a double blind, randomized, controlled, partial crossover trial, which showed anti-obsessional effects of cathodal and not anodal monocephalic tDCS over bilateral pre-SMA [D'Urso, under review in Depression and Anxiety]

A computational study has been conducted to simulate the path of the electric current through the brain during cathodal tDCS, aiming to optimize the use of tDCS in OCD and to help designing future trials [20]. This study found that the application of the active electrode (cathode) over the pre-SMA, with the reference electrode (anode) positioned in an extracephalic location (i.e., the subject's right deltoid), resulted in a distribution of the electrical field from the medial prefrontal cortex to the striatum, therefore reaching the cortical and subcortical brain areas which are crucially involved in the pathophysiology of OCD. Based on this model and on the promising results about the efficacy of cathodal tDCS to pre-SMA in treatment-resistant OCD, a large randomized controlled trial testing the clinical and neurobiological effects of tDCS in OCD is underway.

Therefore, as with rTMS, the most promising brain areas for tDCS application in OCD seem to be pre-SMA and OFC.

tDCS in Anxiety Disorders

Anxious patients typically show negative biases in perception and memory, and such biases in emotional processing are believed to play a fundamental role in the maintenance of anxiety disorders. Coherently, the cognitive neuropsychological model of antidepressants action assumes

that in anxiety disorders such treatments work by reversing negative cognitive biases [21]. Following the administration of anxiolytic and antidepressant treatment, early changes in emotional processing have been observed in healthy subjects and clinical groups; specifically, the cognitive changes might be predictive of later therapeutic response in patients [22].

In addition, attentional control is highlighted in models of trait anxiety [23] and DLPFC activity has been negatively correlated with trait anxiety in neuroimaging studies examining attentional control over emotional and nonemotional stimuli [24]. This suggests that modulating DLPFC activity has the potential to causally modify attentional control, which has particular relevance to trait anxiety. In fact, in a study by Heeren et al., tDCS to the DLPFC led to reduced vigilance to threatening stimuli in healthy subjects [25]. In this study the attentional bias (faster reaction times) to fearful faces was present in the sham tDCS group, whereas in the active tDCS group it was reversed, likewise with antidepressant and anxiolytic treatment [26]. Specifically, the bipolar-balanced montage (anode on the left DLPFC and cathode on the right DLPFC) significantly abolished the normal pattern of fear vigilance observed in the sham condition and suggests that intervening bilaterally, to change activity in both left and right DLPFC, may be critical for the observed anxiolytic-like effects.

The above results in healthy volunteers reveal an anxiolytic-like effect of DLPFC tDCS on a cognitive biomarker relevant to clinical anxiety and indicate a potential neurocognitive mechanism (reduced fear vigilance) that may partially mediate the clinical efficacy of prefrontal tDCS in anxiety disorders [27].

One more evidence that subjects with anxiety disorders show an attentional bias for threat is that Attention Bias Modification (ABM) procedures have been found to reduce this bias; results indicate that combining ABM and anodal tDCS over the left DLPFC reduces the total duration that participants' gaze remains fixated on threat, as assessed using eye-tracking measurement. As the tendency to maintain attention to threat is known to play an important role in the maintenance of anxiety, these findings suggest that anodal tDCS over the left DLPFC may be considered as a promising tool to reduce the maintenance of gaze to threat [25].

The next logical step is to assess whether an enduring therapeutic effect can be found and if early neurocognitive changes in patients can predict response to treatment of anxiety.

In a case report on the effect of tDCS in GAD Shiozawa et al. [28] performed 15 consecutive daily tDCS sessions in 3 weeks (except for weekends). The cathode was positioned over the right dorsolateral prefrontal cortex (DLPFC), and the anode was placed extracephalically over the contralateral deltoid. In each daily session a direct current of 2.0 mA for 30 min was administered. Anxiety symptoms substantially improved during the 15-day treatment course. After 1 month of treatment, the patient was asymptomatic and reported significant clinical improvement. The use of cathodal stimulation over the right DLPFC was chosen based on recent neuroimaging and brain stimulation studies. In an open-label trial with ten patients, Bystritsky et al. [29] used an anxiety task during functional neuroimaging to identify the cortical brain area to be stimulated with low-frequency rTMS. In all patients, the right prefrontal cortex was consistently activated and, after low-frequency rTMS over the right DLPFC over 6 weeks, all participants improved. Interestingly, low-frequency rTMS over the right DLPFC was also associated with improvement in anxiety symptoms in treatment-resistant depression [30] and in panic disorder with depression [31, 32]. In the tDCS case study, cathodal stimulation over the right DLPFC might have diminished neuronal activity in this area, secondarily modulating other cortical and subcortical structures involved in GAD pathophysiology such as the medial prefrontal cortex, the amygdala, and the insula [33]. It is also possible that the left DLPFC was secondarily modulated by the decrease in activity of the right DLPFC.

tDCS in PTSD

Brain regions involved in the anxiety network including the amygdala, hippocampus, ventromedial prefrontal cortex (vmPFC), dorsal anterior cingulate cortex (dACC), and the insular cortex somewhat overlap with the network involved in the acquisition of fear and its extinction, particularly relevant to PTSD [34]. PTSD patients seem to have deficits in extinction learning and/or recall [35], impairments that seem to be acquired after having developed PTSD [36]. It has been suggested that the deficit in recall extinction could explain the maintenance of PTSD symptoms and/or relapse following treatment [37]. In terms of neural correlates, this impaired ability for extinction memory has been linked with less activation in the vmPFC and the hippocampus and higher activation in the amygdala and the dACC [35].

If we understand the circuit and its maladaptive plastic changes, we can formulate and test hypotheses about the therapeutic efficacy of selective manipulation of these brain regions and networks. This can be achieved by using neuromodulation techniques in an attempt to reestablish homeostatic balance and healthy patterns of information processing.

More specifically, if we can find ways of enhancing fear extinction memory in the laboratory within samples of healthy participants and replicate them in clinical population, we could consider these tools as potential adjuncts to augment the memory trace formed during exposure therapy, which could ultimately lead to a decrease in symptoms severity and a lesser likelihood of relapse. The combination of tDCS and exposure therapy, as already shown for the combination of tDCS and CBT in depression [38], might have a synergistic effect in producing a clinical result in PTSD. The principle of the two interventions is the same: promoting the memory trace being formed during exposure therapy so that it becomes stronger. Because PTSD is well known for the deficit in recall extinction, enhancing extinction could benefit patients suffering from this disorder as well as from those anxiety disorders which share this cognitive feature. Clearly, this idea taps into the neural mechanisms of fear extinction that are relevant to some but certainly not all features and symptoms of PTSD.

Evidence for modulation of fear learning and extinction using tDCS remains scarce. In one study cathodal stimulation of the left DLPFC led to an inhibitory effect on fear memory consolidation compared to anodal and sham stimulations, as indicated by decreased skin conductance response to the conditioning stimulus presentation during extinction training at day 2. Thence this study suggests that left DLPFC cathodal stimulation interferes with processes of fear memory consolidation [39]. Furthermore, tDCS has been used in combination with a computerized working memory training in four patients suffering from both PTSD and poor working memory. This combined treatment led to the improvement of the cognitive and emotional disturbances as well as to the change of the neurophysiological measures which are usually found altered in PTSD, such as the P3a component of event related potentials (ERP) in response to novelty stimuli and the alpha peak frequency [40].

Nonetheless, we need a better understanding of how different tDCS parameters impact the PTSD circuitry to be able to design hypothesis-driven trials and confirm both safety and clinical efficacy.

Conclusion

Despite an intriguing rationale and some encouraging preliminary results, the application of tDCS in OCD, anxiety disorders, and PTSD is still in its infancy, and many mechanistic as well as clinical questions remain to be answered.

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Neurodegenerative Cognitive Disorders

16

Tarek K. Rajji

Abstract

Neurodegenerative cognitive disorders have a huge impact on our societies, especially as the general population continues to grow older. These disorders include various dementias including Alzheimer's dementia as the most common one. To date no effective treatments have been identified. Transcranial Direct Current Stimulation (tDCS) has been tested for its effects in patients with neurodegenerative disorders, especially patients with Alzheimer's dementia. In general, studies show a positive effect on cognition with good tolerability. However, studies to date are limited by small sample sizes, large variability in parameters of stimulation, and lack of long-term interventions and assessments. Future studies need to address these limitations. Further, future research could focus on combining tDCS with other cognitive enhancing interventions, more personalization of stimulation using modeling approaches, and aiming at preventing cognitive decline and cognitive manifestation of neurodegenerative disorders.

Keywords

Alzheimer's dementia • Cognition • Lewy body dementia • Neurodegeneration • Parkinson's disease • Prevention • tDCS

Neurodegenerative cognitive disorders, also referred to as dementias, affect more than 46 million people worldwide [1]. By 2050, this number is estimated to be more than 131 million. The current costs associated with dementia are estimated to be US $818 billion. To date, there are no interventions to prevent, cure, or even slow down these disorders. Alzheimer's dementia (AD) is the most common form of dementia. Other forms of dementia include vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease dementia, and others.

Transcranial Direct Current Stimulation (tDCS) is a noninvasive brain stimulation method

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that can be safely administered to conscious outpatients (i.e., it does not require general anesthesia or surgical implantation of a device). It utilizes low intensity electrical current either to increase cortical excitability with an anodal electrode or to suppress cortical excitability with a cathodal electrode [2]. Given its ease of use, portability, and high potential of scalability, several studies have tested the effect of tDCS in patients with dementia. Most studies have focused on patients with AD.

Alzheimer's Dementia

In Ferruci et al. [3], ten participants with AD (mean age: 75.2, SD: 7.3) received three 15-min tDCS sessions in a random order and 1 week apart: anodal tDCS, cathodal tDCS, and sham tDCS. Two stimulators were used. For each stimulator, one electrode was placed over the temporoparietal area (left or right) and the other over the right deltoid muscle. Current was 1.5 mA. Cognition was assessed before and 30 min after each session. Anodal tDCS improved word recognition and discrimination (by 17 %) while cathodal tDCS impaired both.

In Boggio et al. [4], ten participants with AD aged 70–92 years received two 30-min sessions of unilateral anodal tDCS—one session to the left DLPFC, another to the left temporal cortex—and a third session of sham tDCS. Reference electrode was placed over the right supraorbital area. Current was 2 mA. Cognition was assessed during stimulation. Anodal tDCS at both sites improved performance on a visual recognition memory task by 18 % for the DLPFC and 14 % for the temporal cortex [4].

The above two studies were followed by others that assessed the impact of a course of tDCS on cognition. In Boggio et al. [5], 15 participants with mild to moderate AD (mean age: 78.9, SD: 8.2) received daily for 5 consecutive days 30-min sessions of bilateral anodal or sham tDCS in a random order. Anodes were placed over the temporal lobes. Reference electrode was placed over the right deltoid muscle. Current was 2 mA. Cognition was assessed before the first tDCS session, at the end of treatment on day 5, 1 week later, and then 4 weeks later. Anodal tDCS not only resulted in improvements in visual recognition memory, but also these improvements persisted for 4 weeks following the course of tDCS. The percent change from baseline was about 11 %. tDCS was well tolerated by all participants.

In Khedr et al. [6], 34 participants with mild to moderate AD (mean age: 69.7, SD: 4.8) were randomized to receive anodal tDCS, cathodal tDCS, or sham tDCS. tDCS was applied to the left DLPFC for 25 min daily for 10 days. The reference electrode was placed over the contralateral supraorbital region. Current was 2 mA. Follow up assessments were conducted immediately, 1 and 2 months following tDCS course. Other than for a couple of participants experiencing transient itching, headache, and dizziness, tDCS was well tolerated. Both anodal and cathodal tDCS resulted in improvement on Mini-Mental State Examination (MMSE) [7] compared with sham tDCS. The two forms of active tDCS did not differ. Improvement on MMSE was by about four points with an initial improvement immediately following tDCS, an additional improvement 1 month later, and persistence of this improvement one additional month later.

Thus, studies that assessed the impact of a course of tDCS on cognition not only demonstrated a positive effect but also persistence of these effects several weeks following the end of the intervention. A parallel line of research is to investigate whether these pro-cognitive effects of tDCS can optimize performance in response to other cognitive enhancing interventions, or whether they can be augmented through these other interventions.

In Cotelli et al. [8], 36 participants with mild to moderate AD (mean age ~77) were randomized to receive anodal tDCS combined with memory training, sham tDCS combined with memory training, or anodal tDCS combined with motor training. tDCS was applied to left DLPFC for 25 min, 5 days a week for 2 weeks. The reference electrode was placed on the right deltoid muscle. Current was 2 mA. tDCS was initiated at

the beginning of each training session which also occurred 5 days a week for 2 weeks. Memory training consisted of training on face-name association task. Assessments were conducted at baseline, after the 2 weeks of tDCS course, and then 3 and 6 months from the start of the tDCS course. Both groups who received memory training experienced improvement in face-name association talk compared with the group who received motor training. The improvement persisted at 3 month follow-up. However, there was no significant generalization to other cognitive tasks beyond what the participants trained on. More importantly, groups who received anodal or sham tDCS, combined with memory training, did not differ in performance. These findings are in contrast with a single case report published on the combination of tDCS with cognitive training. In Penolazzi et al. [9], one patient with mild AD, age 60, received one course of anodal tDCS, daily for 20 min for 10 days, over the left DLPFC. Reference electrode was placed over the right supraorbital area. Current was 2 mA. Each tDCS was followed by 45 min of cognitive training. Two months later, the patient received the same course of cognitive training but with sham tDCS. Following the first course, the patient experienced improvement in global cognitive function and it persisted for 1 month. There was no such improvement following the second course.

Patients with AD not only experience cognitive dysfunction, but also significant behavioral and psychological symptoms. One study focused on the effects of tDCS on apathy. In Suemoto et al. [10], 40 participants with moderate with AD (mean age: 80.5, SD: 7.5) were randomized to receive anodal or sham tDCS delivered to the left DLPFC for 20 min, every other day for six sessions over 2 weeks. Reference electrode was placed over the right orbit. Current was 2 mA. Assessments were conducted at baseline, 1 week into the tDCS course, at the end of the 2-week course, and then 1 week after completing the course. The primary outcome measure was the score on the Apathy Scale [11]. tDCS was well tolerated with minor side effects, mainly scalp burning sensation and tingling. The two groups did not differ on Apathy Scale at any of the time points of assessments, nor did they differ on other secondary measure, including cognitive, mood, and caregiver burden measures.

Given the preliminary yet positive evidence supporting a pro-cognitive effect of tDCS in patients with AD, it is logical to assess its effects in pre-AD stages of the illness for potentially more impact on the course of illness. In Meinzer et al. [12], 18 participants with mild cognitive impairment (MCI) due to AD (11 amnestic MCI and seven multiple domain MCI) (mean age: 67.4, SD: 7.3) received, in a cross-over design, one session of anodal or sham tDCS to the left inferior frontal gyrus for 20 min. The sessions were separated by 1 week. The reference electrode was placed over the right supraorbital region. Current was 1 mA. Participants received tDCS while performing a semantic word-retrieval task and undergoing fMRI. tDCS was well tolerated. During sham tDCS, participants performed worse than healthy control participants. In contrast, during anodal tDCS, their performance normalized to become comparable to that of the healthy control participants. This normalization was accompanied by normalization of task-related and resting-state brain activity as measured with fMRI.

Notwithstanding that those studies to date need to be replicated in larger samples, the mechanism underlying any pro-cognitive effect of tDCS in patients with AD is largely unknown. In one study, repetitive tDCS with ten 20-min sessions delivered daily over 2 weeks to the frontal cortices of rats models of AD has been shown to reduce spatial learning and memory deficits that these rats experience. It also resulted in histological changes suggestive a protective effect of tDCS against Aβ induced neurotoxicity [13].

Lewy Bodies Dementia and Parkinson's Disease

Lewy body dementia accounts for 3–15 % of all dementias [14, 15]. It is typically characterized by fluctuating cognitive impairments, visual hallucinations, and Parkinsonian motor symptoms. It is also considered an umbrella that includes

dementia of Lewy bodies and Parkinson's disease dementia. The diagnosis of dementia with Lewy bodies is made when the motor symptoms develop within 1 year of the onset of cognitive deficits. In contrast, a Parkinson's disease dementia diagnosis is made when the motor symptoms had been present for more than 1 year prior to the cognitive deficits [16]. Cholinesterase inhibitors are recommended for the treatment of Lewy body dementia, though their clinical impact is modest [17, 18].

In contrast to patients with AD, patients with Lewy body disease experience significant impairments in attention, executive function, and visuospatial abilities early on during the illness. These impairments may even precede deficits in learning and memory [19–21].

tDCS has been tested for its effects on Lewy body dementia associated cognitive deficits. It has also been tested for its effects on cognitive impairment associated with Parkinson's disease per se, i.e., without a full manifestation of dementia.

In Boggio et al. [22], 18 participants with Parkinson's disease (mean age: 61.1) received one session of anodal tDCS delivered to the left DLPFC for 20 min. Reference electrode was placed over the right orbit. They also underwent a session of M1 stimulation and sham tDCS to the left DLPFC. Current was 1 mA in one set of experiments and 2 mA in another set. Before and during the last 5 min of each tDCS session, participants were administered a working memory task. All experiments were well tolerated. tDCS at 1 mA did result in any working memory change, In contrast, at 2 mA, left DLPFC stimulation resulted in more correct responses than M1 or sham tDCS. No change in speed of response was found.

In Pereira et al. [23], 16 participants with Parkinson's disease (mean age: 61.5, SD: 9.9) were randomized to receive one session of anodal tDCS to the left DLPFC or left temporoparietal cortex in a counterbalanced order, for 20 min. Reference electrode was placed over the right supraorbital area. Current was 2 mA. Anodal tDCS to the DLPFC resulted in improved phonemic but not semantic fluency. It also resulted in enhanced functional connectivity and task-related deactivation as measured with fMRI.

In Doruk et al. [24], 18 participants with Parkinson's disease (mean age: 61, SD: 8) were randomized to receive anodal tDCS delivered to the left or right DLPFC, or sham tDCS for 20 min, daily, 5 days a week, for 2 weeks. Reference electrode was placed over the contralateral supraorbital region. Current was 2 mA. Assessments were conducted at baseline, at the end of tDCS course, and 1 month following baseline. Overall, tDCS was well tolerated with reports of tingling, sleepiness, mild headache, neck pain, skin redness, and trouble concentrating. Anodal tDCS, irrespective of laterality, resulted in improved performance on Trail Making Test B, an executive function test, at the end of the tDCS course and that persisted at 1 month of follow-up. Sham tDCS resulted in improvement at the end of tDCS course, but the improvement did not persist. No significant effects were observed on other cognitive functions.

In Elder et al. [25], 13 participants with Lewy body dementia (mean age: 64.8, SD: 7.7), including eight with Parkinson's disease dementia and five with dementia with Lewy bodies, received a single session of anodal tDCS delivered to the left DLPFC for 20 min. Reference electrode was placed over the right deltoid muscle. Current was 2.8 mA. Before and 10 min after the stimulation, attentional and visuospatial cognitive tasks that have been shown to detect Lewy body dementia specific deficits were administered. Participants experienced improvements on some of the attentional but on none of the visuospatial tasks following tDCS. tDCS was well tolerated (Table 16.1).

Conclusions and Future Directions

Overall the current literature suggests that tDCS is potentially a useful nonsurgical neurostimulation modality to improve cognition in patients with neurodegenerative disorders. The literature is limited by the generally small samples studies.

Table 16.1 Publication on tDCS and cognition in neurodegenerative disorders

Authors (year)	Disease	*N*	Age (SD)	tDCS current (mA)	tDCS number of sessions	Electrode placement	Results
Ferruci et al. (2008) [3]	Alzheimer's dementia	10	75.2 (7.3)	1.5	1	Anodal, cathodal, or sham over left or right temporoparietal Reference over right deltoid	Anodal stimulation at both sites improved word recognition and discrimination. Cathodal stimulation impaired both
Boggio et al. (2009) [4]	Alzheimer's dementia	10	70–92	2	1	Anodal or sham over left dorsolateral prefrontal cortex or left temporal cortex Reference over right deltoid	Anodal stimulation at both sites improved visual recognition memory
Boggio et al. (2012) [5]	Alzheimer's dementia	15	78.9 (8.2)	2	5 consecutive	Anodal over bilateral temporal cortices Reference over right deltoid	Compared to sham stimulation, active stimulation improved visual recognition memory and these improvements persisted for 4 weeks
Khedr et al. (2014) [6]	Alzheimer's dementia	34	69.7 (4.8)	2	10 consecutive	Anodal, cathodal, or sham over left dorsolateral prefrontal cortex Reference over supraorbital region	Anodal and cathodal stimulation improved performance on Mini-Mental State Examination immediately and the improvement persisted at 1 and 2 months
Cotelli et al. (2014) [8]	Alzheimer's dementia	36	~77	2	10 (5 days a week for 2 weeks)	Anodal, or sham over left dorsolateral prefrontal cortex Both combined with memory or motor training Reference over right deltoid	Memory training improved face-name association and the improvement persisted at 3 months. Anodal tDCS did not affect performance
Penolazzi et al. (2015) [9]	Alzheimer's dementia	1	60	2	10 consecutive	Anodal over left dorsolateral prefrontal cortex Each tDCS session was followed by cognitive training Two months later, cognitive training without tDCS Reference over right supraorbital region	tDCS combined with cognitive training improved global cognitive function that it persisted for one month. No improvement without tDCS

(continued)

Table 16.1 (continued)

Authors (year)	Disease	*N*	Age (SD)	tDCS current (mA)	tDCS number of sessions	Electrode placement	Results
Suemoto et al. (2014) [10]	Alzheimer's dementia—focus on apathy	40	80.5 (7.5)	2	6 every other day	Anodal over left dorsolateral prefrontal cortex Reference over right supraorbital region	tDCS had no impact on apathy
Meinzer et al. (2015) [12]	Mild cognitive impairment	18	67.4 (7.3)	1	1 during a semantic word-retrieval task and functional MRI	Anodal or sham over left inferior frontal gyrus Reference over right supraorbital region	Anodal stimulation normalized performance, and task-related and resting-state brain activity compared to healthy participants
Boggio et al. (2006) [22]	Parkinson's disease	18	61.1	2	1 or 2	Anodal over left dorsolateral prefrontal cortex or left motor cortex Reference over right orbital region	2 mA anodal stimulation improved working memory
Pereira et al. (2013) [23]	Parkinson's disease	16	61.5 (9.9)	2	1	Anodal over left dorsolateral prefrontal cortex or left temporoparietal cortex. Reference over right orbital region	Stimulation improved phonemic but not semantic fluency
Doruk et al. (2014) [24]	Parkinson's disease	18	61 (8)	2	10 (5 days a week for 2 weeks)	Anodal or sham over left or right dorsolateral prefrontal cortex or left motor cortex Reference over contralateral supraorbital region	Both anodal stimulation improved executive function and it persisted for 1 month
Elder et al. (2015) [25]	Lew body dementia	13 (including eight with Parkinson's disease dementia)	64.8 (7.7)	2.8	1	Anodal over left dorsolateral prefrontal cortex Reference over right deltoid	Stimulation improved attention

Hence, confirmatory and adequately powered studies are urgently needed.

The literature suggests that if tDCS is to be effective with a persistent impact, it needs to be delivered repetitively, similar to most other interventions for brain disorders. Studies assessing different durations of courses of tDCS along with different frequencies per week will help characterize the dosing of tDCS. This is especially critical for patients with neurodegenerative disorders who may either need to commute to a center where tDCS is to be delivered or may depend on caregivers and their availabilities to administer it.

Electrodes placement and current intensity are two other variables that need further studying in various disorders. The current literature supports the use of anodal tDCS in general and 2 mA currents. Further personalization could be supported by modeling studies. Modeling studies predict the flow of current during tDCS [26] and help minimize the impact of morphological variation on tDCS effects. Again, this is highly salient to patients with neurodegenerative disorders who are likely to have experienced cortical shrinkage and tissue loss and using individualized tDCS dosing based on patient's specific morphological characteristics may be necessary in future trials [27].

Combining tDCS with other interventions will add also another level of complexity to be systematically investigated. tDCS interferes with neuroplasticity mechanisms [28, 29] as do other interventions such as cognitive training [30]. Timing of tDCS in relationship with another intervention will need to consider the potential interference of one intervention with another at the level of neuroplasticity mechanisms.

Finally, there are other neurodegenerative disorders that tDCS would still need to be tested for, e.g., frontotemporal dementia. It also needs to be further tested in pre-dementia stages such as mild cognitive impairment as well as in populations that are at high risk of developing dementia to assess whether it will have any cognitive preventative impact, e.g., patients with depression [31], schizophrenia [32], or others.

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Impulsivity and Substance-Use Disorders

17

Sara Labbe and Shirley Fecteau

Abstract

Substance-use disorders (SUD) have devastating consequences since the relapses are recurrent even after years of abstinence. The compulsive and repetitive drug intake is associated with neurobiological adaptations in the dopaminergic reward pathway and abnormality in the activity of frontal areas. In past years, there has been growing interest for applying transcranial direct current stimulation (tDCS) to the dorsolateral prefrontal cortex (DLPFC) as a tool for modulating safely and noninvasively the reward pathway in patients with SUD. Enthusiastic results have shown that a single tDCS session can reduce symptoms of SUD such as craving, a major factor contributing to relapse. The actual state of literature is encouraging since repeated tDCS sessions led to neuroplasticity and induce long-term effects such as reducing drug intake. Although several questions still remain to be addressed, there is growing evidence that tDCS has the potential to be used as a clinical tool in the treatment of substance and non-substance abuse. This chapter gives an overview of the recent use of tDCS in SUD studies. We also point out hypotheses that could explain the neural mechanisms underlying the beneficial effects of tDCS in these subjects. We suggest that tDCS applied to frontal areas modulates the reward pathway through direct top-down processes and indirectly by improving cognitive processes such as impulsivity.

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Introduction

Substance-use disorders (SUD) are defined as "a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems" (American Psychiatric Association, 2013). SUD is a major problem of public health, especially because of its recurrence. The current approaches to maintain abstinence, reduce withdrawal symptoms, and prevent relapses mainly consist of pharmacological treatments and psychotherapy. Despite these treatments, SUD remains one of the most important chronic disorders in our society. The development of new therapies to treat SUD is thus much needed. Application of noninvasive brain stimulation such as transcranial direct current stimulation (tDCS) in patients with SUD has brought encouraging results in reducing substance use and craving. In this chapter, we first review the neural substrates of substance use and craving; two important outcomes in studies on SUD. We then discuss the rationale for targeting the dorsolateral prefrontal cortex (DLPFC) with tDCS in patients with SUD. This is followed by a review of the effects of tDCS in tobacco, cannabis, alcohol, and stimulant-use disorders. We then conclude by discussing two hypotheses that may explain the effects of tDCS in patients with SUD. Indeed, the exact mechanisms underlying the beneficial effects of tDCS remain unclear and two neurocognitive hypotheses, which are not mutually exclusive, have been proposed. The ultimate aim of this chapter is to contribute to the discussion on the potential hypotheses that may underlie beneficial effects of tDCS in SUD in order to promote development of future tDCS protocols for these clinical populations.

Neural Substrates of Substance-Use Disorders

The use of substances as well as pleasant food or even some behaviors (e.g., gambling) can be perceived as rewards that increase dopamine secretion in subcortical structures. The increase of dopamine in the nucleus accumbens core (NAc) (ventral striatum) through the ventral tegmental area (VTA) is the starting point of the mesolimbic dopaminergic circuit, also called the reward pathway. These sublimbic structures have connections with limbic structures, among these, the hippocampus. The reward pathway also involves mesocortical connections with frontal areas, such as the medial prefrontal cortex, the orbitofrontal cortex (OFC), and the DLPFC. These cortical structures are associated with higher cognitive and motivational functions responsible for driving the actions through top-down processes [1, 2]. For example, the mesocortical pathway enables the organism to remember the pleasant aspects of stimuli and repeat complex behaviors that lead to these rewarding stimuli. The reward pathway had a role in the evolution to satisfy basic needs such as eating, drinking, and reproduction. However, when stimulated by chemical substances or by repeated reward-related behaviors (e.g., gambling), the reward pathway may become maladaptive and associated with substance and non-substance related disorders (e.g., pathological gambling) [3–5].

Neural Substrates of Craving

Craving is a DSM 5 criterion of SUD and is characterized as "an intense desire or urge for the drug that may occur at any time but is more likely

when in an environment where the drug previously was obtained or used" [62]. Craving contributes to relapse, which may occur even after several years of substance abstinence [6–8]. Thus, reducing and resisting craving seem to be a key goal to prevent relapse and maintain abstinence.

In SUD studies, craving can be measured by standardized questionnaires in which subjects are asked to rate their levels of craving on a visual-analog scale (VAS). Most of SUD studies used cue-reactivity paradigms in which craving level is assessed before and after presentation of stimuli depicting substance intake, manipulation of the substance itself, and/or by asking subjects to recall previous experiences of substance intake [9]. An interesting aspect of cue-reactivity paradigms is that resisting craving can also be assessed [10]. Neuroimaging studies have extensively used this paradigm to study the neural activation underlying craving and craving resistance. It has been reported that resisting craving elicits activity in the dorsal medial prefrontal cortex whereas craving itself has been extensively associated with activity in the DLPFC [11–14]. Further, positive correlation between the level of self-reported craving and activation in the DLPFC have been reported in Positron Emission Tomography (PET) [11–13] and functional Magnetic Resonance Imaging (fMRI) studies [14–16]. Moreover, the activation in the DLPFC is of similar extent in both patients with SUD and non-substance-use disorders (e.g., pathological gambling) as demonstrated by a recent fMRI study using a cue-reactivity paradigm inducing cocaine craving or gambling urge [17].

The Use of tDCS Applied to DLPFC in SUD

Most tDCS studies in patients with SUD applied the electrodes bilaterally (e.g., one electrode to each hemisphere) or unilaterally to the right or left DLPFC. In the latter case, one electrode is positioned to one hemisphere and the other one to the contralateral orbit. The DLPFC has been the region of interest to apply tDCS in SUD for three main reasons. First, the DLPFC can be noninvasively targeted with surface electrodes that tDCS devices use. Second, as mentioned previously, this region is involved in the reward pathway through the mesocortical tract and its activity has been associated with craving. Thus, the activity of prefrontal areas could affect the dopamine secretion in limbic structures through top-down processes [18]. Finally, the DLPFC is involved in cognitive functions that are known to be impaired in patients with SUD. As it will be discussed below, tDCS applied to the DLPFC might promote some cognitive processes such as cognitive impulsivity or decision making which in turn contribute to prevent relapse. This is further discussed in the conclusion of this chapter.

Tobacco-Use Disorder (TUD)

The *World Health Organization* estimates that tobacco use causes six millions of deaths per year, worldwide. Tobacco intake results in the binding of nicotine on nicotinic cholinergic receptors (nAChRs) which target dopamine secretion in the reward pathway. Neuroimaging studies demonstrated that the activity of prefrontal areas, including the DLPFC, increases following cue-reactivity paradigms [11, 14, 19–22].

A pioneering study in TUD [23] investigated the effects of tDCS using a sham-controlled, crossover design. The authors exposed patients who smoked an average of 18 cigarettes a day to a cue-reactivity paradigm involving smoking videos and cigarettes manipulation. Craving levels were measured using a 5-item VAS before and after 20 min of tDCS at 2 mA and sham. Subjects received three conditions in a random order: (1) anodal to the right DLPFC coupled with cathodal to the left DLPFC, (2) reverse electrode montage, and (3) sham tDCS. Interestingly, both active conditions similarly decreased craving (reduction of 20 %) when comparing levels between pre- and post-tDCS whereas there was no significant change for the sham condition. The same team then applied five daily repeated tDCS sessions in

patients with TUD using the same stimulation parameters (20-min sessions at 2 mA) in a two-arm, sham-controlled parallel design [24]. Patients received either (1) active stimulation with the anode and cathode to the left and right DLPFC, respectively or (2) sham tDCS. After each session, the active tDCS group reported reduced cue-induced craving levels as compared to the sham tDCS group. The decrease in craving was cumulative following each of the consecutive sessions (except the last, fifth session). Furthermore, most patients in the active group (11 out of 13) but not in the sham group showed a decrease of 30% of cigarette smoked. Later, Fecteau et al. [25] investigated the effects of repeated tDCS sessions in patients with TUD who wished to quit smoking. The authors applied 5-day tDCS regimen (30-min sessions at 2 mA) in a sham-controlled, crossover design targeting both DLPFC (right anodal/left cathodal). The number of cigarettes smoked, cue-induced craving, and decision-making process were measured with the Ultimatum Game and the Risk Task. When patients received active as compared to sham tDCS, they smoked a lesser number of cigarettes. This decrease was still significant 4 days following the end of the last (fifth) tDCS session. Also, when comparing craving scores on the subscale of *Desire to Smoke* (*Questionnaire of Smoking Urges*) before and after the end of the fifth session, craving was reduced when patients received active as compared to sham tDCS. There was however no significant changes on the other subscales (*Anticipation of Positive Outcome, Intention to Smoke and Relief from Negative Affect*). Also, when patients received active as compared to sham condition, they rejected more often offers of cigarettes but not offers of money at the *Ultimatum game*. Finally, there was no difference between active and sham conditions at the *Risk Task*. This indicates that active tDCS modulates the decision-making process related to cigarettes (e.g., *Ultimatum game*) but did not modulate the risk taking of the tobacco users.

The effects of tDCS applied to the frontal-parietal-temporal (FPT) association area (20 min at 1 mA) on cigarette consumption were also studied using a sham-controlled, parallel design [26]. Two electrodes montage were used: (1) two cathodes to the FPT of each hemisphere and two anodes over the occipital cortex of each hemisphere, and (2) the anode and the cathode to the left and right FPT, respectively. Subjects who received cathodal tDCS over both FPTs reduced their daily cigarette consumption, whereas those who received other tDCS conditions reported no change.

Finally, in a sham-controlled, parallel design, Xu et al. [27] investigated whether anodal tDCS (20 min at 2 mA) to the left DLPFC modulates craving, negative affect, and attentional processing in abstinent tobacco smokers. Subjects were asked to remain abstinent of cigarette consumption since overnight. They were exposed to a cue-reactivity paradigm including videotapes, images depicting cigarettes, and cigarette manipulation. There was a significant reduction in the *urge to smoke* score following active tDCS as compared to before tDCS. However, this was not significantly different from the sham session. However, the total score of the *Profile of Mood States* questionnaire were significantly different between active as compared to sham tDCS. This implies a decrease in the score of subscales of anxiety, depressive mood and confusion. Finally, there was no significant effect of active tDCS as compared to sham on a computerized attentional task. This task however involved digits instead of smoking-related stimuli.

Among the tDCS studies on SUD, the most investigated population remain subjects with TUD. These results provide insights that tDCS applied to the DLPFC can modulate tobacco craving and consumption. The next steps would be to include longer follow-up in order to target the optimal tDCS parameters (e.g., electrode montage, intensity, number of sessions) and to identify the most susceptible patients to respond to tDCS treatment (e.g., light as compared to heavy smokers).

Cannabis-Use Disorders

Cannabinoids is the most widely illicit drug used in the United States (American Psychiatric Association, 2013). The cannabinoid molecule

bind to the cannabinoid receptors CB1 and CB2 located in VTA and into the shell of the NA; both regions involved in the reward pathway. To date, there is only one study that investigated the effects of tDCS on cannabis use disorder [28]. Using a sham-controlled, parallel design, the authors studied the effects of tDCS (15 min at 2 mA) to the DLPFC on craving and risk taking in 25 chronic cannabis users. The subjects were however asked to remain sober for 24 h before the session. Subjects received either 1—left anodal/right cathodal, 2—left cathodal/right anodal or 3—sham tDCS session. The Risk task was assed following tDCS session. The right anodal/left cathodal tDCS montage decrease the self-reported craving. Further, on the *Risk Task*, subjects in both active tDCS groups showed an increase in risk taking as compared to the sham group.

Alcohol-Use Disorders (AUD)

AUD is a common disorder with a prevalence of 29 % in the USA and is widely associated with the presence of comorbidity. The active molecule of alcohol is ethanol which is a nonselective agent. One of the non-specific effects of ethanol is to increase the dopamine secretion in mesolimbic area, leading to the pleasurable effect. As with other SUD, activity in prefrontal cortex has been associated with presentation to cue-reactivity paradigm. Specifically, it has been reported that exposure to alcohol-related cues increases activity in the DLPFC in subjects with AUD but not in healthy subjects [29].

In a sham-controlled, crossover design, Boggio et al. [30] investigated the effects of tDCS (20 min at 2 mA) applied to DLPFC on alcohol craving in patients with AUD. The subjects were involved in a rehabilitation program and were abstinent for 41 days at the time of testing. The conditions consisted of one single tDCS session with (1) the anode to the right and cathode to the left DLPFC; (2) the opposite montage; and (3) sham tDCS. Craving was measured using a cue-reactivity paradigm with videos of alcoholic drinks before and after tDCS. Following both active tDCS conditions, the cue-reactivity paradigm failed to induce craving. There was no significant difference between the two active conditions. In contrast, there was an increase of craving following the paradigm for the sham tDCS condition.

In a larger phase II clinical trials study, Klauss et al. [31] investigated whether repeated tDCS sessions to the DLPFC could reduce alcohol consumption in patients with AUD. In a sham-controlled, parallel design, subjects received two daily sessions for 5 consecutive days with the anode and cathode applied to the right anodal and left DlPFC, respectively. Subjects received either active (2 mA) or sham tDCS. Each daily session lasted 13 min and was separated by 20 min. There was significantly more sober subjects 6 months after the end of active condition (8/16 subjects) as compared to sham condition (2/17). There was however no significant decrease in craving between group as measure by the *Obsessive Compulsive Drinking Scale* (OCDS).

In a recent study [32], the effect of tDCS on the negative perception of alcohol-related cues was investigated in patients with AUD. The authors proposed that tDCS modulates the negative affect associated with alcohol, which may, in turn, contributes to reduce alcohol craving. The authors conducted a sham-controlled, parallel study in which subjects received 10 min of tDCS (1 mA). The electrodes were positioned either (1) to the DLPFC or (2) to the right inferior frontal gyrus (IFG). To assess how alcohol is perceived (e.g., as positive or negative), subjects performed the *Implicit Association Task* (IAT) before and after tDCS sessions. The IAT consists of classifying alcohol-related words as positive or negative. Subjects who received the active tDCS condition reported a decrease in craving. However, their negative and positive perception of alcohol-related words was not modulated as compared to the sham group. Thus, the authors concluded that the reduction in craving induced by tDCS may not be explained by an increase of the negative perception for alcohol.

In summary, the study of Boggio et al. and den Uyl et al. [30, 32] showed that tDCS could decrease alcohol craving. Furthermore, in a study with a larger sample size, Klauss et al. [31] demonstrated

that repeated tDCS sessions led to higher rate of sobriety without decreasing the self-reported craving. These results raised the hypothesis that repeated sessions increased the craving resistance and reduce alcohol consumption. Futures studies should include large sample size and repeated sessions to investigate this hypothesis.

Stimulant-Use Disorders

Stimulants substance such as cocaine or methamphetamines are highly addictive and powerful drugs as they directly stimulate the mesocorticolimbic reward pathway. As others drugs, relapses are often preceded by exposure to drug-related cues leading to craving [33]. It has been reported that subjects with stimulant use disorders as compared to healthy subjects do not show the same frontal brain activation when watching videotapes of cocaine use. According to fMRI and PET studies, an increased activity in the frontal areas such as the DLPFC, orbitofrontal and the anterior cortex cingulate (ACC) has been reported during a cue-reactivity paradigm in these subjects [13, 15, 34–39]. This activity is also related to the intensity of the self-reported craving [37].

In a sham-controlled, parallel design, Conti et al. [40] studied the effect of bilateral tDCS for 20 min at 2 mA on the activity of the ACC during exposure to crack-related images. Recent crack-cocaine abstinent (≤31 days) subjects received either (1) tDCS applied to the DLPFC (right anodal/left cathodal) or (2) sham tDCS. Using the low-resolution brain electromagnetic tomography (LORETA), they found that the sham tDCS group showed the predicted increase of activity during the cue-reactivity paradigm whereas the active group showed a decrease in activity of this region. This indicates that tDCS could decrease the activity related to exposure to cue-reactivity paradigm. The same team then applied repeated sessions of tDCS to the DLPFC [41]. They studied the effect on the event-related potentials in the ACC following cue-reactivity paradigm. In this study, recent abstinent crack-cocaine users were randomly assigned to receive five daily consecutive sessions of active (right anodal/left cathodal, for 20 min at 2 mA) or sham tDCS. There was however a high dropout rate: only nine subjects completed the entire protocol (three in sham group and six in active group). That could explain the non-significant effect between the active and the sham group on the event-related potentials in ACC. They however reported that five out of six subjects in the active group were sober until the 3-month follow-up whereas only one subject remained abstinent in the sham group.

On a larger clinical trial including 36 recent abstinent crack-cocaine users, Batista et al. [42] administrated five daily anodal tDCS sessions to the right DLPFC (cathodal to the left DLPFC). The subjects were separated in two groups: (1) active (20 min at 2 mA) and (2) sham tDCS. The active tDCS group led to significant decrease in the self-reported craving. This study did not include a cue-reactivity paradigm. The authors also reported an increase in the overall perception of quality of life in the active group, as measured by the World Health Organization questionnaire. In contrast, the score for perception of quality of life decrease in the sham group.

Another team investigated the effects of tDCS on risky behavior on recent abstinent cocaine users and healthy subjects using the *Balloon Analog Risk Task* (BART) [43]. This computerized task consists to pump virtual balloon where each pump give an amount of money. However, if the balloon reaches his individual explosion point, the subject loses all the accumulated money. In a sham-controlled, crossover design, the subjects received three tDCS sessions to the DLPFC: (1) left cathodal/ right anodal, (2) left anodal/right cathodal, and (3) sham tDCS. Before applying tDCS, Gorini et al. [43] measured the impulsivity in cocaine and healthy users using an impulsivity scale (BISS-11). As expected, the cocaine users presented higher impulsivity score as compared to healthy subjects. The right anodal tDCS condition decreased the risk taking in the BART for the cocaine users and the healthy subjects. Conversely, the left anodal condition led to an increase in risk-taking but only for the cocaine user group.

In a sham-control crossover study, Shahbabaie et al. [44] investigated the effect of a single tDCS

session on methamphetamine craving in meth-abstinent patients. This team administrated a cue-reactivity paradigm before, during, and after 20 min of tDCS at 2 mA. The montage consists to uni-hemispheric stimulation with the anode placed to the right DLPFC and the cathode to the contralateral supraorbital area. The authors administrated a computerized cue-induced craving assessment task in which subjects were ask to rate their level of craving in a VAS scale following each drug-related or neutral images. There was a significant decrease in craving during active tDCS as compared to sham tDCS but this effect was no longer significant for the measure following the tDCS session.

The results of tDCS studies applied on subjects with stimulant-use disorders provide promising preliminary results on craving. However, dropout is a major problem in this population, especially when the protocols involved repeated tDCS sessions. All of the studies discussed above recruited abstinent patients involved in rehabilitation programs instead of current stimulant users. For these reasons, the effects of repeated tDCS sessions on cocaine consumption have been little studied.

Discussion and Conclusion

In this review, we reported that the current state of knowledge pointed toward beneficial effects of the application of tDCS to the DLPFC in patients with SUD. In most of these studies, the main outcome was the self-reported craving following a cue-reactivity paradigm. Promising results showed that craving is reduced following a single tDCS session. A summary of the effects of tDCS on craving in patients with SUD is presented at Table 17.1.

Several studies revealed encouraging results following daily repeated sessions which could in return reduce substance intake. However, it remains unknown how tDCS modulates neuronal functionality considering SUD symptoms are reduced. Two hypotheses, not mutually exclusive, could explain the underlying mechanisms of tDCS in SUD.

The first one postulates that tDCS applied to DLPFC directly affects the neural substrates associated with craving. Indeed, a change in the activity of the DLPFC may in turn modify the dopamine secretion in the sub-limbic structures through mesocortical connections. Thus, the reduction in craving frequently reported in the studies discussed above could be explained by a direct effect of tDCS on the dopaminergic pathway.

A second hypothesis suggests an indirect effect of tDCS on craving by improving cognitive functions. Studies have extensively shown that patients with SUD as compared to healthy subjects differ in their decision-making process and impulsivity [35, 45–49]. Indeed, subjects with SUD exhibited more risk taking decisions than healthy subjects. The implication of the frontal cortex in these functions is now well established. For instance, it has been reported that activity of the DLPFC decreases in patients with SUD performing decision-making and impulsivity tasks [50, 51]. High level of impulsivity also contributes to not resisting craving, to relapse and is a predictor of developing SUD [49, 52]. It has also been reported that patients with SUD showed abnormalities in their frontal cortical activity which could explain a lack of self-control and an increase in the salience of the substance [1]. The combination of impulsivity with a reinforcing reward pathway could thus guide patients with SUD toward maladaptive behaviors in presence of the substance, despite their wish to quit using it.

Moreover, it has been demonstrated that tDCS applied to the DLPFC modulates cognitive functions in healthy subjects. Specifically, tDCS applied to prefrontal areas increases the response inhibition in healthy subjects [53–55] and decreases risk-taking [56, 57]. Thus, tDCS applied to the DLPFC in patients with SUD could improve their cognitive functions by decreasing risk taking behavior and impulsivity (e.g., increases response inhibition) and contribute to resist craving and maintain abstinence. Indeed, neuropsychological studies showed that a recovery of these cognitive functions is associated with abstinence [58, 59]. These cognitive improvements are also associated with neural recovery such as increase in thalamic metabolism [60].

Table 17.1 Description of transcranial direct current stimulation studies on craving in substance-use disorders

Author, year	Design (*n*)	tDCS parameters	Targeted regions (anode position)	Methods to evaluate craving	Main results
Tobacco-use disorder					
Fregni et al. 2008, [23]	Sham-controlled crossover (24)	1 session/condition, 2 mA, 20 min	L DLPFC (bilateral) R DLPFC (bilateral).	Cue-provoked craving, VAS	Decreased cigarette craving in both active tDCS conditions and sham
Boggio et al. 2009 [24]	Sham-controlled parallel (27)	5 daily consecutive sessions, 2 mA, 10 min	L DLPFC (bilateral)	Cue-provoked craving, VAS	Decreased cigarette craving in active group
Xu et al. 2013 [27]	Sham-controlled crossover (24)	1 session/condition, 2 mA, 20 min	L DLPFC with cathode over right supraorbital	Urge to Smoke Scale (UTS)	No difference between active and sham sessions
Fecteau et al. 2014 [25]	Sham-controlled crossover (12)	5 daily consecutive sessions, 2 mA, 30 min	R DLPFC (bilateral)	Cue-provoked craving, Questionnaire of Smoking Urges	Decreased craving in the *desire to smoke* subscale following the last (fifth) active tDCS session. No effect on other subscales
Cannabis-use disorders					
Boggio et al. 2010 [28]	Sham-controlled parallel (25)	1 session, 2 mA, 10 min	L DLPFC (bilateral) R DLPFC (bilateral)	VAS	Decreased cannabis craving for the R DLPFC group only
Alcohol-use disorder					
Boggio et al. 2008 [30]	Sham-controlled crossover (13)	1 session, 2 mA, 20 min	L DLPFC (bilateral) R DLPFC (bilateral)	Cue-provoked craving, Alcohol Urge Questionnaire (AUQ)	Decreased alcohol craving on both active tDCS condition and sham session
Klauss et al. 2014 [31]	Sham-controlled parallel (35)	2 daily sessions for 5 consecutive days, 2 mA, 13 min	R DLPFC (bilateral)	Obsessive Compulsive Drinking Scale (OCDS)	No difference between active and sham group on craving
Den Uyl et al. 2015 [32]	Sham-controlled parallel (48)	1 session, 1 mA, 10 min	R inferior frontal gyrus, cathode over left supraorbital L DLPFC, cathode over right supraorbital	Alcohol Approach and Avoidance Questionnaire (AAAQ)	Decreased alcohol craving after the DLPFC stimulation group only
Stimulant-use disorders					
Gorini et al. 2014 [43]	Craving not assessed				
Shahbabaie et al. 2014 [44]	Sham-controlled crossover (30)	1 session/condition, 2 mA, 20 min	R DLPFC and cathode over L supraorbital	Cue-induced craving task (CICT), VAS	Decreased stimulant craving in active as compared to sham session
Conti et al. 2014a [40]	Craving not assessed				
Conti et al. 2014b [41]	Sham-controlled parallel (9)	5 daily consecutive session, 2 mA, 20 min	R DLPFC (bilateral)	Crack-related cue, Brief Cocaine Craving questionnaire	No changes in craving for both groups
Batista et al. 2015 [42]	Sham-controlled parallel (36)	5 daily consecutive session, 2 mA, 20 min	R DLPFC (bilateral)	Items from the Obsessive Compulsive Drinking Scale	Decreased stimulant craving in active as compared to sham group

N sample size, *R* right, *L* left, *mA* milliampere, *min* minutes, *VAS* Visual Analog Scale, *DLPFC* dorsolateral prefrontal cortex

Several challenges still remain for future tDCS studies in patients with SUD. Among these, the optimal stimulation parameters still need to be established. Studies in SUD mostly deliver tDCS bilaterally (one electrode to each DLPFC) instead of unilaterally (e.g., cathode over contralateral supraorbital). However, both positive and negative results were obtained with either the anode or cathode applied to the right hemisphere. Future work is required to determine whether the effect of anodal is more effective in one hemisphere than the other. Also, future tDCS studies should screen participants according to their history of consumption. For example, older participants with SUD suggest a longer history of consumption as compared to younger participants. Indeed, the neurobiological adaptation of the dopaminergic pathway may not be the same for a participant with recent SUD as compared to years of substance abuse. In order to avoid confounding variables, the presence of comorbid disorders altering neuronal functioning (e.g., depression) should also be taken into consideration. Finally, although substance craving seems to share a common neurophysiological basis, this feeling is complex and can be expressed differently between subjects. Thus, futures studies should assess craving using different subscales. For example, the *Standardized Questionnaire of Smoking Urges* distinguishes between the *intention to smoke* and *the desire to smoke* which are two separate components of craving [61].

Finally, as described previously, the frontal areas such as the DLPFC and the OFC contribute to the maladaptive behaviors related to substance intake through the mesocortical pathway. Most studies on tDCS in SUD are presently focused on craving intensity assessed with VAS. However, since tDCS modulates the activity of these frontal and prefrontal regions, the resistance of craving including the patient self-control in the presence of the substance as compared to the craving itself should also be studied.

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Epilepsy

18

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Abstract

Treatment of drug-resistant epilepsy has seen major advancements in the recent years with the availability of several neurostimulation techniques, among which noninvasive tDCS has emerged as a viable option. Cathodal tDCS has the capacity to induce reductions in cortical excitability in humans resembling classical forms of long-term depression. The tDCS antiepileptic potential has been tested in three controlled clinical trials thus far, outcomes of which are mixed with respect to seizure suppression. In general, more profound suppression of epileptiform EEG activity, rather than suppression of clinical seizures has been observed after cathodal tDCS. As a result, preclinical in vivo and in vitro tDCS studies aimed at obtaining mechanic insights into tDCS effects are on the rise as means to improve clinical tDCS protocols for focal and patient-specific stimulation, and also as studies that will identify tDCS–pharmacotherapy combination therapies.

Keywords

Epilepsy • Seizures • Cortical excitability • NMDA receptor • GABA-A receptor • Long-term depression • In vivo • In vitro

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Introduction

Introduction: Neuromodulation in Epilepsy

The rise of interest in neuromodulation is particularly relevant in epilepsy, where seizures are resistant to pharmacotherapy in approximately 1/3 of all instances, a statistic that has not changed despite the introduction of >20 new antiepileptic drugs in the late twentieth and early twenty-first

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century [1, 2]. Accordingly, neurostimulation protocols are emerging as potentially valuable tools for seizure control.

Stimulating the nervous system with electricity to treat neuropsychiatric symptoms that include epilepsy is not new. In the first century AD, the Roman physician Scribonius Largus documented treating headaches by applying electric torpedo fish to the head, and another Roman physician, Pedanius Dioscorides, in 76 AD applied the torpedo fish to a patient with epilepsy [1]. As brain stimulation in general, neuromodulation for epilepsy has advanced considerably in recent years. Neurostimulation protocols can be coarsely divided into either invasive or noninvasive. Among the invasive options are vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS). Noninvasive protocols include trigeminal nerve stimulation (TNS), transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS).

tDCS in Epilepsy

Applied to the mammalian cerebral cortex, tDCS induces both acute and sustained change in cortical excitability. After a short exposure time to one session, typically 20–30 min, cathodal tDCS leads to a reduction in cortical excitability, while anodal tDCS predictably increases cortical excitability. Beyond the neocortex, experimental in vitro DC stimulation (DCS) indicates a potential for similar modulation of excitability in the hippocampus [3–5]. In epilepsy, the capacity of cathodal tDCS to reduce cortical excitability has prompted research into this technique's antiepileptic potential [6, 7].

The relatively low intracranial currents associated with tDCS likely account for its favorable safety profile. In contrast to other noninvasive neurostimulation techniques like TMS, seizures have not been associated with tDCS in humans, even in the vulnerable population with epilepsy. The remaining side-effects are largely limited to skin irritation at the electrode sites [8, 9].

Clinical Studies

In humans with epilepsy, clinical tDCS data are limited. In a review of published clinical data in epilepsy through 2015, San Juan and colleagues [7] identified data from 65 individual patients where five were participants in a randomized sham-controlled double-blind crossover study, 55 were divided between two randomized sham-controlled studies (both double-blinded with respect to EEG interpretation), and the remaining five were described in case reports.

tDCS clinical trial results, while inconclusive, are overall encouraging. In a randomized sham controlled study of adults ($N = 19$; average age 24 years) with medically refractory epilepsy secondary to MRI-positive malformations of cortical development, 1mA cathodal tDCS was delivered in a single session for 20 min using surface sponge electrodes (35 cm^2) arranged with the cathode over the seizure focus and the anode over the region with either normal EEG, or the least frequent epileptiform abnormalities in case of multifocal epilepsy. In the sham control condition, the stimulator was turned off after 5 s to generate the similar initial itching sensation without any current for the remainder of the stimulation period. Clinical seizures were monitored by diary and electrographic abnormalities were measured by 20-min EEGs obtained at baseline, as well as immediately after, 15 days, and 30 days after stimulation. EEG readers were blinded to the treatment condition. The results indicate that cathodal tDCS was safe and well-tolerated in this population. The frequency of interictal epileptiform discharges was reduced by 64 % immediately after tDCS. A favorable trend towards seizure reduction (44 % in treatment group vs. 11 % in control group) was detected, but significant differences in clinical seizure frequency between treatment and control groups were not identified. Notably, the electrographic response and the trend toward seizure reduction lasted as long as one month in some patients [10].

In a study of pediatric patients with refractory focal epilepsy ($N = 36$), children (6–15 years old) received a single treatment session of sham tDCS

or verum cathodal 1 mA tDCS for 20 min. Cathodal tDCS in this study was also administered via a 35 cm^2 sponge electrode placed over the epileptogenic focus as cathode, centered on the electrode with the international 10–20 EEG electrode placement system location where interictal spikes of sharp waves were greatest in amplitude, and the reference anode was placed on the contralateral shoulder. While the treatment group received the current for 20 min, in sham stimulation, the current was discontinued just after 30 s in a blinded setting. Epileptiform discharges (spikes and sharp waves) per 30 min of EEG recording at baseline, over time after treatment: 15 min, 24 h, 48 h, and 4 weeks were compared. EEG readers in this study as well were blinded of the treatment condition. The results indicate that tDCS was well tolerated and corresponded to significant 50 % decrease in the EEG spike frequency at 24 h and 58 % at 48 h after active stimulation. Moreover, a statistically significant, but small decrease of 5 % in the clinical seizure frequency was observed in the verum tDCS group with no difference in sham treated group [8]. However, in another study on five pediatric patients with focal, refractory continuous spikes and waves during slow sleep, cathodal tDCS (1 mA, 20 min) applied over a seizure focus failed to suppress continuous focal spikes in sleep [11]. Here the active cathodal tDCS was administered via a 25 cm^2 sponge electrodes placed on the area of peak negativity, and the anode was placed on the opposite end of the spike dipole, corresponding to the area of peak positivity the discharge. Stimulation in this instance was during wakefulness, and spike-wave index measures were in sleep. There were no adverse events reported during the study or follow-up.

In addition to seizure suppression, tDCS may have a role in mitigating behavioral symptoms that are commonly comorbid with epilepsy. In a recent pilot study of 37 adults with temporal lobe epilepsy, Liu and colleagues explored the tDCS effects on depression and memory dysfunction in these patients [12]. Two milliamps, 20 min tDCS was delivered for 5 days with anode over the left dorsolateral prefrontal cortex and cathode over the right supraorbital area. While the active treatment group received current for 20 min, the current during sham control stimulation was ramped up only for 30 s and thereafter ramped down. The 5-day tDCS course corresponded to a modest improvement in depressive symptoms immediately after active treatment. Notably, investigators did not find an increase in interictal discharge frequency thus indicating tDCS safety for applications other than seizure suppression in patients with epilepsy.

Data from the three clinical studies that include cephalic placement of the anode electrode also support the relative safety of anodal tDCS in the population with epilepsy. A natural concern for anodal tDCS is the potential for seizure exacerbation by mechanisms that enhance cortical excitability in the healthy population. Such cortical activation may be even more relevant in the population that is defined by a vulnerability to seizure. Yet, neither seizure exacerbation nor increase in epileptiform EEG activity was found in conditions where the anode electrode was over quiescent cortex, or the positive side of the spike dipole, or the dorsolateral prefrontal cortex [10–12].

Preclinical Studies

The mixed outcomes of human tDCS trials in epilepsy underscore the need for preclinical studies that may inform future clinical tDCS study design. Notably, as the term “transcranial” is not relevant for in vitro brain stimulation, “DCS” rather than “tDCS” is often used to describe the stimulation condition in preclinical studies.

Preclinical DCS research can provide insight is the mechanism by which DCS may produce a sustained antiepileptic effect. This was recently addressed by Chang and colleagues who studied the cathodal DCS effect on acute chemoconvulsant in isolated mouse thalamocingulate brain slices, an in vitro model of frontal lobe epilepsy. In their experiment, brain slices were stimulated by two parallel Ag/Ag-Cl electrodes connected to an isolated stimulator were placed external to the slice in a recording chamber to generate a uniform electric field (4 mV/mm). Spontaneous

excitatory postsynaptic currents (EPSCs) were recorded, as were epileptic EPSCs induced by bath application of either the potassium channel blocker 4-aminopyridine or the $GABA_A$ receptor antagonist bicuculline. Consistent with past studies, cathodal DCS suppressed evoked synaptic transmission and spontaneous EPSCs, a finding that the authors attributed to real-time neuronal membrane hyperpolarization. However, the antiepileptic effect persisted in this model, and was shown to be dependent on activation of the n-methyl-D-aspartate (NMDA) type glutamate receptor, thus behaving in ways like the well-described phenomenon of NMDA-dependent long-term depression (LTD) of excitatory synaptic strength [13]. The value of such data is in identification of a molecular pathway by which DCS may suppress seizures. This not only satisfies a scientific curiosity, but offers an opportunity to test whether pharmacotherapy that facilitates a component of this pathway may also facilitate the antiepileptic efficacy of tDCS, which, as above, is incomplete in clinical practice. However, systematic in vitro studies that investigate the molecular substrate of the DCS antiepileptic effect are rare. More commonly, in vitro DCS data provide insight into the electrophysiologic basis of seizure suppression by tDCS. For instance, early in vitro studies in a low-calcium hippocampal slice model identified that epileptiform discharges may be suppressed by field strengths in the 1–5 mV/mm range and that such suppression is polarity dependent [14, 15].

Among the more specialized applications that can be tested in animal epilepsy models is the capacity for cathodal tDCS, applied as a pretreatment to prophylaxis against seizures. This was first tested by Liebetanz and colleagues in a modified cortical ramp-stimulation focal seizure model in rats. In these experiments, tDCS was delivered with unilateral epicranial conductive electrodes to rat sensorimotor cortex, and threshold for localized seizure activity was determined by trains of pulsatile stimulation (50 Hz; 2 ms; 2 mA) delivered through the same epicranial contact. One group of animals received cathodal tDCS (100 μA) for 30 and 60 min, or anodal tDCS for 60 min. In another group the current intensity was doubled (200 μA) and stimulation durations were halved in all three condition. The main finding of the work was that cathodal tDCS caused an elevation of localized seizure threshold lasting for ≥2 h. In contrast, anodal tDCS had no significant effect on seizure threshold, confirming in vivo a polarity-dependent anticonvulsant tDCS effect, and absence of seizure exacerbation by anodal stimulation, as suggested also by clinical tDCS trials [16].

In complement to the preclinical study of tDCS in focal seizures [16], the antiepileptic potential of cathodal tDCS was also demonstrated in a rat amygdala-kindling temporal lobe epilepsy model. Here, Kamida and colleagues demonstrated that cathodal tDCS reduced clinical seizure severity and EEG after discharge duration, while elevating the afterdischarge threshold in amygdala-kindled rats, and these effects lasted at least 1 day after the last tDCS session (30-min daily treatment at 200 μA for 1 week). This treatment regimen also corresponded to improved cognitive performance on the Morris water maze [17]. The same group also investigated the effects of cathodal tDCS on convulsions in a rat pup lithium-pilocarpine status epilepticus model. In this study, rats were treated for 2 weeks with 200 μA cathodal tDCS delivered for 30 min per session using epicranial electrodes. Monitored over 2 weeks post stimulation, the authors found a significant 21 % reduction in the frequency of convulsions between sham and cathodal tDCS treated rats suggesting an antiepileptic effect. Among other findings, long-term treatment with cathodal tDCS also had neuroprotective effects on the rat hippocampus and led to improvements in performance of the water maze spatial memory task [18].

The above data indicate an intriguing prospect for tDCS as a means to interfere with epileptogenesis, rather than just seizures. The search for an effective and safe antiepilepotgenic treatment is an active field in experimental epilepsy. The unmet need for such treatment is underscored by complete absence of clinical antiepileptogenic interventions: for instance, none of the approximately 40 drugs that are prescribed to treat seizures are antiepileptogenic. Thus further studies

of tDCS in its capacity to prevent the onset of epilepsy after an epileptogenic brain injury such as trauma, stroke or status epilepticus may yield valuable product.

In contrast to in vivo experiments that tested a delayed antiepileptic tDCS effect, in a recent study by Dhamne and colleagues, cathodal tDCS was tested in the acute seizure setting that approximates status epilepticus to assess an immediate anticonvulsant effect. In this experiment, investigators modeled the realistic scenario that seizures will have already started by the time tDCS is deployed in the clinical arena. Moreover, a patient with status epilepticus will be likely to have received an anticonvulsant before the start of tDCS. Cathodal tDCS in this experiment was delivered via a scalp electrode for 20 min at either 1 mA, 0.1 mA or, in the control condition, 0 mA. And to simulate a likely clinical combination, tDCS was also tested in combination with lorazepam, a first-line anticonvulsant benzodiazepine that is routinely administered to human patients with epilepsy. The results identify electrographic seizure suppression within minutes of 1 mA cathodal stimulation. Moreover, a combination of tDCS and a sub-effective lorazepam dose suppressed seizures better than either intervention, suggesting that cathodal tDCS may act synergistically with lorazepam [19]. Of translational relevance for future clinical application, these data indicate an important direction for neuromodulation research toward systematic testing of combination drug-device therapy in epilepsy

Conclusion

Given that the rate of drug-resistant epilepsy has not changed much in recent years, tDCS offers a plausible noninvasive and nonpharmacologic option to improve seizure control in patients with intractable seizures. Although tDCS antiepileptic effects have yet to be substantiated in large clinical trials, the benign tDCS side-effect profile suggests a favorable risk–benefit ratio and high likelihood of near-future implementation in clinical epilepsy. The inconsistent findings with respect to seizure suppression in the few controlled trials underscore the need for improved protocols for focal and patient-specific stimulation to enable superior targeting of the seizure focus [20–22]. Additionally, clinical tests of tDCS antiepileptic capacity have been limited to trials of single stimulation sessions. This is in contrast to other fields where tDCS is delivered daily in multiple sessions to produce a sustained neuromodulatory effect [12, 23–25], and preclinical studies that test multiple tDCS exposures [17, 18]. Thus, future trials may incorporate a multi-session stimulation strategy. Last, novel neuroprotective and antiepileptogenic tDCS applications are suggested by preclinical research, and also may lead to disease-modifying treatment strategies in future clinical embodiments of this technology.

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Pain Syndromes

19

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Abstract

The twentieth century was characterized by great discoveries in medical sciences, which enhanced our knowledge of mechanisms of disease and allowed for the development of pharmacological therapies to treat a large number of pathologies. During the same period, striking advances were accomplished in the pain field, particularly after the introduction of the concept of pain as a complex phenomenon rather than a simple sensation or a mere symptom. Moreover, at least part of the brain mechanisms related to such a complex experience has been revealed over the last decades with the advance of the neuroimaging field. Nonetheless, adequate pain control, especially in chronic pain patients, is still considered a challenge for clinicians worldwide. In this context, tDCS emerges as a promising mode to provide noninvasive modulation of dysfunctional neural networks present in chronic pain. Indeed, the results of several studies suggest that tDCS can produce long-lasting pain relief in different chronic pain syndromes, including migraine, fibromyalgia, and neuropathic pain. Nevertheless, it is still necessary to establish the most suitable protocols for each chronic pain disorder. Moreover, it is imperative to reveal the neuromechanisms related to tDCS-induced analgesia.

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Introduction

Pain is a phenomenon that has been identified and explored since the beginning of time, in distinct cultures and civilizations. Pain is a disabling symptom common to several pathologies and it is considered the primary reason that leads individuals to seek medical care [1]. Nevertheless, its concepts and definitions have been modified considerably throughout the centuries and especially during the second half of the twentieth century, when it evolved from a notion of a purely sensory event to a model of a complex and multifaceted experience. Indeed, since the outstanding work of Melzack and Casey (1968), it has been accepted that pain is not restricted to a sensory-discriminative dimension, which is unquestionably important to the full characterization of a given noxious stimulus (e.g., nature, location, intensity, and duration). Instead, pain is considerably more complex than that, since it includes not only nociception but also encompasses motivational-affective properties, intrinsically connected to the reticular formation and limbic system, and a cognitive-evaluative dimension, processed by higher order cortical areas, and that exerts control over the other two dimensions (e.g., sensory-discriminative and cognitive evaluative) [2]. Such concept led clinicians and researchers that take part in the field to define pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage," a concept that goes beyond nociception [3].

Pain is classically differentiated into two basic categories: acute or chronic. Although overly simplistic, this classification can be extremely useful in the clinical setting, since acute and chronic pain has distinct clinical presentations. Furthermore, chronic pain is usually incapacitating and associated with greater psychological and social impairment to the sufferers [4–7]. The adequate management of chronic pain is still considered a challenge for clinicians worldwide and its prevalence as well as the impact it produces in healthcare systems have been hugely studied and debated in the last years [8]. Therefore, other than distinguishing acute and chronic pain based only on arbitrarily chronological markers (classically 3 or 6 months) it is important to understand the pathophysiological events underlying both conditions.

In fact, the struggle to treat chronic pain derives mostly from the difficulty to understand its complex mechanisms, which leads researchers in the field to focus their attention towards the biological mechanisms related to this. In fact, the intricate machinery that triggers and maintains chronic pain has been partially unveiled. It has been established that a maladaptive plasticity affecting both the peripheral and the central nervous systems and associated with central and peripheral sensitization plays a major role [9].

Another essential aspect that must always be considered is that chronic pain does not represent a single nosological entity, since it comprises a variety of conditions of somatic, neuropathic, or even psychological origins, each one with particular characteristics [10]. For instance, it has been reported that different symptom profiles (e.g., pain quality and its spatial properties) can distinguish patients with neuropathic pains (e.g., postherpetic neuralgia painful diabetic, painful idiopathic sensory polyneuropathy, peripheral neuropathy) from those subjects with nociceptive pain (e.g., non-neuropathic low back pain and osteoarthritis) [11, 12]. Such findings very likely reflect the presence of specific events, concurring to the mechanisms of each particular chronic pain syndrome. For instance, a reduction in the intracortical inhibition has been shown in patients

with peripheral neuropathic pain, but not in osteoarthritis patients, which might suggest the presence of specific mechanisms related to neuropathic and nociceptive pain [13]. Moreover, a huge variability occurs in the course of chronic, especially neuropathic, pain among the individuals affected. This variability depends on the body region affected and is believed to be the result of interactions between etiological and environmental factors as well as genetic polymorphisms. In the future, the precise identification of dysfunctional mechanisms, representative of each chronic pain syndrome, will permit the development of more individualized treatments, which will probably result in a significant improvement of efficacy and decrease of side effects [14].

Due to the enormous challenge of treating chronic pains with the pharmacological therapies and surgical interventions currently available, clinicians and researchers have devoted to develop and enhance clinical strategies to provide relief for chronic pain patients, especially those suffering from refractory conditions. In this context, despite the long history in the use of electrical brain stimulation to provide pain relief [15], the use of neuromodulatory techniques to this purpose has only received considerable attention in the last three decades, especially after the studies of Tsubokawa et al. in the early 1990s [16, 17] that successfully applied motor cortex stimulation (MCS) to treat chronic neuropathic pain syndromes. As a matter of fact, the choice of the motor cortex as a target for pain treatment occurred after the unexpected discovery that thalamic hyperactivity could be decreased by MCS, while sensory cortical stimulation failed to produce comparable results [16–18]. In reality, a possible connection between the motor cortex and pain had emerged years before with the report of successful facial pain relief after cortical removals of both postcentral (sensory) and precentral (motor) cortex facial representations, in two patients [19], while cortical removals limited to the postcentral gyrus did not result in lasting pain relief for central pain sufferers [20]. In the following years after Tsubokawa work, clinical studies investigated the efficacy of MCS as well as noninvasive neuromodulatory techniques, to treat chronic pain disorders [21–25]. Furthermore, the ability of those methods to modulate the activity of faulty neural networks was also demonstrated [26].

Among the noninvasive neuromodulatory therapies applied for pain control, transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) are the most investigated. One of the main advantages of adopting protocols restricted to noninvasive methods of neuromodulation is the lower incidence of side effects. Although rare cases of TMS-related seizures have been documented [27, 28], typically only minor and transient side effects, such as tingling, transient headaches, skin irritation, itching, burning sensation, and nausea, occur with noninvasive procedures [29, 30] as long as the safety criteria are followed [31, 32].

With respect to tDCS, it is considered an effective method to modulate brain activity. Moreover, it permits a reliable sham condition and its technical operation is relatively simple [24, 25, 33, 34]. All these features make this procedure particularly suitable for pain studies. Not surprisingly, since its reintroduction in neurophysiological and clinical research, during the late 1990s and early 2000s [35, 36], several studies have reported that it is an effective method to treat distinct chronic pain syndromes, including fibromyalgia [25, 37–40], pain due to traumatic spinal cord injury [24, 41–43], chronic pelvic pain [44], refractory orofacial pain [45], postherpetic neuralgia [46], painful diabetic polyneuropathy [47], chronic neuropathic pain following burn injury [48], neurogenic pain [49], trigeminal neuralgia [50], low back pain [51], migraine [52–54], and chronic temporomandibular disorders (TMD) [55]. However, the effectiveness of tDCS for pain control is still a matter o debate in the literature. Although the results of a recent meta-analysis suggest that tDCS provides a significant reduction of pain levels [56], according to the results of another study, there is insufficient evidence that this method is effective to treat chronic pain in all patients [29]. Nevertheless, it is important to emphasize the elevated heterogeneity of the samples evaluated

in those studies, which included subjects affected by chronic pains associated with a great variety of diseases (e.g., fibromyalgia, spinal cord syndrome, multiple sclerosis, and migraine), the majority presenting completely unrelated pathophysiological mechanisms, which in turn may have impacted the findings.

Another important aspect that must be considered when interpreting the results of these clinical trials is the presence of adequate subject blinding during active and sham stimulation. As a matter of fact, it has been reported that incomplete blinding may exaggerate the clinical outcome by 25 % [57]. This aspect is especially prominent with TMS, since auditory clues along with the sensation of stimulation occur with active but not sham stimulation [58, 59]. Thus, some novel TMS strategies have been elaborated to address this concern [60]. Regarding tDCS, the feasibility of conducting double-blind sham-controlled clinical trials has been reported at current intensities of 1 mA in tDCS-naive participants [61, 62]. However, it has been reported that similar to TMS, active tDCS stimulation could be distinguished from sham at a current intensity of 1.5 mA [30], and both subject and operator blinding would be compromised at intensities of 2 mA since active and sham stimulations could be markedly differentiated [63].

One crucial feature, specifically related to tDCS, is the type of montage chosen. *M1-SO* is the montage classically adopted for pain studies. In this setup, the anode (positive pole) is placed over the region corresponding to primary motor cortex (M1) and the cathode (negative pole) over the contralateral supra-orbital (SO) area [64, 65]. Nevertheless, along the recent years other montages have been successfully built and tested, including *DLPFC*, that used both electrodes (anode and cathode) positioned over the dorsolateral prefrontal cortex (DLPFC) and *Cz-Oz*, with the anode over the vertex and the cathode over the occipital cortex. *M1-SO*, *DLPFC*, *and Cz-Oz* have been referred as conventional montages, since they use the same large electrodes (5 × 7 cm) positioned in different locations [53, 54, 66], and some of those methods have been compared. It has been reported that fewer subjects can distinguish sham, anodal, and cathodal stimulation when Cz-Oz is the montage applied. On the other hand, more subjects would recognize the type of stimulation when M1-SO is applied [67]. However, future studies must confirm such findings.

More recently, high-definition-tDCS (HD-tDCS) montages, using smaller, ring electrodes, have been developed, with the goal of increasing the focality of the electrical current. HD-tDCS montages include *HD-tDCS 4 × 1*, with the anode centered on the EEG 10–20 location C3, surrounded by four cathodes, over Cz, F3, T7, and P3 and HOPE *HD-tDCS 2 × 2*, with two anodes and two cathodes positioned across the face/head region of M1. In the case of 2 × 2 HD-tDCS, it was especially tailored based on MCS parameters [55, 64, 68–70]. On chronic temporomandibular disorder (TMD) patients, five daily sessions with this montage provided significant improvements on clinical pain and motor measurements compared to the placebo group, with pain relief above 50 % at 4-week follow-up, and increase in pain-free mouth opening at 1-week follow-up. There was also decrease in pain area, intensity, and their sum measures contralateral to the M1 stimulation, not the ipsilateral side, during the treatment week. In addition, no changes in emotional values were shown between active and placebo TMD groups.

Interestingly, recent studies, using computational models, have demonstrated that the strength of the regional current flow generated by tDCS differs significantly among distinct conventional and HD-tDCS montages [68] (Figs. 19.1 and 19.2) and even changes in the intracortical functional connectivity generated by conventional tDCS depend on the montage chosen [71]. Therefore, it is possible to postulate that each tDCS montage could be utilized to target specific dysfunctional areas in chronic pain patients, or extrapolating this concept, different montages could be chosen to treat distinct pain disorders. Further, HD-tDCS montages should be preferable when increased focality is a goal. Another important feature that should be considered is the possible reduction of undesirable

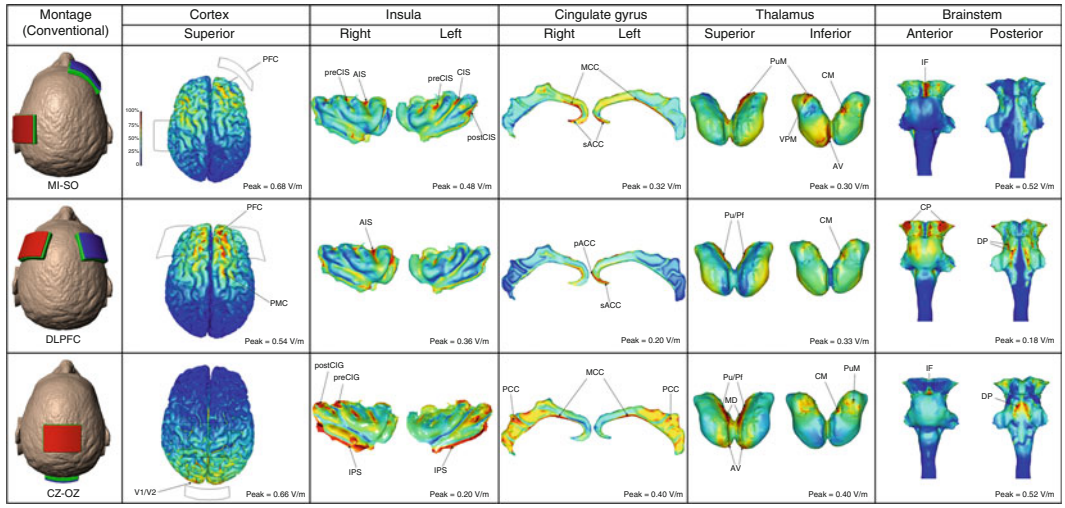

Fig. 19.1 Electrical current distribution through cortical and subcortical brain structures in three distinct conventional tDCS montages [68]

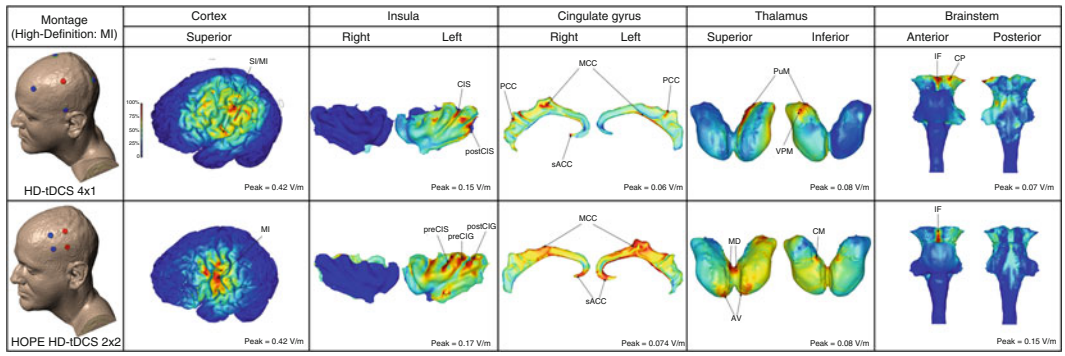

Fig. 19.2 Electrical current flow delivered through the brain in two HD-tDCS montages [68]

effects with more focused stimulation techniques, though the safety profile is considered very good particularly in the case of tDCS [29].

Despite the vast number of studies investigating the clinical effects of tDCS and the mounting evidence suggesting its analgesic effects, many of its mechanism aspects remain practically unexplored and it is still not possible to fully comprehend how it modulate the brain activity. Nevertheless, some of the underpinnings related to tDCS mechanisms have been elucidated by recent studies. Past studies reported the occurrence of immediate as well as long-lasting changes in the cortical excitability [31, 36, 72]. In addition, studies with computational models, which can predict the patterns of the current distribution throughout the central nervous system (CNS), have indicated that not only outer brain areas but also deeper and even more remote brain regions, such as insula, cingulate, thalamus, and brainstem, can be reached by tDCS [52, 68]. Considering that the presence of neuroplasticity, occurring at the structural [73–80], functional [81–86], and even molecular level [87–91], has been consistently reported in patients with a variety of chronic pain conditions, it is possible to speculate that acting at cortical and subcortical structures tDCS could contribute to revert the

ingrained neuroplastic changes developed by chronic pain patients. Remarkably, the effects of anodal and cathodal tDCS on cortical excitability can be suppressed by the *N*-methyl-D-aspartate (NMDA) receptor antagonist dextromethorphan (DMO) [92]. Such results support the hypothesis that synaptic plasticity can be driven by tDCS and that the analgesic effects of this neuromodulatory technique can be related to neuroplasticity changes involving brain areas related to pain and pain-related neural networks, which are dysfunctional in chronic pain patients.

Supporting this hypothesis, tDCS-induced changes in the levels of Glx, a combined marker of glutamine and glutamate, and *N*-acetylaspartate (NAA) that provides information regarding neuronal integrity, have been recently demonstrated in anterior cingulate cortex [93]. Such findings confirm the results of a previous study that had reported changes in the levels of Glx with tDCS. However, in that case, the changes were detected in the parietal area beneath the anode [94]. Another interesting result is the trend of increase in the levels of GABA, a major inhibitory neurotransmitter, in the anterior insula, produced by tDCS [93].

Furthermore, changes in the mu-opioid neurotransmission induced by M1 tDCS have been documented in both healthy subjects [46] and in a case report of chronic pain patient [95]. Interestingly, the activation of the endogenous mu-opioid system occurred with both active and sham stimulation. However, the pattern of regional opioidergic activation permitted the differentiation between sham and active tDCS (Fig. 19.3). While changes in the mu-opioid

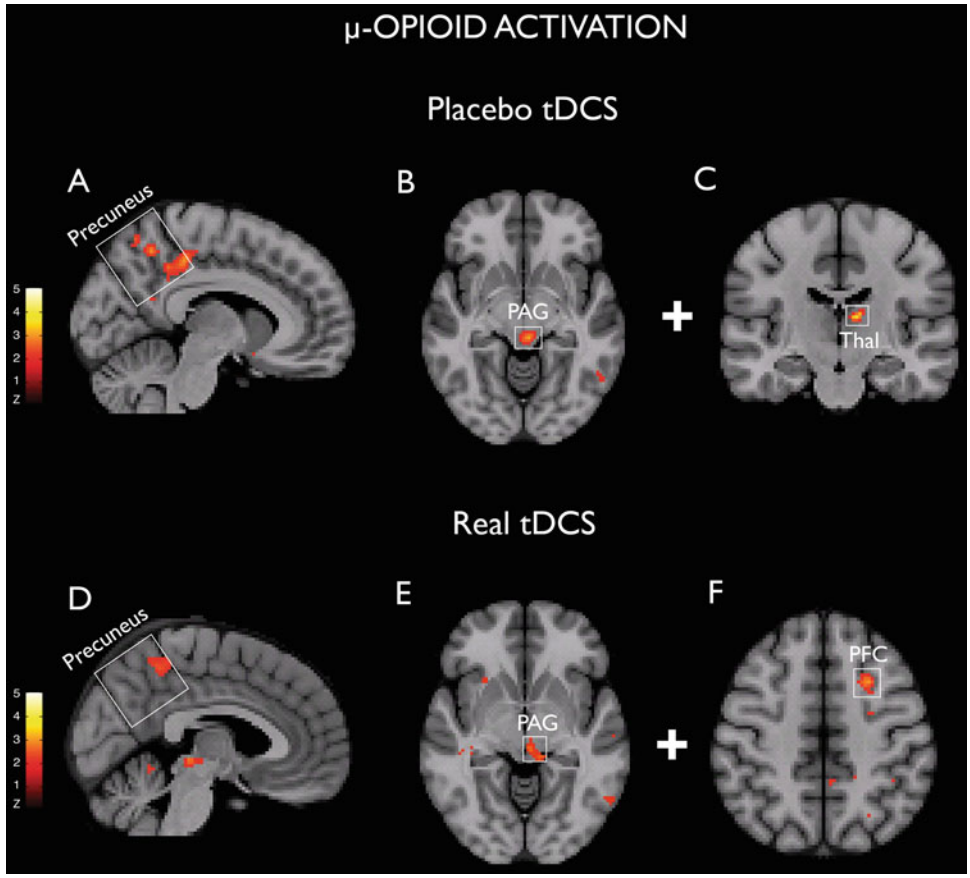

Fig. 19.3 μ-Opioid receptor (MOR) activation induced by placebo (**a**–**c**) and active (**d** and **e**) tDCS. (**a** and **d**) Precuneus MOR activation in the sagittal plane. (**b** and **e**) PAG MOR activation in the axial plane. (**c**) Left thalamus (Thal) MOR activation in the coronal plane. (**f**) Left prefrontal cortex (PFC) MOR activation in the axial plane [95]

receptor availability in the periaqueductal grey matter (PAG) and precuneus occurred during both sham and active stimulation, changes in the thalamus were specific for sham tDCS, corroborating the thalamic mu-opioid activation reported in previous placebo studies [96, 97]. On the other hand, changes in the prefrontal cortex (PFC) were only observed during active tDCS. Those findings possibly indicate that a placebo effect contributes to the beneficial effects obtained with tDCS, when applied to produce analgesia. Supporting this hypothesis, changes in the levels of NAA were found in the posterior insula after M1 tDCS [93]. Although still very preliminary, these findings also suggest that mutual as well as specific mechanisms can be associated with placebo and active tDCS [95]. Nevertheless, there are several aspects related to the neuromechanisms elicited by tDCS that still must be answered. At the current stage, it is important to establish a complete characterization of the clinical effects as well as the putative mechanisms associated with tDCS in each chronic pain syndrome. The following sections discuss the main findings of studies investigating the effects and mechanisms of tDCS in some major chronic pain syndromes (e.g., migraine, fibromyalgia) and also in neuropathic pains.

Effects and Putative Mechanisms of tDCS in Different Chronic Pain Syndromes

Fibromyalgia

Fibromyalgia is a condition that affects 2–8 % of the general population [98–100]. This syndrome was originally defined by the presence of tenderness and chronic spontaneous widespread pain [101]. Since women have much more tender points than men, fibromyalgia was almost exclusively found in women, when using that characterization [102]. Nonetheless, recent diagnostic criteria do not require counting the number of tender points. Instead, it is entirely based on patient's symptoms [103]. With this diagnostic criteria, the female:male ratio is 2:1 [100]. Multiple symptoms occur in fibromyalgia, including widespread pain, cognitive and physical fatigue, mood disturbance, pain catastrophizing, autonomic dysfunction, and sleep and memory disturbances [102]. History of regional musculoskeletal pain, irritable bowel syndrome, headache, and TMD, among other conditions, is also usually observed in fibromyalgia patients [104].

Fibromyalgia has been referred as a centralized pain state, implying CNS origin of or amplification of pain [102]. In fact, there is mounting evidence, deriving mainly from neuroimaging studies, that confirms the occurrence of functional changes in the CNS activity of fibromyalgia patients. Those changes involve not only the cerebral blood flow [105] but also regional changes in the γ-aminobutyric acid (GABA) concentrations [106], dopaminergic [107] and opioidergic systems [87], as well as altered brain connectivity [84, 86, 108]. Linking those findings with the lack of effectiveness of drugs commonly applied to treat peripheral pains and higher effectiveness of centrally acting drugs in the treatment of fibromyalgia patients [102], it is very likely that neuromodulatory methods can provide some degree of pain relief for individuals affected by this syndrome.

As a matter of fact, one of the pioneer studies exploring the possible use of tDCS for pain treatment was performed in fibromyalgia patients [25]. In that study, positive results that lasted for 3 weeks after the end of the treatment period were obtained with five sessions (2 mA/20 min of stimulation) of M1-SO tDCS but not with DLPFC tDCS or sham. The outcomes of that proof of concept research were also important to confirm the safety of the procedure, especially when applied in chronic pain patients, since only few and mild adverse effects, with a frequency similar in the verum and sham groups, were found. Furthermore, the absence of antidepressant effects could suggest that DLPFC-tDCS might not be the most suitable montage in fibromyalgia patients. Nonetheless a subsequent study demonstrated significant improvements of pain and quality of life with both M1-SO and DLPFC montages, when applying protocols consisting of

ten sessions (2 mA/20 min) of stimulation [40]. Interestingly, M1-SO montage resulted in long-lasting outcomes, as assessed at 30 and 60 days after the end of the period of stimulation, stressing the importance of the treatment duration to the long-term effects of tDCS, at least in fibromyalgia patients. The analgesic and long-term effects of tDCS in samples that included fibromyalgia patients have been confirmed in other studies, even when applying lower currents [109], unusual montages (e.g., cathodal-SO) [38], or the combination of tDCS and rehabilitation programs [37]. More recently, significant pain decreases have been reported with only a single session of anodal or cathodal 4×1 HD-tDCS, when compared to sham [39]. These findings endorse the use of HD-tDCS montages in future fibromyalgia trials. As previously discussed, HD-tDCS techniques enhance the current focality, which remains practically restricted to M1. Considering that the most pronounced analgesic effects are achieved with M1 stimulation, it is reasonable to advocate that HD-tDCS montages specifically targeting M1 should be preferred to treat chronic pain syndromes, including fibromyalgia. In fact, the question whether the use of a somatotopically oriented stimulation through smaller electrodes optimizes the analgesic effects induced by tDCS has been proposed since the first study of tDCS in chronic pain [24]. However, the clinical relevance of increasing focality must be confirmed, since modeling studies have proved that conventional montages are able to modulate several deeper structures related to pain. Although also affected by the electrical current, those areas are not reached at the same intensity with HD-tDCS montages [52, 68].

Despite the increasing number of studies investigating the clinical aspects of tDCS in fibromyalgia, the specific mechanisms by which tDCS modulates pain pathways in this disorder have not been explored in depth. The results of one of the few studies in the topic suggest that M1-SO tDCS could possibly act by altering the levels of GABA, glutamate, and glutamine (Glx) and NAA in pain-related brain areas, such as the anterior cingulate, the anterior insula, and the thalamus (Fig. 19.4). In addition, the

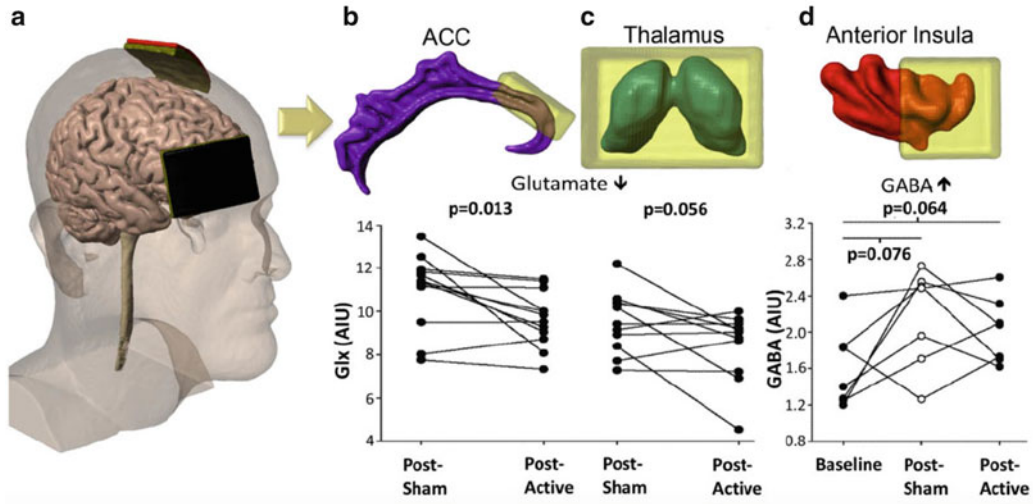

Fig. 19.4 tDCS and 1H-MRS protocol. *Top left image* (**a**): M1-SO tDCS montage. This is followed on the *right* by the segmentation of the regions of interest (ROIs): cingulate cortex (**b**), thalamus (**c**), and anterior insula (**d**). *Bottom images*: Longitudinal changes in glutamate + glutamine (Glx) as well as GABA following five daily active tDCS in patients with fibromyalgia (FM). *Left bottom graph*: Individual data points show Glx concentrations in ACC in patients with FM, in whom post-sham and post-active tDCS samples were obtained. Glx decreases in ACC ($p = 0.013$) following active tDCS treatment. *Center bottom graph*: Same for thalamus ($p = 0.056$). *Right bottom graph*: Individual data points show a trend on increasing GABA concentrations (AIU) in the anterior insula ($p = 0.064$) following active tDCS treatment [93]

baseline levels of Glx in the anterior cingulate can predict the clinical responses to tDCS [93]. Interestingly, significant increases in the levels of NAA in the posterior insula were found after sham tDCS, which suggests the presence of a placebo effect underlying the tDCS-induced analgesia. Nevertheless, more studies are needed to confirm those findings and to expand the current understanding regarding the mechanisms by which tDCS acts in fibromyalgia.

Migraine Headache

Migraine is characterized by recurrent attacks of unilateral pulsating headache, associated with nausea and/or photophobia and phonophobia [110]. Its lifetime prevalence is around 14 % [111]. Two subtypes are encountered: migraine without aura and migraine with aura. Migraine without aura is characterized by headache with some specific aspects and symptoms associated. Migraine with aura is characterized by the presence of transient focal neurological symptoms (e.g., visual or sensory symptoms) that precede or accompany the headache [110]. In some patients migraine evolves from an episodic form to a chronic condition, referred as chronic migraine (CM). CM is defined as a headache that occurs on 15 or more days per month for more than 3 months, and that features the aspects of migraine headache on at least 8 days per month [110]. Besides, medication overuse has been considered the main cause of symptoms suggestive of chronic migraine [110]. As in other painful syndromes, the progression from an episodic to a chronic form is marked not simply by an increase in the number of episodes, but also by the occurrence of other phenomena, such as allodynia (pain due to a stimulus that usually does not provoke pain) as well as hyperalgesia (increased response to a normally painful stimulus). In fact, allodynia affects a large proportion of migraine sufferers [112–115] and is more common in migraine than in other primary headaches [116].

Along with the largely documented neural and neurovascular mechanisms, it has been proposed that central sensitization, which may lead to cutaneous allodynia, plays a role in the migraine pathophysiology [117, 118]. Interestingly, our group has recently demonstrated the presence of altered mu-opioid receptor functioning in the periaqueductal grey and red nucleus associated with ictal trigeminal allodynia, developed during a thermal challenge, in migraine patients [91]. Furthermore, neuroimaging studies have confirmed the presence of neuroplastic changes associated with migraine headache [74, 75, 77, 82, 83, 90]. When analyzed together, these findings corroborate the development of research protocols to investigate the use of noninvasive neuromodulatory tools, such as tDCS, to modulate the activity of pain-related structures and perhaps reverse faulty mechanisms that constitute the basis of the migraine pathophysiology.

Regarding the clinical use of tDCS in migraine patients, there are still few studies in the literature and they differ with respect to the montage chosen as well as the patient selection. The most used montages are M1-SO [52] and Cz-Oz [53, 54, 66]. Positive effects, such as pain reduction, decrease in the duration of attacks and in the number of migraine-related days posttreatment were reported in a study that applied Cz-Oz tDCS [53]. On the other hand, the frequency of migraine attacks was not affected, which might be explained by the relatively low intensity (1 mA), duration (15 min), and frequency of the stimulation applied (three sessions per week during 3 weeks). Increasing those parameters might have produced stronger effects in that study but it might have also impacted the sham arm of the study and the placebo condition, which was considered optimal, based on the side effects reported. Nonetheless, another limitation of that preliminary study that must be considered when interpreting the results is the heterogeneity of the experimental group analyzed, consisting of patients diagnosed with migraine with aura and without aura and chronic migraine. Interestingly, persistent analgesic effects induced by tDCS were found in a sample consisting only of patients diagnosed with episodic migraine without aura [54]. In that study, each subject received preventive treatment with anodal tDCS applied to the visual cortex (1 mA/15 min) twice a day, during

8 weeks. Active stimulation reduced the frequency and duration of the migraine attacks as well as migraine days and the acute medication intake for a period of 4.8 weeks [54]. The same study showed that tDCS is able to induce a transient increase in the habituation in migraineurs, which could be one of the mechanisms underlying tDCS-induced analgesia in migraine patients.

In another tDCS study, significant decreases in the pain intensity, length of episodes, and clinical impression have been reported in chronic migraine patients treated with M1-SO tDCS [52]. Unexpectedly, only long-term effects (4 months after the period of treatment) were detected in that study, while immediate effects could not be demonstrated. Such findings could also be related to the protocol chosen, consisting of every other day stimulation, instead of daily sessions. Nevertheless, the most important contribution of that study was the detection of peaks of current flow in deeper pain-related structures (e.g., cingulate, thalamus, insula, and brainstem), demonstrated through a finite element model analysis, which has been confirmed afterwards [68].

tDCS can also provide insights into the pathophysiology of migraine headache, as demonstrated by a study that reveled, through a combination of tDCS and TMS, different patterns of changes in the cortical excitability induced by tDCS [119]. Anodal tDCS stimulation produced an increase in the visual cortex excitability in both healthy subjects and migraine patients, with larger variations observed in the group of migraine patients with migraine with aura. Conversely, cathodal tDCS (Cz-Oz) resulted in a decrease in the cortical excitability of healthy volunteers, but did not alter the cortical excitability in migraine patients, suggesting the presence of deficient inhibitory process in the cortex of migraine patients and indicating that a more prominent inhibitory dysfunction occurs in migraine with aura, when compared to migraine without aura [119]. In a following study that also combined TMS and tDCS, cathodal tDCS, but not anodal tDCS, restored the abnormal facilitatory response to hf-rTMS in migraine patients [120]. The presence of interictal visual cortical hyperexcitability has also been found in another study applying a similar methodology [121]. The same study reported significant reductions in duration and number of migraine attacks as well as painkiller intake when cathodal visual cortex stimulation was applied as a prophylactic therapy. Nevertheless, such effects were not higher than in a group of migraine patients that received sham stimulation [121]. Intriguingly, the beneficial effects obtained in the active group were not correlated to changes in cortical excitability, indicating that the analgesic effects induced by tDCS in migraineurs may occur independently of cortical excitability normalization.

Although still scarce, the data currently available suggest that tDCS can be a useful tool to treat migraine headache. However, it is still necessary to define the specific montage that offers more beneficial effects as well as the ideal parameters (e.g., current intensity, duration and frequency) that should be used in migraine patients. To accomplish those objectives, furthers studies, with larger sample sizes and individualizing different forms of migraine headache, will be necessary.

Neuropathic Pains

The IASP taxonomy (Merskey et al. 1994), revised in 2012 (http://www.iasp-pain.org/Taxonomy#Neuropathicpain), defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system." However, neuropathic pain is considered an umbrella term that encompasses distinct disorders, such as trigeminal and postherpetic neuralgias, painful diabetic polyneuropathy, painful nerve lesions, radiculopathies, and postamputation pain. Moreover, several CNS disorders (e.g., spinal cord injury, multiple sclerosis, and stroke) can be associated with neuropathic pain [122, 123]. The prevalence of neuropathic pain on the general population ranges from 2 to 3% [124, 125] but this number can be even higher. It has been estimated that the prevalence of pain with neuropathic characteristics can be around 6.9–10% [126]. Neuropathic pain is considered challenging to manage [127]. Furthermore, it often produces significant negative impact on quality of life [128]. The mechanisms that trigger and

maintain neuropathic pain symptoms have not been totally unveiled. Nonetheless, peripheral as well as central mediation, which involves complex physiological events, is certainly important [9, 129, 130]. Considering the satisfactory results produced by MCS in neuropathic pain patients [17, 23, 131], it is reasonable to consider the use of tDCS to reduce the negative impact provoked by such disorders on the patients affected, or even as a predictive method for invasive therapies.

In fact, the first study investigating the efficacy and safety of tDCS in chronic pain was performed in patients with refractory neuropathic central pain due to traumatic spinal cord injury. The results indicated the presence of significant positive results on pain, without significant effects on anxiety and depression associated with five consecutive sessions of M1-SO tDCS but not with sham [24]. Remarkably, the magnitude of the results obtained in that study was impressively high, with a mean pain response of 58 %. Besides, the lack of changes in cognitive and motor performed associated with tDCS verified in that study corroborated the safety of the procedure and supported the development of further tDCS studies in chronic pain patients. A recent study confirmed the safety and efficacy of anodal M1 stimulation in patients with neuropathic pain associated with spinal cord injury. Strikingly, a significant association was found between the decrease of pain intensity and increase in the peak theta–alpha frequency at the site of stimulation, with only a single session of tDCS [132].

A further study, evaluating patients with painful diabetic polyneuropathy, showed significant higher analgesic effects of M1-SO tDCS, when compared to DLPFC tDCS and sham, indicating that M1-SO tDCS might be an optimal montage for neuropathic pain studies [47]. In other studies, M1-SO tDCS produced more significant and in some cases longer lasting results in neuropathic pain patients when combined with another therapy, such as transcutaneous electrical nerve stimulation [49] or visual illusion [41]. Nonetheless, in both examples tDCS alone also granted beneficial effects to the patients evaluated.

Little is known regarding the mechanisms of M1-SO tDCS in chronic neuropathic pain syndromes. In a previous study, our group demonstrated for the first time significant changes in the availability of mu-opioid receptor in pain-related structures (insula, cingulate, nucleus accumbens, and thalamus) during a single session of M1-SO tDCS in a postherpetic neuralgia patient [46]. Such findings are very similar to those obtained with MCS in refractory neuropathic pain patients [133, 134] and strongly suggest the contribution of the mu-opioidergic system to the tDCS-driven analgesia in neuropathic pain patients.

It is important to emphasize that negative results have also been reported with tDCS in neuropathic pain conditions. For example, in one study, five sessions of anodal M1 tDCS stimulation failed to produce analgesia in patients with neuropathic pain due to spinal cord injury, contrasting the findings of previous studies. Noteworthy, the duration of the injury in the patients of that study was longer than in other studies, suggesting that the pain decreases related to tDCS also depend on the pain duration [43]. Negative results of M1-SO tDCS in neuropathic pain have been documented in other studies. Nonetheless, those results should be interpreted cautiously, since in those cases the protocol consisted of single sessions of stimulation [42, 48], which in some cases could not be enough to produce significant analgesia and especially in refractory neuropathic pain patients.

Concluding Remarks

The current scientific literature indicates that tDCS is a safe and well-tolerated procedure that can be effectively used as a prophylactic or even acute therapy in different chronic pain syndromes. Nevertheless, there are still many questions that must be answered before it can be clinically applied in a large scale. Future studies should not only focus on establishing the ideal montages and protocols for each pain syndrome, but also on determining to what extension a placebo effect contributes to its analgesic effects and more important the pain-related neural mechanisms that can be targeted and potentially modulated by tDCS.

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Stroke

20

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Abstract

Stroke is the leading cause of long-term disability due to various impairments such as motor weakness, visuospatial neglect, aphasia, dysphagia, cognitive decline, spasticity, depression, and central pain. Although functional improvement from these impairments is important to reduce the burdens of stroke survivors, the effects of conventional rehabilitation approaches are still modest and the novel therapeutic approaches are being needed. TDCS could be applied as an adjuvant therapy for rehabilitation in stroke patients as it can potentially facilitate motor, cognitive, and language recovery after stroke, by providing the methods to modulate brain activity or plasticity in a specific region at the network level. Therefore, TDCS is currently under active investigation in the stroke rehabilitation field. In this chapter, the clinical application of TDCS in the field of stroke rehabilitation is discussed.

Keywords

Stroke • Rehabilitation • Neuromodulation • Transcranial direct current stimulation • Impairment • Plasticity

Stroke is defined as a "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 h or leading to death, with no apparent cause other than that of vascular origin" by the "World Health Organization" [1].

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Stroke is one of the leading causes of long-term severe disabilities worldwide [2], and about 50 % of stroke survivors have some kinds of long-term disabilities [3]. The absolute number of stroke survivors is increasing worldwide and the increase in global burdens of stroke is expected [4]. Impairments after stroke include motor weakness, coordination and balance problems, apraxia, spasticity, sensory loss, hemispatial neglect, aphasia, dysarthria, aphasia, central pain, shoulder pain, depression, cognitive problems, and behavioral

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problems depending on the affected area of the brain. Although many treatment strategies including conventional rehabilitative approach have been applied to reduce these disabilities, their effects are still limited and the novel therapeutic approach is being needed [5].

TDCS provides the methods to modulate brain activity or plasticity in a specific region at the network level [6]. TDCS is under active investigation in the stroke rehabilitation field. Modern theory states that functional recovery after stroke is a re-learning process with a partially disrupted neural network [7]. This re-learning process can be enhanced by inhibiting competing maladaptive cortical areas or facilitating local cortical activities during rehabilitation practice using TDCS. Recent bench-to-bedside research has demonstrated promising results on stroke recovery by using either brain stimulation alone or in combination with conventional rehabilitation. TDCS could be applied as an adjuvant therapy for rehabilitation in stroke patients as it can potentially facilitate motor, cognitive, and language recovery after brain injury. Theoretically, it is more beneficial to apply TDCS earlier than later because this period is an active period of brain reorganization or plasticity [8, 9]. The changes of brain network after stroke can be monitored using neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET).

Up to now, among noninvasive brain stimulation (NIBS) techniques, only application of the repetitive transcranial magnetic stimulation (rTMS) device for treatment of drug-resistant depression has been granted US Food and Drug Administration approval [10, 11]. Applications of TDCS for stroke patients are currently off-label. Large-scale phase III clinical trials and meta-analysis in the field of TDCS application in stroke are required to achieve a high level of evidence.

Currently, according to proof-of-concept studies, the beneficial effect of TDCS in the clinical setting is still modest. Optimal stimulation protocols in terms of optimal clinical samples, delivery timing, duration, and stimulation parameters are still unclear [12].

In this chapter, the clinical application of TDCS in the field of stroke rehabilitation is discussed, as well as post-stroke impairment syndromes such as motor weakness, visuospatial neglect, aphasia, dysphagia, cognitive decline, spasticity, post-stroke depression, and post-stroke central pain.

Motor Recovery

Acute stroke therapies such as tissue plasminogen activator (tPA) and mechanical thrombolysis that promote brain reperfusion within an optimal time period are presently available. Yet, half of stroke patients still suffer from residual motor weakness [13]. Also, these therapies are effective only when delivered in a very short period of time of a few hours after stroke onset.

To promote motor recovery after stroke, exercises featuring task-oriented high-intensity repetitive training are being clinically applied [5]. Constraint-induced movement therapy (CIMT), robotic training, neuromuscular electrical stimulation, training with virtual reality, and body weight-supported treadmill training are a few examples.

Small placebo-controlled trials have investigated the clinical effects of TDCS for motor recovery as an adjuvant modality to these behavioral therapies. These studies revealed a change in cortical motor excitability or improvement of motor function after TDCS.

One possible strategy to enhance motor recovery after stroke is to simply increase the cortical excitability of affected motor cortex. Another possible strategy is mainly based on the theory of inter-hemispheric competition or rivalry [14–16]. In the inter-hemispheric rivalry theory, the activities of motor cortexes are counterbalanced by trans-callosal inhibitory projections. However, trans-callosal inter-hemispheric inhibitory influences from the unaffected motor cortex to the affected motor cortex are relatively increased compared to the opposite direction (from the affected to unaffected motor cortex) after stroke, leading to over-inhibition of the affected motor cortex and impeding motor recovery of the

paretic side [16, 17]. Therefore, restoration of the excitability of affected hemisphere can be expected by inhibiting the motor cortical activity of the unaffected hemisphere [16].

Therefore, trans-cranial induction of either facilitation of the affected motor cortex (M1) using anodal TDCS or inhibition of unaffected M1 using cathodal TDCS can enhance motor recovery of the paretic limb (Fig. 20.1).

Single or multiple sessions of either facilitatory anodal TDCS applied to affected M1 [16, 18] or inhibitory cathodal TDCS to unaffected M1 [19, 20] have shown to enhance paretic upper limb recovery beyond the stimulation period.

If repeated sessions of stimulation are applied, longer lasting after effect can be expected [21]. Reis et al. [22] showed that multiple sessions of anodal TDCS enhance long-term retention and consolidation of acquired motor skills as compared to sham stimulation in healthy participants.

Although first positive results for enhancement of motor function came out from anodal TDCS protocols, anodal protocol over affected M1 is reported to produce less beneficial effects than cathodal TDCS protocol over unaffected M1 according to recent studies [23, 24]. Kim et al. [23] tested whether multiple sessions of TDCS in combination with occupational therapy could induce greater motor recovery in the paretic upper limb than sham stimulation plus occupational therapy in subacute stroke patients. The authors recruited 18 patients with hand paresis and randomly assigned them to one of the three 10-day sessions of intervention: anodal TDCS over the affected motor cortex, cathodal TDCS over the unaffected motor cortex, or sham stimulation. Only cathodal TDCS led to a greater recovery of paretic hand assessed with the Fugl-Meyer assessment score than the sham stimulation at 6-month follow-up, whereas anodal TDCS just showed trends toward greater improvement.

Bi-hemispheric TDCS, combining anodal TDCS over the affected hemisphere plus cathodal TDCS over the unaffected hemisphere, has been applied in healthy subjects [25, 26] and stroke patients [27, 28]. Kang and Paik [25] compared unilateral versus bilateral TDCS when performing a motor learning task in 11 healthy subjects and found no significant difference in induced implicit motor sequence learning between two interventions, although both interventions were more effective than sham TDCS. Therefore, it is still not clear whether bi-hemispheric TDCS is more effective on motor recovery than unilateral TDCS.

TDCS can be combined with other therapies. One study tested whether combining somatosensory stimulation and TDCS induces larger or longer lasting after effects than somatosensory stimulation or TDCS alone [29]. The study combined peripheral nerve stimulation to the affected hand with anodal TDCS on the ipsi-lesional M1, and combined stimulation resulted in a greater improvement in the number of correct key presses relative to either stimulation alone or sham stimulation. This improvement was maintained until 6 days after the end of the interventions. However, combining TDCS during robot-assisted bilateral arm training in subacute stroke patients showed no differences in motor improvement between TDCS and sham stimulation [30].

Recently, Triccas et al. reported the results of a meta-analysis for multiple sessions of TDCS on upper extremity function after stroke [31]. Eight randomized controlled trials were included for analysis (Table 20.1). Real TDCS combined with rehabilitative therapy showed a small, nonsignificant effect on upper extremity functional recovery after stroke. This result was consistent with a recently published Cochrane review, which reported no beneficial effect of TDCS for improvement of activity of daily living and only moderate positive effect on upper limb motor recovery [32]. Clinical trials using TDCS for upper limb impairment in stroke patients were heterogeneous in terms of chronicity of stroke, mode of TDCS delivery, and combined intervention, and their sample sizes were relatively small.

TDCS for motor recovery after stroke mainly focused on upper limb impairments. This may be due to deep midline location of leg motor area close to the medial longitudinal fissure and unclear pathophysiological reorganization of leg motor areas after stroke [33]. Clinical trials using TDCS to improve the gait functions have not been reported, although several small pilot

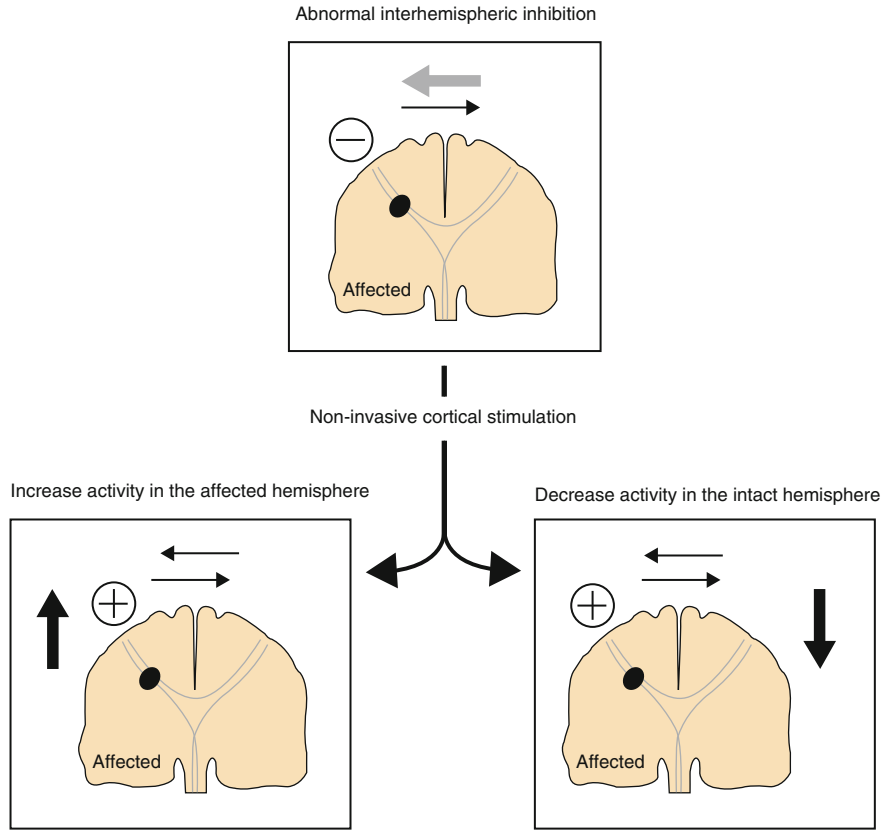

Fig. 20.1 Strategy to improve motor function after stroke. After stroke, trans-callosal inter-hemispheric inhibitory projection from the unaffected motor cortex to affected motor cortex is elevated compared to inhibitory tone from affected to unaffected motor cortex after stroke. Therefore, either facilitation of affected motor cortex using anodal TDCS or inhibition of motor cortex of the unaffected hemisphere using cathodal TDCS could be a strategy to improve motor function of paretic upper limb (figure modified from Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet neurology 2006;5:708–12.)

studies using rTMS for gait improvement in chronic or subacute stroke patients reported positive results [34, 35].

The recent absence of positive results of a multicenter phase III clinical trial on cortical epidural stimulation to enhance motor improvement after stroke suggested important caveats in applying TDCS to stroke patients for motor recovery [41]. A previous phase II feasibility trial with epidural stimulation guided by functional MRI for the optimal stimulation site in patients with chronic stroke was successful [42]. However, in phase III trial, a limited number of patients (less than 20% of participants) showed a motor-evoked response, which may be one of the main factors that led to unexpected failure. Post hoc subgroup analysis showed a significant improvement in patients with evoked motor response, in whom corticospinal integrity was supposed to be preserved. When we consider that functional recovery after stroke is an essentially motor relearning process with a partially disrupted neural circuit [7], the corticospinal integrity has to be at least sufficient to allow motor recovery to occur. Therefore, integrity of corticospinal descending pathways should be checked using TMS or tractography before applying TDCS.

Improvement of motor function after TDCS is still modest and more studies are needed to assess its long-term benefits on a larger number of patients [43]. Further fine establishment of stimulation protocols to maximize the beneficial

Table 20.1 Characteristics of TDCS studies included in the meta-analysis (reprinted with permission from Triccas et al. Multiple sessions of transcranial direct current stimulation and upper extremity rehabilitation in stroke: A review and meta-analysis. Clinical Neurophysiology 2015) [31]

	Objective	Design	Groups	*N*	Mean age (years)	Mean time since stroke	TDCS stimulation intensity/duration/ hemisphere	Training period (weeks)	Outcomes according to the ICF (I = impairment, A = activity, P = participation)
Kim et al. [23]	TDCS and OT on UL motor recovery	Single-blinded RCT	Anodal and OT	6	55.3	34.0 days	(1) 2 mA (2) 20 min (3) TDCS during rehabilitation (4) Anodal: ipsi-lesional cathodal: contra-lesional	10 sessions over 2 weeks and 30 min OT	FMA[a] (I) MBI[a] (A)
Lindenberg et al. [27]	TDCS and PT and OT on UL motor recovery	Double-blinded RCT	Cathodal and OT	5	53.6	19.4 days	(1) 1.5 mA (2) 30 min (3) TDCS during rehabilitation (4) Anodal: ipsi-lesional cathodal: contra-lesional	Daily sessions of 60 min OT and PT	FMA (I) fMRI[a] (I) WMFT[a] (A)
			Sham and OT	7	62.9	22.9 days			
			Bi-hemispheric and OT	10	61.7	30.5 months			
Bolognini et al. [36]	TDCS and CIMT on UL motor recovery	Double-blinded RCT	Sham and OT	10	55.8	40.3 months	(2) 2 mA (2) 40 min (3) TDCS during rehabilitation (4) Anodal: ipsi-lesional cathodal: contra-lesional	14 daily sessions of 4-h CIMT[a]	FMA (I) JTT[a] (I), HG[a] (I), Resting Motor Threshold and trans-colossal inhibition (I), MAL[a] (A), BI (A)
			Bi-hemispheric and CIMT	7	42.6	44.4 months			
Hesse et al. [30]	TDCS and RT on UL motor recovery	Double-blinded RCT	Sham and CIMT	7	50.9	26.0 months	(2) 2 mA (2) 20 min (3) TDCS during rehabilitation (4) Anodal: ipsi-lesional, cathode: contra-lesional	30 sessions over 6 weeks involving 20-min RT	FMA (I) MRC[a] (I) MAS[a] (I) BI[a] (A) BBT[a] (I)
			Anodal and RT	32	63.9	3.4 weeks			
Nair et al. [37]	Cathodal/sham TDCS and OT on UL motor recovery	Double-blinded RCT	Cathodal and RT	32	65.4	3.8 weeks	(1) 30 min (2) 1 mA (3) TDCS during rehabilitation (4) Cathodal: contra-lesional	5 daily sessions of 1-h OT	ROM[a] (I) FMA[a] (I) fMRI (I)
			Sham and RT	32	65.6	3.8 weeks			
			Cathodal and OT	7	61.0	33 months			
Khedr et al. [38]	Anodal/cathodal/sham TDCS and rehabilitation UL motor recovery	Double-blinded RCT	Sham and OT	7	56.0	28 months	(1) 25 min (2) 2 mA (3) TDCS before rehabilitation	6 daily sessions of 1-h rehabilitation (passive movement and range of motion exercises)	National Institute of Health Stroke Scale (I) Orgogozo MCA scale (I) MRC (I) Resting and Active Motor Threshold
			Anodal and therapy	14	58.1	13.8 days			
Lee et al. [39]	Cathodal TDCS and virtual reality program on UL impairments	Double-blinded pilot RCT	Sham and PT	45	49.3	4.9 months	(1) 20 min (2) 2 mA (3) TDCS during OT and virtual reality (4) Cathode over contra-lesional M1	5 sessions per week for 3 weeks of 30 min each session of virtual reality	MAS (I), Manual Muscle Test (I) Manual Function Test (I). FMA (I). BBT (I). Korean MBI (A)
			Cathodal and OT	21	60.3	17.4 days			

(continued)

Table 20.1 (continued)

	Objective	Design	Groups	*N*	Mean age (years)	Mean time since stroke	TDCS stimulation intensity/duration/ hemisphere	Training period (weeks)	Outcomes according to the ICF (I=impairment, A=activity, P=participation)
Viana et al. [40]	Anodal TDCS and virtual reality on UL impairments	Double-blinded RCT	Anodal TDCS and virtual reality	10	56.0	31.9 months	(2) 13 min (2) 2 mA (3) ?before/during and after rehabilitation (4) Anode over ipsi-lesional M1	3 sessions per week for 5 weeks of 1 h each session	FMA (I), WMFT (I), MAS (I) Dynamometry (I), Stroke Specific Quality of Life Scale (P)
			Sham TDCS and virtual reality	10	55.0	35.0 months			

[a]*BI* Barthel index, *BBT* box and block test, *CIMT* constraint-induced movement therapy, *fMRI* functional magnetic resonance imaging, *FMA* Fugl-Meyer assessment, *HG* hand grip, *MAS* modified Ashworth scale, *MAL* motor activity log, *MBI* modified Barthel index, *MEP* motor-evoked potential, *MRC* Medical Research Council Strength, *ROM* range of motion, *MT* motor threshold, *OT* occupational therapy, *PT* physiotherapy, *WMFT* Wolf motor function test

effect of TDCS, in terms of parameters revealing better effect and maintenance, optimal candidate, and time selection for intervention and individualized stimulation target localization depending on the pattern of reorganization, should be pursued [44].

TDCS seems to be a safe and promising intervention for motor recovery after stroke and may be potentially used as an adjuvant therapy when appropriately combined with conventional or other new rehabilitation therapies. It is unlikely that TDCS alone makes the brain form appropriate connections required for recovery. TDCS may strengthen existing connections or help the brain to form new connections. Therefore, TDCS techniques should always be accompanied by behavioral training.

Visuospatial Neglect

Neglect is defined as an impaired or lost ability to respond to various sensory stimuli presented from the contra-lesional side in a patient with cortical damages [45]. Visuospatial neglect in the first months after a stroke is common, and is estimated to occur in about 82 % of right cerebral hemisphere strokes and 65 % of left cerebral hemisphere strokes [46]. Neglect is related with poor functional recovery [47].

Various rehabilitation therapies for neglect have been investigated such as visual scanning, optokinetic stimulation, neck muscle vibration, caloric- or galvanic-vestibular stimulation, and prism adaptation [48]. However, these preexisting treatment tools have shown limited effect.

Recently, TDCS has emerged as a possible treatment tool for neglect. The current rationale for application of TDCS for visual spatial neglect after stroke is also based on the theory of interhemispheric rivalry. Usually a right hemispheric lesion after stroke causes the attention vector generated by the right hemisphere to be weaker and results in reduced inhibition on the left hemisphere [49]. This disinhibition of left hemisphere supposedly leads to increase in the excitability of the intact left hemisphere and rightward deviation of the visual field [49]. Therefore, the current purpose of TDCS for neglect is to reduce the hyperexcitability of intact left hemisphere and/or to increase the excitability of injured right hemisphere, which are expected to rebalance the rightward deviation.

In one study using TDCS for post-stroke neglect, only one session of anodal TDCS over the affected posterior parietal cortex with 2 mA demonstrated improvement in the percent deviation score of the line bisection test and the omissions of cancellation test [50]. In another study, the effect of anodal TDCS over the affected posterior parietal cortex and cathodal TDCS over the unaffected posterior parietal cortex was investigated in ten post-stroke neglect patients [51]. Both anodal and cathodal TDCS showed some improvements in the clinical test, compared to sham TDCS.

Based on these two small studies, the expected increase of cortical activity on the affected hemisphere induced by anodal TDCS or decrease of cortical activity on the unaffected hemisphere induced by cathodal TDCS seems to improve the neglect symptom after stroke. However, randomized controlled parallel design studies with adequate sample size have not been reported yet, convincing that evidence for TDCS on post-stroke neglect is currently lacking.

Aphasia

Aphasia is defined as an acquired loss or impairment of the language after brain damage [52]. About 24–30 % of patients show various types of aphasia after stroke and the pattern of recovery varies among patients [53, 54]. Aphasia causes substantial disability in daily life and is an important prognostic factor for general functional outcome in stroke patients [55].

Speech language therapy is usually the primary therapeutic modality in aphasia rehabilitation following stroke [56]. Although many speech language therapeutic approaches are being applied for clinical practice, current evidence is lacking to draw any conclusion regarding the effectiveness of a specific speech language therapy approach [57].

The recent development of neuroimaging allows the investigation of brain connectivity in language and neuroplastic changes during aphasia recovery. Recovery from aphasia is a process of reorganization and neuroplasticity in the complex language network, and initial severity and recovery potential depend on the extent of damage to the bi-hemispheric functional network [58, 59]. TDCS can modulate the excitability of cortical regions that are connected with specific language networks involved in aphasia, and can enhance the reorganization process leading to better recovery [60]. Promising results from some studies using TDCS have been reported in post-stroke aphasia patients.

Currently, TDCS for aphasia therapy has been based on the pattern of reorganization. One strategy is to recruit peri-lesional area by increasing the excitability using anodal TDCS. Another strategy is to recruit right unaffected homologous cortical area using anodal TDCS (when they are beneficial and subserve some language function), or inhibit right homologous cortical area using cathodal TDCS, when they are deleterious and exerting increased inhibitory influence on left cortical area, impeding functional recovery of peri-lesional reorganization [61, 62].

Restoration of the original activation pattern within the preserved language network seems to be the most effective strategy toward good aphasia recovery and a satisfactory recovery can be expected if peri-lesional areas are activated. In a sham-controlled crossover study, five sessions of anodal TDCS over the left hemisphere that was activated during picture-naming task on an fMRI demonstrated more improvement than sham TDCS [63]. Fridriksson et al. got similar results in a double-blind, sham-controlled study, showing reduced reaction time during naming task after anodal TDCS [64]. However, Polanowska et al. recruited early-phase Broca's aphasia patients and delivered 15 consecutive sessions of anodal TDCS or sham TDCS on Broca's area, followed by 45 min of speech language therapy. The authors did not show beneficial effect of anodal TDCS over sham TDCS [65]. Monti et al. also failed to demonstrate the positive effect of anodal TDCS over the left frontotemporal area on post-stroke aphasia. In their study, cathodal TDCS over lesioned hemisphere rather than anodal TDCS showed positive results [65].

Anodal TDCS can be applied to the healthy hemisphere when recruitment or disinhibition of homotopic language areas in the non-dominant hemisphere seems to be beneficial. Vines et al. pursued this approach and showed that combining anodal TDCS with melodic intonation therapy further induced recovery from post-stroke aphasia [66].

Previous reports have documented increased activation in right frontal areas during the performance of various language tasks in non-fluent aphasia, and this increased activation might be the consequence of a loss of active interhemispheric inhibition from homologous regions in the lesioned hemisphere [67].

Along with this line, the effect of inhibitory cathodal TDCS over the right hemisphere on post-stroke aphasia has been studied. Kang et al. investigated whether inhibitory cathodal TDCS over the contra-lesional right Broca's homologue area could enhance picture naming in aphasia after stroke [65]. Ten right-handed patients received an intervention of cathodal TDCS (2 mA for 20 min) and of sham TDCS (2 mA for 1 min) for 5 consecutive days in a crossover design combined with simultaneous conventional speech therapy. Picture-naming performance was improved after cathodal TDCS, but no significant changes were found after sham TDCS. The authors further investigated the factors associated with better responses to TDCS combined with speech therapy in 37 post-stroke aphasia patients [68]. Ten sessions of speech therapy for 30 min over 2–3 weeks were applied and cathodal TDCS over the Broca's homologous area in unaffected hemisphere with 1 mA for 20 min was combined during speech therapy. After this intervention, significant improvement in aphasia quotient was observed and patients with less severe (over 10 % in the aphasia quotient) and fluent type of aphasia showed greater improvement.

A recent Cochrane meta-analysis reviewed six studies using TDCS for enhancing recovery from aphasia in stroke patients [69]. They concluded that currently there is no evidence of the

effectiveness of either anodal or cathodal TDCS when correct picture naming was used as an outcome, although it appears that cathodal TDCS over the non-lesioned hemisphere might be a more promising approach.

Dysphagia

Dysphagia is a common impairment after stroke. Reported incidences are widely discrepant, ranging from 19 to 81 % depending on the definition, time, and assessment tool [70]. Post-stroke dysphagia has been known to increase the risk of aspiration pneumonia and mortality [71]. Current management for post-stroke dysphagia includes diet and fluid modifications, compensatory maneuvers, position changes, and rehabilitation exercises [65].

Reorganization of the swallowing motor cortex after stroke is associated with recovery from dysphagia [72]. TDCS is expected to play a role to enhance the swallowing motor cortex reorganization after stroke. Swallowing is a neuromuscular process dually innervated by both hemispheres. It has been proposed that activation of contra-lesional hemispheric projections may be beneficial for dysphagia recovery after stroke [65]. However, it is still controversial whether the stimulation of lesional vs. the contra-lesional hemisphere is more beneficial [65].

In one small pilot study, anodal TDCS over the sensorimotor cortex in the unaffected hemisphere representing the swallowing muscles was applied to 14 patients with subacute unilateral cortical infarction, over the course of 5 consecutive days associated with concurrent standardized swallowing therapy [65]. This intervention showed a transient improvement in swallowing function. Jafferson et al. showed that anodal TDCS increased the excitability of pharyngeal motor cortex in an intensity-dependent manner, with little influence on trans-callosal spread [73].

Yang et al. also investigated the effects of TDCS combined with conventional swallowing therapy on dysphagia after stroke [74]. Sixteen patients received anodal (1 mA for 20 min) or sham TDCS over the pharyngeal motor cortex in the affected hemisphere during 30 min of conventional swallowing training for 10 days. Greater improvement after anodal TDCS was observed compared to the sham group at 3 months post-intervention, after controlling for age, initial stroke severity, lesion size, baseline dysphagia score, and time from stroke onset. Shigematsu et al. also showed similar results in post-stroke dysphagia patients [75].

Pisegna et al. recently published a meta-analysis result of NIBS (four rTMS and three TDCS studies) for post-stroke dysphagia [65]. In this meta-analysis, NIBS showed a significant moderate pooled effect size and studies stimulating the unlesioned hemisphere showed a better effect size compared to those stimulating the lesioned hemisphere.

Cognitive Decline

Cognitive decline after stroke is common and gives a substantial burden to patient's caregivers and society [76]. Therefore, effective rehabilitative intervention to improve cognitive function such as attention and memory is crucial.

Recently, in the field of cognitive rehabilitation after stroke, TDCS has been investigated as a new therapeutic tool to improve attention and working memory. Kang et al. [77] demonstrated that anodal TDCS over the left dorsolateral prefrontal cortex (DLPFC) improves attention in stroke patients. This suggests that TDCS could potentially be used during concurrent rehabilitative training to improve attention. Another randomized crossover trial showed that cathodal TDCS over unaffected primary motor area could improve the selective attention measured by the Stroop interference test in chronic stroke patients [65]. For memory improvement, a small sample-sized single-blind randomized crossover trial showed that anodal TDCS over DLPFC improved accuracy in a two-back working memory task in stroke patients [65].

These small pilot studies using TDCS for cognitive decline after stroke showed promising results, but further studies with larger sample size are required.

Spasticity

Spasticity is defined as "a velocity-dependent increase in tonic stretch reflexes or muscle tone with exaggerated tendon jerks as one of components of the upper motor neuron syndrome" [78]. Spasticity occurs during the recovery stage after stroke and the prevalence at 12 months after stroke reaches about 38 % [79]. Post-stroke spasticity is associated with poor motor recovery, activity limitations, pain, and contractures [65]. Non-pharmacological interventions including stretching, splint, and heat or cold modalities can be applied as a first-line therapy, but the effect may be temporary and may not be effective in some cases. Pharmacological intervention with oral medications can be used for general spasticity but side effects or possible harmful effects for neuroplasticity should also be considered [80]. Therefore, TDCS has a room for therapeutic application for post-stroke spasticity by modulating the cortical activity and hence decreasing the muscle tone.

Only two TDCS studies for post-stroke spasticity have been reported. Wu et al. conducted a sham-controlled randomized trial with 90 stroke patients with spasticity [65]. Patients received cathodal ($n=45$) or sham stimulation ($n=45$) over the affected primary sensory motor cortex, 20 min per day, 5 days per week, for 4 weeks along with conventional physical therapy. Significantly more patients in the cathodal TDCS group showed a clinically important difference after treatment. In a randomized, double-blinded, crossover study of Ochi et al.[81], 18 chronic stroke patients with moderate-to-severe arm impairments were allocated to either anodal TDCS over the affected hemisphere or cathodal TDCS over the unaffected hemisphere along with the robot-assisted arm training. Both interventions showed significant improvements in spasticity measured by modified Ashworth scale.

Post-stroke Depression

Post-stroke depression (PSD) is common and prevalence varies from 15 to 30 % according to the population characteristics and time from stroke onset [65]. PSD is a strong predictor for poor functional recovery [65]. PSD is usually responsive to pharmacologic treatments with serotonin reuptake inhibitors such as citalopram [82] but there are some cases that are refractory to medications.

TDCS can be a potential useful modality to treat this refractory PSD, considering the positive effect in previous major depression studies [83], lower side effect profile [83], and more immediate effect than a serotonin reuptake inhibitor [84]. However, randomized clinical trials using TDCS for PSD have not been reported yet. Only one case report demonstrated the improvement of PSD after anodal TDCS over the left DLPFC (2 mA for 30 min for 10 days) [85]. Further pilot studies for PSD are needed.

Central Post-stroke Pain

Central post-stroke pain (CPSP) is a chronic neuropathic pain, persisting more than 3 months, after stroke [86]. CPSP can develop immediately or years after stroke onset and the prevalence at 6 months and 1 year after stroke is 2.7–25 % [87, 88]. Pharmacological intervention using tricyclic antidepressants, pregabalin, or opioid analgesics can be approached, but its effect is usually limited and lack in clinical evidence [89].

One hypothesis for development of CPSP is a disorder of brain network reorganization after stroke [90]. Therefore, TDCS, applied to modulate the brain network, can be a potential application for CPSP refractory to pharmacological treatments. Although high-frequency rTMS over the primary motor cortex showed a short-term benefit on pain after single-session application [91] and guidelines published by European Federation of Neurological Societies commented a transient reduction in pain after rTMS in central neuropathic pain (Level B recommendation) [92], evidence of effectiveness of TDCS on CPSP is still lacking. A recent Cochrane review demonstrated that TDCS over the primary motor cortex could not reduce the pain in various neuropathic conditions including CPSP [91].

Conclusions

TDCS can enhance the recovery from various impairments after stroke in combination with preexisting conventional rehabilitation approaches, through the modulation of brain activity and connectivity. Portability, safety, and easy applicability enable the TDCS to be applied more widely than other brain stimulation techniques in the stroke rehabilitation. To maximize the beneficial effect of TDCS, more researches to establish optimal stimulation protocols in terms of parameters according to the different impairments and reorganization patterns after stroke are required.

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Transcranial Direct Current Stimulation in Disorders of Consciousness

21

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Abstract

Transcranial direct current stimulation (tDCS), a noninvasive cortical stimulation modulating cortical excitability, has been previously reported to transiently improve working memory and attention by stimulating the left dorsolateral prefrontal cortex (DLPF) in patients with stroke as well as Parkinson's and Alzheimer's disease. As regards disorders of consciousness (DOC), we have recently shown that a single session of tDCS over the left DLPFC can improve sign of consciousness in about 43 % of patients in minimally conscious state (MCS). The transient clinical improvement observed in patients in MCS following tDCS seem to require residual grey matter and metabolic activity in the stimulated area and in structures known to be involved in awareness and arousal, such as the precuneus and the thalamus. These findings suggest that tDCS might be a feasible treatment to promote recovery of new signs of consciousness in patients with DOC. Nevertheless, it also suggests that some patients may be more suited to benefit from tDCS than others. Apart from clinical treatment, tDCS combined with transcranial magnetic stimulation has been shown to induce different responses in terms of connectivity and excitability in MCS as compared with unresponsive patients.

Although tDCS on patients with DOC has not been yet fully investigated, the so far reported studies have revealed promising results as regards improvement of signs of consciousness.

We here provide an overview of the tDCS studies on patients with DOC.

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Introduction

Definition of Disorders of Consciousness (DOC)

Various definitions of consciousness have been so far proposed by scientists, neuroscientists, or philosophers. Nevertheless, a universally accepted definition has not been yet agreed. As such, it is widely accepted that consciousness is a multicomponent term involving a series of cognitive processes such as attention and memory [1, 2]. At the bedside, mainly for scientific purposes and didactical reasons, consciousness has been oversimplified into two main components: arousal and awareness. Arousal (also referred to as vigilance or wakefulness) is necessary to experience awareness and has been considered as the level of consciousness. Anatomically it is related to structures in the brainstem, and it is clinically evidenced by opening of the eyes [3]. Awareness refers to the ability to live experiences of any kind and has been felt to represent the content of consciousness [4]. Awareness itself has been subclassified into internal awareness (i.e., awareness of self) and external awareness (i.e., awareness of the environment). At present there is no singular marker of awareness, but its presence can be clinically deduced from a range of behaviors and motor outputs (e.g., responses to command, visual pursuit) which indicate that an individual can perceive self and surroundings [5]. From the anatomic point of view, internal awareness is related to midline frontoparietal regions such as the mesioprefrontal cortex (MPFC)/anterior cingulate cortex (ACC) and precuneus/posterior cingulate cortex (PCC). External awareness seems to depend on lateral frontoparietal regions [6, 7]. Functional connectivity within these networks and between these networks and the thalamus has shown to be important for consciousness sustainment [8].

Patients in coma are neither awake nor aware [9]. This condition is self-limited and usually cannot last longer than 4 weeks, after which patients either evolve to brain death (i.e., permanent loss of brainstem functions) or recover consciousness or evolve to a vegetative state, recently termed also unresponsive wakefulness syndrome (VS/UWS) [10]. Patients in VS/UWS are awake but they are unaware of themselves and their surroundings, hence exhibit only reflex behaviors [11]. When patients regain minimal and fluctuating signs of awareness, not encompassing the ability to communicate consistently, they are considered in minimally conscious state (MCS) [12]. Based on their capacity to follow commands, MCS patients have been further classified in MCS– and MCS+ [13]. Patients who recover a level of consciousness sufficient for functional communication and/or object use are referred to as emerging from minimally conscious state (EMCS). The boundaries between these different states of consciousness are not always sharp but often are progressive transitions. The gradual transition from coma to recovery is illustrated in Fig. 21.1.

Current Treatment and Limitations in Patients with Disorders of Consciousness (DOC)

Clinical management of patients in VS/UWS and MCS is particularly challenging as this population is susceptible to misdiagnosis [15, 16] and lacks effective treatment options [17].

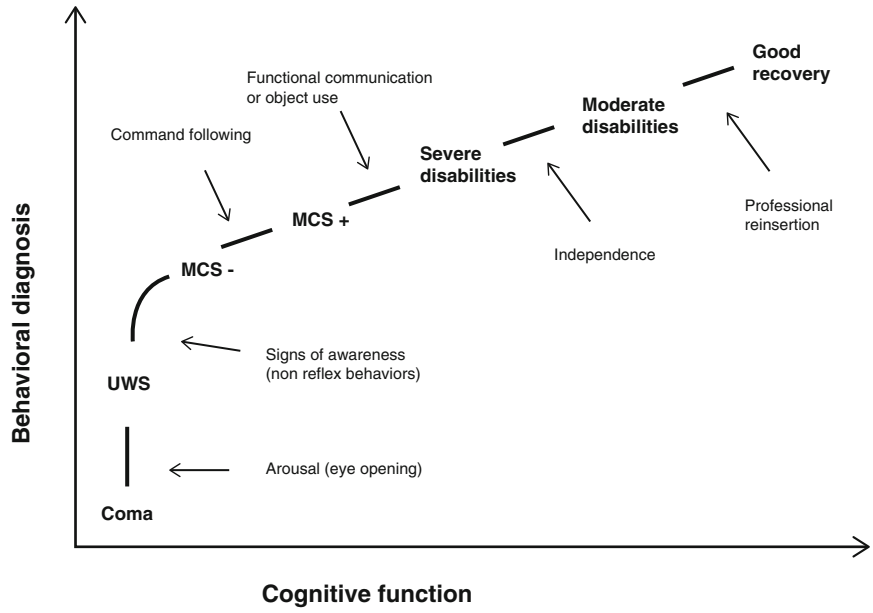

Fig. 21.1 Different clinical entities encountered on the gradual recovery from coma, illustrated as a function of cognitive and motor capacity. Restoration of spontaneous or elicited eye-opening, in the absence of voluntary motor activity, marks the transition from coma to unresponsive wakefulness syndrome (UWS). The passage from the UWS to the minimally conscious state minus (MCS−) is marked by reproducible evidence of "voluntary behavior." Simple command following characterizes the MCS plus (MCS+). Emergence from MCS is signalled by the return of functional communication or object use. Adapted from ref. [14]

The gold standard for the diagnosis of this population is the clinical evaluation through use of standardized and sensitive clinical scales such as the Coma Recovery Scale-Revised (CRS-R) [18]. Through behavioral assessment we can evaluate motor responsiveness and we only indirectly deduce the consciousness level. But the lack of motor responsiveness does not necessarily implies the lack of consciousness, as patients can suffer from different disabilities impairing their responsiveness, such as paralysis, aphasia, and fluctuation in arousal level [15, 19].

Advances in neurophysiology and neuroimaging techniques witnessed in the last decade can now offer the possibility to overcome the limits of the clinical assessment in the detection of possible retained consciousness in unresponsive patients.

A proper diagnosis in this patients' population is imperative, especially if one considers that a misdiagnosis may contribute to premature withdrawal of life-sustaining care and lead to inappropriate medical management such as neglect of pain treatment [17]. Indeed, an accurate diagnosis would have a strong impact on the quality of life and rehabilitation of the patient. For example, failure to detect sign of consciousness may limit access to specialized neuro-rehabilitation centers and, therefore, somehow decrease patients' possibilities to recover.

While several studies have focused on improving the diagnosis of these patients, to date only a few studies have investigated treatment options in order to improve their rehabilitation and their quality of life. At present, there are no evidence-based guidelines regarding the treatment of patients with DOC [17]. Until recently, the medical community has viewed patients in VS/UWS and MCS with great pessimism regarding both prognosis and effective treatments. Unfortunately, this pessimism results in the negligence of patients, especially in the chronic stage, in terms of health care as no improvement is expected. Nevertheless, in the past 10 years a number of

studies have reported that some patients in MCS could improve even several years after the insult [19, 20] and several treatments can enhance signs of consciousness [21–23].

So far, there are no universally accepted drug options to treat these patients. As regards pharmacological agents, some studies have shown that amantadine [22], apomorphine [25], intrathecal baclofen [26], and zolpidem [27] can sometimes improve behavioral signs of consciousness in patients with DOC (see Table 21.1). However, only amantadine has been shown to increase signs of consciousness in a large cohort of acute and subacute patients with DOC in a placebo-controlled trial [22]. One of the most common adverse effects of this drug is the occurrence of epileptic seizures, which can be extremely frequent in this population and can significantly affect their cognitive state [28]. Moreover, the mechanisms underlying the recovery of behavioral signs of consciousness observed in some patients with DOC following the administration of these drugs are still poorly understood.

Zolpidem, a selective beta agonist, has shown to be impressively efficient, inducing the recovery of communication or functional use of objects in patients in MCS (i.e., emergence from MCS). Nevertheless, an extremely low percentage of patients benefit from this drug and so far its mechanism of action and the reason why only a few subject respond to it needs still to be elucidated [23, 28, 29].

As regards neurophysiological treatment, deep brain stimulation (stimulation of the intralaminar

Table 21.1 Main studies using amantadine, apomorphin, baclofen, or zolpidem treatment in patients with disorders of consciousness

Authors	Drug	Design	*N* (etiology)	Time since injury	Results
Giacino et al. [22]	Amantadine (antiviral and an anti-parkinsonian; NMDA antagonist and indirect dopamine agonist)	Prospective, multicentric, randomized, double-blind, placebo-controlled	184 (TBI)	1–3 months	Amantadine group: faster recovery; decrease of DRS scores and increase of behavioral bench markers on the CRS-R
Fridman et al. [25]	Apomorphine (dopamine agonist used in Parkinson disease)	Prospective case series	8 (TBI)	1–4 months	Functional recovery with decrease of the CNC, DRS and increase of GOS scores
Whyte and Myers [24]	Zolpidem (nonbenzodiazepine GABA agonist hypnotic used to treat insomnia)	Mutlicentric, double-blind, randomized study	15 (8 TBI)	3 months to 23 years	1 responder (UWS to MCS+); increase in CRS-R score, visual pursuit, response to command
Thonnard et al. [27]	Zolpidem	Open label study	60 (31 TBI)	2 months to 26 years	12 patients showed improvement in CRS-R scores. Change of diagnosis in 1 patient (from MCS+ to EMCS)
Sara et al. [26]	Baclofen (GABA agonist used to decrease spasticity)	Case report	5 (2 TBI)	6–10 months	Clinical improvement in all patients after 2 weeks (increase in CRS-R scores)

DRS disability rating scale, *CRS-R* Coma Recovery Scale, *CNC* Coma/Near-Coma Scale, *GOS* Glasgow Coma Scale, *NMDA N*-methyl-D-aspartate, *GABA* γ-aminobutyric acid, *TBI* traumatic brain injury, *UWS* unresponsive wakefulness syndrome, *MCS* minimally conscious state, *EMCS* emergence from MCS

nuclei of the thalamus) [23] has shown to improve signs of consciousness in patients in MCS. However, this technique is invasive and did not induce such a clinical improvement to progress into a different clinical diagnostic entity [30].

Transcranial direct current stimulation (tDCS) is a form of cortical stimulation which has shown to improve recovery in several disabling neurological pathologies, such as Parkinson's, Alzheimer disease, stroke, and traumatic brain injury [31]. tDCS is noninvasive, safe, inexpensive, easy to carry out device and, importantly, it does not induce seizure or severe side effects as observed with Amantadine or deep brain stimulation.

tDCS in Disorders of Consciousness (DOC)

Pilot Studies

Several studies have shown that a single anodal stimulation of a damaged cortical area in post stroke or TBI patients can improve the function of the stimulated area. An anodal session of tDCS over the motor cortex (M1) can enhance motor function [32, 33]. Likewise the stimulation of the prefrontal cortex has shown positive effects on memory [34, 35, 36] and attention [37]. Given the abovementioned encouraging results showing enhancement of motor and cognitive functions following tDCS, we decided to test its efficacy on behavioral recovery in patients suffering from DOC [37, 38].

In a first pilot study, we aimed to test the effect of prefrontal tDCS on patients with DOC, both VS/UWS and MCS, acute-subacute (<3 months) and chronic, and with traumatic and nontraumatic etiologies. We assessed the effect of a single session of anodal tDCS of the left DLPF cortex on consciousness, as evaluated by means of the Coma Recovery Scale-Revise [18], known to be, to date, the most sensitive scale for behavioral assessment in patients with DOC. Fifty-five patients with DOC were recruited to receive both anodal and sham tDCS in a crossover study design: 25 in VS/UWS (age: 42 ± 17 years; nine women; interval since insult: 24 ± 48 months; 6 posttraumatic) and 30 in MCS (age: 43 ± 19 years; seven women; interval since insult: 43 ± 63 months; 19 posttraumatic). During tDCS, the current was increased to 2 mA from the onset of stimulation and applied for 20 min. Treatment effect was assessed by means of standardized CRS-R [18].

At the individual level, tDCS responders were defined as those patients who presented a sign of consciousness (i.e., command following; visual pursuit; recognition, manipulation, localization, or functional use of objects; orientation to pain; intentional or functional communication; after tDCS that was not present before anodal nor before or after sham tDCS sessions).

At group level, a treatment effect was observed in the MCS ($p = 0.003$) but not in the VS/UWS ($p = 0.952$) patients' group (Fig. 21.2).

At individual level, 13/30 (43%) patients in MCS showed a tDCS-related improvement (i.e., showed a clinical sign of consciousness never observed before). Two acute (<3 months) patients in VS/UWS out of 25 (8%) showed a tDCS response (i.e., showed command following and visual pursuit present after the anodal stimulation not present at baseline or pre- or post-sham tDCS). In addition, no tDCS related side effects were observed.

These results have shown that a single session of left DLPF tDCS may transiently improve CRS-R scores in patients in MCS in the absence of side effects, suggesting a residual capacity for neural plasticity and temporary recovery of (minimal) signs of consciousness in some patients in MCS. These findings appear of critical importance especially if one considers there are limited evidence-based pharmacological or nonpharmacological treatment options for severely brain-damaged patients with DOC, and particularly in the chronic setting [16, 40]. Indeed, in this study, out of the 13 patients in MCS who showed a tDCS response, five were included >12 months (115 ± 101 months) after the acute insult. This suggests that chronic MCS patients, even years after the brain injury, have still the ability to improve and recover some new signs of consciousness. On the other hand, no improvements were observed in

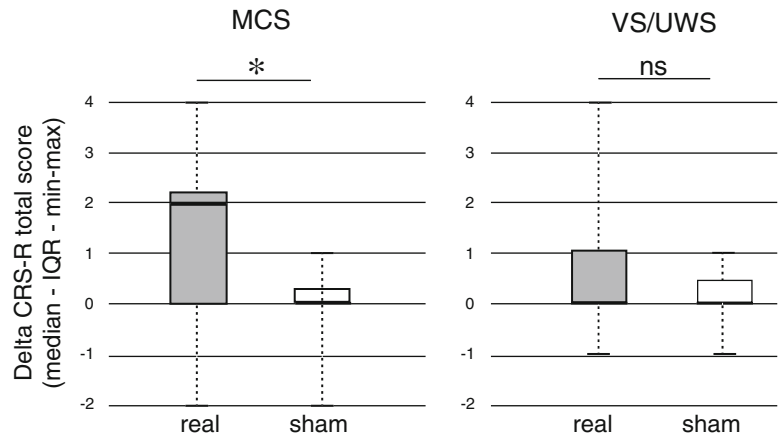

Fig. 21.2 Median (*black line*) of Coma Recovery Scale-Revised (CRS-R) total scores delta (i.e., CRS-R post tDCS minus CRS-R pre tDCS) and interquartile range for patients (IQR, *boxes*) in minimally conscious state (MCS) and unresponsive wakefulness syndrome/vegetative state (VS/UWS), with minimal and maximal values. In *grey*, the results for the real tDCS and in with the sham tDCS. An *asterisk* denotes statistical significance at $p < 0.05$ and NS stands for nonsignificant. From ref. [38]

patients in VS/UWS, in line with previous studies showing capacity for neural plasticity in patients in MCS rather than VS/UWS [41].

The main limit of this study is the short term beneficial effect of the tDCS. Indeed, behavioral improvements were observed for not longer than 2 h from the stimulation. As in daily clinical practice longer effects are required, studies using repeated tDCS sessions are warranted to elucidate whether this technique might be a feasible treatment in clinical practice.

In another study five repeated tDCS sessions (one daily) were performed on patients with DOC [39]. Ten patients with DOC were included (age range: 19–62; three women, duration since insult: 6 m to 10 years; five post-traumatic). All patients received sham tDCS for 20 min per day, 5 days per week, for 1 week, and real tDCS for 20 min per day, 5 days per week, for 2 weeks. An anodal electrode was placed over the left primary sensorimotor cortex (2 MCS − 3 VS/UWS) or the left DLPF cortex (1 MCS − 4 VS/UWS), with cathodal stimulation over the right eyebrow. Improvements were assessed with the CRS-R.

All patients in MCS showed clinical improvement immediately after tDCS session. Only one patient in MCS received tDCS over the left DLPF cortex, as well as four patients in VS/UWS. The MCS patient who received tDCS over the left DLPF cortex showed a behavioral improvement (i.e., recovery of localization to pain). One patient who received the primary sensorimotor stimulation and was in an MCS for 1 year before treatment (postoperative infarct) emerged from MCS at 12-month follow-up. No effects on patients in VS/UWS were observed.

Taken together, the above described studies suggest that tDCS, on both left DLPF (MCS, n = 31) and primary sensorimotor cortex stimulation (MCS, n = 4), might be a promising tool in the rehabilitation of patients in MCS. Nevertheless, future studies are warranted to investigate the long-term effect of the repeated tDCS session, as they required by clinical practice.

In this context it is worth to stress that tDCS seems to be a safe device. Indeed, in a total of 65 patients (both MCS and VS/UWS) included in the two studies no severe side effects were observed, even considering that many of these patients had severe brain injuries with widespread lesion possibly involving the stimulated areas. Moreover, although it is well know that brain injured patients are more vulnerable to epileptic seizure, and some of them were even under an epileptic

treatment due to previous seizures, no seizures as side effects were observed. With the limits of a small population, the abovementioned findings suggest that tDCS can be safely used in the treatment of patients with severe brain injury and DOC.

Neuronal Correlates of tDCS in DOC

The mechanisms of action of tDCS remain only partly understood and several clinical trials have shown that the proportion of tDCS responders may vary from 40 to 80 % [41–44]. Concerning patients with DOC, we recently reported that left DLPF tDCS could improve signs of consciousness in 43 % of patients in MCS [38]. If these findings suggest the potential interest of tDCS as a treatment for DOC, they also highlight the lack of a clinical improvement following tDCS in more than half of the patient population. The natural step was, therefore, to define the structural and functional brain features of those patients that are likely to respond to tDCS [45].

Using multimodal neuroimaging analyses, including fludeoxyglucose positron emission tomography (FDG-PET) and magnetic resonance imaging (MRI), the previously described subgroup of tDCS responders [38] has been characterized. Out of the 21 patients in MCS that were included in the analyses, eight were tDCS responder (four posttraumatic, four nontraumatic, four men) and 13 were nonresponder (eight posttraumatic, five nontraumatic, ten men).

A common pattern of metabolic preservation (as detected by FDG-PET) and grey matter preservation (as detected by MRI), was observed in tDCS responders as compared with nonresponders, whilst no specific behavioral patterns of improvement among the patients who showed clinical improvement following left DLPF cortex tDCS could be detected. The transient improvement of signs of consciousness following tDCS seemed to require grey matter integrity and/or residual metabolic activity in three brain regions: (a) the presumed stimulated area (i.e., left DLPF cortex), (b) long distance cortical areas such as the precuneus, and (c) subcortical brain areas known to be involved conscious processes (i.e., thalamus) see Fig. 21.3.

tDCS as a Diagnostic Tool

It has been recently shown that tDCS could also be used as a diagnostic tool to differentiate MCS from VS/UWS patients [47]. In a recent study, cortical connectivity and excitability were assessed by means of dual-site TMS approach [48]. More specifically the authors recorded resting motor threshold, motor evoked potential amplitude and latency, central conduction time, intracortical facilitation and short-interval inhibition, as well as interregional interactions between left primary motor cortex (M1) and right dorsal premotor cortex (PMd) and pre-supplementary motor area (SMA). After the first testing, tDCS (real or sham) was applied over the orbitofrontal cortex (anode between Fp1 and Fp2 and cathode over Cz, according to the 10–20 international system). TMS was performed 60 min after tDCS, as well as 60 min later.

Behaviorally, no patients showed any CRS-R scoring changes after tDCS. The results showed an increase in MEP amplitude, an intracortical facilitation, and a premotor–motor inhibition reduction in MCS. Concerning VS/UWS patients, tDCS had no effects on three patients out of seven, whereas it induced a reduction of premotor–motor inhibition and a partial increase of M1 excitability in the remaining four. Here, a correlation between CRS-R total score and premotor–motor connectivity and M1 excitability modulation was also observed.

The authors suggested that the four patients who were diagnosed as being in VS/UWS but showed an increase in cortical connectivity and excitability had actually covert consciousness not detected by the clinical exam, as previously reported in the literature [49–51].

This study shows that tDCS can detect residual connectivity in clinically VS/UWS patients, who may sub sequentially recover behavioral signs of consciousness, suggesting an added prognostic value.

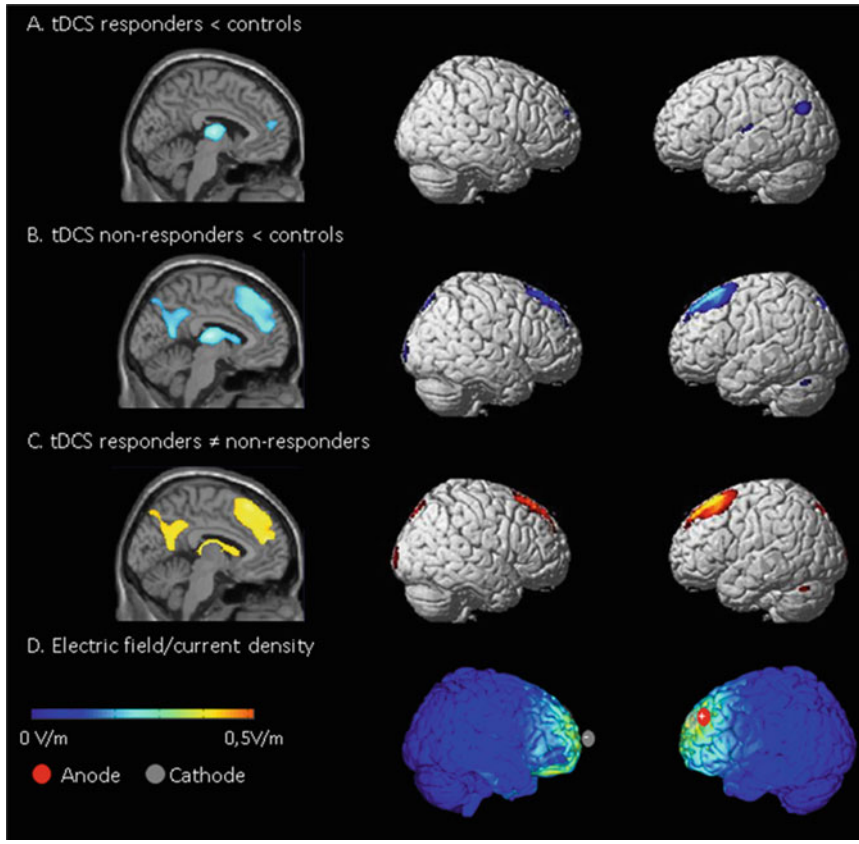

Fig. 21.3 Positron emission tomography (PET): Brain areas showing hypometabolism (in *blue*), as compared to controls, in patients in a minimally conscious state (FEW corrected): (**a**) eight tDCS-responders and (**b**) 13 nonresponders. (**c**) Regions with less hypometabolism in responders as compared to nonresponders (in *red*). (**d**) Theoretical tDCS induced electric fields. Note that behavioral responsiveness to short duration left dorsolateral prefrontal cortex (DLPFC) tDCS correlates with less impaired metabolism in the areas presumed to be stimulated by tDCS (left DLPFC and mesiofrontal cortices) but also of distant cortical (precuneus) and subcortical (thalamus) regions. From [46]

Long-Term Effects

tDCS long-term effects are required in order to be used in a daily clinical practice. In this context, several sessions of tDCS may be required in order to achieve the desired effect. A study of repeated tDCS over the primary motor cortex in healthy volunteers highlighted a consolidation mechanism which lasted up to 3 months after five tDCS sessions [52]. Unfortunately, not enough comparable multiple-day stimulation studies have been carried out to assess whether repeated tDCS sessions could be efficient at improving motor or cognitive skills in healthy volunteers. Nevertheless, in neurological patients with motor or cognitive deficits, tDCS has shown positive effects that last several weeks or even months when the stimulation is repeated for 5 or 10 consecutive days. Based on the abovesaid, we believe that repeated stimulation might be required to induce reliable improvements that could warrant its implementation in clinical daily practice.

Our next challenge is, therefore, to test the effects of repeated stimulation sessions on DOC

patients carried out 5 days consecutively and to evaluate the benefits, in terms of CRS-R, a week from the end of the stimulations. This would elucidate whether tDCS could be used as a therapeutic tool on a daily basis in clinical practice, in rehabilitation centers, nursing homes or even at the patient's home. Moreover, it would demonstrate whether an increased number of stimulations could also enhance the beneficial effect (as measured by effect size) and increase the number of patients who respond to the treatment.

Conclusions and Future Directions

In this chapter we describe the potential therapeutic effects of tDCS on patients with DOC. We show that almost half of the patients in MCS had behavioral improvement after a single stimulation. We also identify that the transient increase of signs of consciousness in patients with DOC upon tDCS requires residual metabolic activity and grey matter preservation in cortical and subcortical brain areas important for consciousness recovery (i.e., left DLPF cortex, precuneus, and thalamus) [46]. Moreover, tDCS, coupled with TMS, has also shown to be able to differentiate MCS from VS/UWS patients. Most importantly, tDCS has shown to be a handy and safe and feasible device, also when applied on patients with DOC.

Even though these first findings seem encouraging, further studies are required in order to investigate the long-term effect of tDCS in this population of patients. A first step would be to perform repeated stimulation sessions in addition to the previously described protocol (i.e., left DLPF tDCS). Furthermore, assessing the tDCS long-term effects would elucidate the duration of its effects and whether it might be a feasible device in the daily clinical practice.

Different areas of stimulations should also be tested according to patients' cortical damage. Indeed, we have recently shown that DOC patients need a partial preservation of the stimulated area to respond to tDCS. Consequentially, a stimulation of a (partially) preserved area would be more effective than stimulating a damaged brain region.

Neuroimaging acquisition before and after a tDCS session should be carried out in order to target the proper area to stimulate. This might give the opportunity (a) to investigate the effect of tDCS on patients' cortical activity and excitability, (b) to reveal the differences between responders and nonresponders, and (c) to better identify the patients who could benefit from left DLPF tDCS or M1 tDCS or any other areas. The final aim is to develop a patient's tailored stimulation to give him/her the best chance to recover a certain degree of autonomy.

It should be kept on mind that although patients with DOC are, by definition, not able to communicate, they may perceive pain and retain emotional behavior [53]. Therefore, we strongly recommend to use solely parameters that have been already tested in healthy subjects or patients with neurological dysfunction (able to give a feedback), without any severe side effects being reported.

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Part III

The Clinical Use of tDCS

Safety and Tolerability

22

André Brunoni, Colleen Loo, and Michael Nitsche

Abstract

TDCS most common adverse effects are burning, tingling, itching, headache, and discomfort on the site of stimulation. These adverse effects occur in up to one-third of patients and are generally mild, short-lived, and well-tolerated. Skin redness is a common adverse effect that occurs in most patients, although skin burning is rare and often associated with repeated tDCS sessions and poor humidification of sponges. Severe adverse effects, including seizures, cardiac arrest, permanent disability and damage, have not been reported in tDCS adult trials thus so far. Regarding safety, studies indicate that the doses used clinically are much lower than necessary to induce lesions and are not associated with damage. Nonetheless, the statement that tDCS is "safe" should be tempered down considering that its adverse effects are often under-reported in most studies and the risk of induction of adverse effects in special populations (e.g., hypomanic switch in depressed patients, or seizures in patients with epilepsy) has not been sufficiently investigated yet.

Keywords

Adverse effect • Safety • Itching • Tingling • Headache • Erythema • Discomfort • Transcranial direct current stimulation • Seizure • Skin

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Introduction

Transcranial direct current stimulation has been applied increasingly in recent years to alter brain function in healthy humans and patients suffering from neurological and psychiatric diseases. Although in many papers the presence or absence of side effects is mentioned, and suggest a favorable profile, systematic data aggregation of safety data and studies primarily aimed to explore safety of the technique are rare. Correspondingly, it is important to distinguish between tolerability and safety in a strict sense. The former describes the presence of uncomfortable and unintended effects, which do not however induce structural or functional damage (e.g., tingling, and itching sensation under the electrodes), whereas the latter refers to damaging effects per se. Similarly, according to the Food and Drug Administration (FDA), an adverse effect—defined as any undesirable experience associated with the use of a medical product in a patient—can be divided into common and serious, the latter referring o patient outcome of death, life-threatening condition, hospitalization, disability or permanent damage, congenital anomaly, need of an intervention to prevent permanent impairment or damage, or other serious, important medical events (notably seizures or convulsions). In this chapter we discuss the main issues regarding safety and tolerability of tDCS.

Tolerability

Common Adverse Effects

Poreisz et al. [1] collected data from 567 tDCS sessions delivered over different cortical areas from previous studies of their group. They observed that a mild tingling sensation (70.6 %) was the most common side effect, followed by fatigue (35.3 %), itching (30.4 %), and, less frequently, headache (11.8 %), nausea (2.9 %), and insomnia (0.8 %). All side effects were mild, short-lived, and well-tolerated, and for most symptoms the rate was not different between active and sham stimulation. Brunoni et al., in a systematic review and meta-analysis, collected data from all tDCS clinical studies performed from 1998 to August 2010 [2]. Of 209 studies (172 articles, encompassing almost 4000 subjects), 56 % monitored adverse effects and, of those, 63 % reported at least one adverse effect. According to the retrieved studies, similar rates in the active vs. sham arms of the most commonly reported adverse effects were observed, namely headache, itching, burning sensation, discomfort, and tingling (Table 22.1).

Table 22.1 Adverse effects of transcranial direct current stimulation

Sensation	Active group	Sham group
Itching	46 (39.3 %)	27 (32.9 %)
Tingling	26 (22.2 %)	15 (18.3 %)
Headache	17 (14.8 %)	13 (16.2 %)
Burning sensation	10 (8.7 %)	8 (10 %)
Discomfort	12 (10.4 %)	11 (13.4 %)
Total	117 studies	82 studies

Rate of adverse effects in clinical transcranial direct current stimulation studies. Adapted from Brunoni et al., International Journal of Neuropsychopharmacology, 2011 [2]

This systematic review also showed, however, that only eight studies systematically addressed the frequency and intensity of adverse effects. In other words, almost all studies failed to systematically report the frequency and intensity of adverse effects. Although this could indicate that these effects might be benign and well tolerated, this also indicates that the prevalence of tDCS-related adverse effects is probably underestimated in literature. Therefore, the authors recommended that all tDCS clinical studies should provide estimates of the frequency and intensity of adverse effects observed.

After this study, Kessler et al. [3] evaluated side effects in 131 subjects undergoing 277 tDCS sessions, finding that sensory side effects are common, of low severity, more common in the active compared to sham tDCS and included tingling (76 %), itching (68 %), burning sensation (54 %), and pain (25 %). In this context, Russo et al. [4] assessed adverse effects and the level of comfort experienced by 149 subjects that received a total of 195 tDCS sessions in a

Table 22.2 Summary of studies evaluating common adverse effects

Author	Study design	*N*	Main adverse effects	Comments
Poreisz et al. [1]	Individual patient data	567	Tingling (71 %), fatigue (35 %), itching (30 %), headache (12 %)	Most rates were similar in active vs. sham tDCS
Brunoni et al. [2]	Meta analysis	3836	Itching (39 %), tingling (22 %), headache (15 %), burning sensation (9 %), discomfort (10 %)	Rates were nonstatistically higher in active tDCS (vs. sham)
Kessler et al. [3]	Individual patient data	277	Tingling (76 %), itching (68 %), burning (54 %), pain (25 %)	Rates were higher in active tDCS. (vs sham)
Fertonani et al. [5]	Individual patient data	693	Itchiness, pain, burning sensation, heat, pinching, iron taste, fatigue, discomfort	Frequency not described, adverse effects' intensity was associated with higher current and larger electrodes

double-blind fashion. The authors reported no serious adverse effects, overall low rate of common adverse effects and also that levels of comfort increased over time, which were discretely higher (i.e., more comfortable) for sham stimulation. Finally, Fertonani et al. [5] analyzed data from 531 subjects—693 different sessions—receiving tES (mostly tDCS, but also other forms of stimulation). Similarly to other studies, they observed that the most common effects were itchiness, pain, burning sensation, fatigue, and discomfort, which were mild, well-tolerated, and short-lived (Table 22.2).

Skin Reddening

Another common and underreported side effect is tDCS-induced erythema, i.e., the reddening of the skin that occurs after tDCS. The intensity of this adverse effect varies in patients; most of them experience only mild redness whereas a few others might have more intense skin reddening. Erythema is due to direct effects of the current on the skin, but may also arise from the physical pressure of the electrode pad, which must be strapped firmly against the skin to ensure good contact. Although not particularly uncomfortable for almost all patients, skin reddening may be a threat to adequate blinding if it occurs more frequently or persistently in the active arm, although redness is also observed after sham due to electrode pressure over the skin. The mechanisms involved in erythema induced by the current are only partially understood, but this phenomenon seems to be caused by increased blood flow in the dermal vessels that occurs as a direct result of the current application, and also probably due to the release of multiple neuropeptides by primary afferent nerves following noxious and non-noxious stimulation, with secondary release of vasoactive substances, histamine and prostaglandins [6]. In a study investigating this issue, Guarienti et al. [7] evaluated the effects of 2 mA, 30-min anodal/cathodal tDCS on skin reddening. They observed that the erythema was more prominent over the anode than the cathode, although it was mild in both conditions. The erythema was also short-lived, lasting less than 18–24 min. Moreover, erythema was less intense in subjects with darker skin color and was not influenced by gender, age, and smoking habits. Finally, the authors observed that erythema intensity was decreased by previous application of topic ketoprofen.

Parameters Associated with Adverse Effects

Several factors influence the perception and intensity of adverse effects. One factor is current intensity - higher intensities are usually associated with more adverse effects. In a systematic investigation of the threshold for perception of stimulation, Ambrus et al. [8] observed that at 0.4 mA half of subjectsreported the presence of sensation, whereas at 1 mA all subjects were able to perceive the stimulation. In addition, composition of electrolyte solution seems to play a role:

electrolyte solutions with lower NaCl concentrations (15 mM) seem to be more comfortable during tDCS than solutions with higher NaCl concentrations (220 mM) [9]. Dundas et al. [10] recommended the use of solutions with relatively low NaCl concentration, in the range 15–140 mM (i.e., of similar or lesser strength as "normal saline" (154 mM), as tDCS at these concentrations is more likely to be perceived as comfortable, requires low voltage, and still allows good conduction of current. A means to enhance tolerability might be also to apply topical anesthetics to alleviate local adverse effects associated with tDCS [9, 11].

The size of the electrodes may influence discomfort. Turi et al. [12] compared different subject groups that received tDCS with 25 or 35 cm^2-sized electrodes. When current density (averaged across the electrode surface) was kept constant, larger electrodes were associated with greater cutaneous discomfort. However, when current intensity was kept constant, there was no difference. This suggests that higher current intensity is related to more cutaneous discomfort, even when electrode size is increased to compensate. Fertonani et al. [5] in a post hoc analysis of more than 600 tES sessions suggested that both current intensity and electrode size affected discomfort. Ambrus et al. [13] observed that in contrast electrode shape does not matter in terms of perception—if both have the same surface area, standard rectangle and circular electrodes induce similar skin sensations.

Acceptability in Clinical Trials

Acceptability is a term used in controlled clinical trials to evaluate the number of dropouts that occur in the experimental treatment compared to the control intervention. Acceptability is low if dropouts occur significantly more frequently in the experimental treatment, since this suggests that the excess dropouts happened due to intolerable adverse effects. It is important to assess if a new treatment is not only effective but also well-tolerated by the patients, otherwise the intervention would only be applied to a restricted number of individuals.

Meta-analyses of tDCS randomized clinical trials that investigated this issue by collecting data from randomized, sham-controlled tDCS trials for depression found that the dropout rate of patients in the active vs. sham arms of tDCS is similar [14, 15]. These results suggest that continuous, daily application of tDCS for several days is an acceptable and tolerable procedure at least for depression studies. In fact, studies evaluating acceptability of tDCS for other neurologic and psychiatric conditions did not report a higher rate of dropouts following active stimulation [16].

Safety

Serious Adverse Effects

No serious adverse effects, according to the FDA literature, regarding tDCS have been reported in any tDCS clinical study performed from 2000 onwards, including induction of seizure, stroke, cardiac arrest, and other life-threatening events. Moreover, safety studies revealed that tDCS does not change heart rate variability at rest [17], does not increase the serum levels of neuron-specific enolase, a brain enzyme associated with neuronal death [18], and does not qualitatively alter electroencephalographic activity [19].

TDCS safety was also explored in animal studies (see Chap. 5 and Chap. 13 in this book). One important study was performed by Liebetanz et al. [20] that explored the safety limits of tDCS stimulation in rats by using increasingly larger current intensities and thereafter performing histological evaluations. The authors found that the threshold necessary to induce brain lesions in rats was 52,400 C/m^2, two orders of magnitude larger than the charge density applied in humans. Although these results cannot be directly transferred to human studies, they corroborate clinical studies showing that the technique is safe when used according to standardized parameters. Stimulation over holes or fissures of the cranial bone, which can result in an increase of current density, should however be avoided [21].

Skin Lesions

Palm et al. [22] reported five cases of skin lesions in a tDCS study on depressed patients. After 5 days of 2 mA stimulation using tap water-soaked sponges, patients presented lesions showing extensive redness and brown crusty lesions under the cathode. Lesions seemed also to be associated with high skin impedance. Frank et al. [23] reported three cases of skin lesions under the anode in patients with tinnitus. The current dose was 1.5 mA and tap water-soaked sponges were used. Rodriguez et al. [24] reported four cases of skin burn under the cathode. In these cases, saline-soaked sponges were used and the impedance was adequate. Finally, Wang et al. [25] reported a skin lesion under the cathode after a single tDCS session, using a 2 mA current and sponges soaked in 46 mM NaCl.

To conclude, skin damage caused by tDCS has been occasionally reported. It is unclear whether this adverse effect is more common under the anode or the cathode or which factors increase its risk, although it seems that tap water-soaked sponges and high impedance were more frequently associated with it—in fact, a higher impedance is observed in tap water (vs. saline) soaked sponges [26]. To avoid this side effect, Loo et al. [27] suggested some precautions such as screening patients for skin diseases and checking the skin site where the electrode is placed for lesions before each session. The authors also advised to avoid abrasion of the skin and to ask patients to report during stimulation whether tDCS induced pain; the latter may serve as a potential early indicator of risk of skin damage. This approach may not be foolproof though, Palm and colleagues noting that cutaneous sensation was not related to the development of skin lesions [26].

Safety in Neuropsychiatric Samples

Many tDCS studies were performed so far in healthy participants and not in neuropsychiatric samples, although this number is rapidly changing given the increasing number of ongoing clinical trials. In patients with clinical conditions, not only the physiologic mechanisms of tDCS should be considered, but also whether tDCS can cause specific side effects when used in a disorder. For instance, in patients with depression, some cases of hypomania/mania have been reported after tDCS treatment, although it is difficult to infer whether tDCS *caused* these symptoms or they occurred as part of the natural history of the disease [28–30] (see Chap. 5 and Chap. 13 in this book).

Anodal (excitability increasing) tDCS was never associated with seizures in healthy subjects, although this event could was reported recently in a patient [31], a 4-year old male with history of prematurity, left dominant spastic paresis and infantile spasms. He had been seizure-free for 2 years on antiepileptic medication. Anodal tDCS (1.2 mA, 20 min) was performed over the right paracentral region. Four hours after the third session of stimulation, the patient developed a partial onset seizure characterized by speech arrest, confusion, leftward eye gaze deviation, left arm clonic movements, and secondary generalization, which required administration of intravenous midazolam. The patient's lateralized semiology suggested that the seizure onset was from the frontocentral region, corresponding to the region of anodal stimulation.

Therefore, though the occurrence of seizures or other serious adverse effects is rare, extra caution may be warranted in neuropsychiatric patients and further studies assessing the safety of tDCS in patients with neuropsychiatric disorders are warranted. Nonetheless, the frequency of adverse effects in these populations is still rare.

Functional Impairment

Functional safety encompasses the induction of cognitive, behavioral, or other disturbances (particularly permanent function reductions), which are not intended by the application of tDCS. Put simply, this occurs because different brain networks interact with each other, and the enhancement of the activity of one region can

occur at the expense of a decrease in activity of another one. In one study with healthy subjects, it was shown that tDCS over the posterior parietal cortex enhanced numerical learning whereas automaticity for learned materials decreased. Vice-versa, tDCS over the dorsolateral prefrontal cortex impaired the learning process and improved automaticity [32]. Another study in depressed subjects found that a single session of bilateral tDCS over the dorsolateral prefrontal cortex impaired implicit learning acquisition compared to sham [33].

Contraindications

There are few, relative contra-indications for tDCS. As the electrodes are placed over the skin, they should not be placed directly above areas of impaired skin (including areas with chronic skin diseases) to avoid skin damage and skin burn. TDCS should also not be applied directly over areas with implanted metallic plates, to avoid heating or preferential conduction over this area. For patients with a history of previous neurosurgical procedures, neurologic malformations or brain neoplasias, it is proposed that the tDCS stimulation approach can be modeled for that individual patient—using high-definition, computational forward models based on that patient's head anatomy, reconstructed from MRI scans—to inform on the brain area that will receive most of the electrical current [34]—however, this approach has not been empirically validated. Likewise, the use of tDCS in special populations such as children and pregnant women should be carefully considered, with recommendations that lower current intensities are used in the young [35]. Finally, there is no data to support the use of tDCS beyond the standard parameters tested so far in research settings, i.e., tDCS sessions given: (a) more than twice daily; (b) more than 40 min per session or (c) using current densities above 0.125 A/m^2 [9, 11]. In such cases, the protocol should be tested first under controlled settings.

Conclusion

Within the standard parameters of use outlined above, the evidence indicates that tDCS is a well-tolerated technique, with few, mild side effects. Although tDCS is considered to be "safe," as the (battery-driven) tDCS device is limited to delivering a low-dose current which has effects on cortical excitability (though not to the extent of directly inducing action potentials), and no major or serious adverse effects for tDCS have been reported, such findings do not imply that tDCS is "universally safe" and should therefore be used without limits or controls. . First, there are no data regarding tDCS use beyond the limits commonly used in experimental setting regarding current intensity, session duration and interval between sessions. Second, it is possible that tDCS enhances activity in one brain area at the expense of decreasing activity in another brain area—for instance, in our clinical trial in which tDCS presented antidepressant effects, we also found that it prevented implicit-learning acquisition during a probabilistic classification learning task, possibly by decreasing activity in brain areas responsible for implicit memory learning [33]. In this context, it is possible that "wrong" stimulation parameters for several days may have unwanted consequences leading to maladaptive plasticity. Finally, tDCS is a relatively novel technique and longer-term follow-up studies are still warranted for fully addressing the clinical safety of tDCS.

Taken together, currently applied tDCS protocols seem to be safe, and well tolerated. This assumption does, however, not necessarily apply for any tDCS protocol, outside parameters and clinical populations tested. Thus, general statements like that "tDCS is safe" independent from protocol specifications should be avoided. Moreover, this assumption is only valid if common exclusion criteria for tDCS/noninvasive brain stimulation (metal in the head, pacemaker, no stimulation over fissures, or cranial holes, causing locally enhanced current density) are respected. Special consideration should also be given when

determining safety and tolerability in children, where parameters safely used in adults may have a different safety and tolerability profile.

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Home-Based tDCS: Design, Feasibility and Safety Considerations

23

Angelo Alonzo and Leigh Charvet

Abstract

Transcranial direct current stimulation (tDCS) utilises straightforward technology but nonetheless has the potential to be used as a treatment for a wide range of neurological and psychiatric conditions. Though modern tDCS devices are relatively recent developments, promising results from a growing number of studies and subsequent interest among clinicians and the broader public are such that manufacturers have begun marketing tDCS devices for home use. This chapter outlines the features of tDCS that position it well for such an application while also discussing the importance of a more measured approach to treatment provision and oversight. tDCS is a safe, well-tolerated procedure when administered correctly and used within established parameters but practical and safety considerations should be taken into account when delegating tDCS administration to patients. The current state of research using home-based tDCS devices is also reviewed and further, although yet to be tested, applications are noted. Whether as a stand-alone or adjunct treatment, devices that enable tDCS to be self-administered in a patient's own environment may constitute a treatment option that is more accessible, cost effective and convenient compared to clinic- or hospital-based brain stimulation treatments.

Keywords

Transcranial direct current stimulation • Device • Noninvasive • Brain stimulation • Self-administered treatment • Remote supervision • Neuromodulation • Efficacy • Safety • Feasibility

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Introduction

Over recent years, there has been a marked increase in the number of tDCS devices being marketed for home use (e.g. the Brain Stimulator; foc.us; Soterix mini-CT). Indeed, there are many features of tDCS technology and operation that lend itself to being more readily adaptable for home use compared to other non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS). However, despite its recognised potential, tDCS has as yet not been approved for any therapeutic applications and current research continues to investigate questions regarding optimal therapeutic parameters and whether there should be limits to its use. Promotion of its wider use, therefore, specifically in the context of home use, should be tempered by an awareness that tDCS is still not yet a fully realised treatment.

Nonetheless, given the burgeoning popular and commercial interest in neuromodulation techniques, a discussion on guidelines for the home use of tDCS is timely. This chapter presents factors that should be taken into account when adapting tDCS for home use particularly with regard to device design, operator training, patient safety and monitoring. While there is growing interest in testing home-based tDCS in clinical trials [1–4], recommendations here are put forward with the view that tDCS will ultimately be more widely available as a treatment option under routine clinical care and supervision.

tDCS Suitability for Home Use

tDCS is typically administered via battery-powered devices that range in dimension from the size of a hand to no greater than a small shoebox and weigh no more than 2 kg. Due to their portability, tDCS devices (including their attendant equipment—electrodes, cables and headbands) have the most potential of all brain stimulation techniques for distribution and use outside clinical centres (see Fig. 23.1 foe examples). In addition, although operation of tDCS devices is not particularly complicated, operation could be further simplified to as easy as pressing a start button as newer machines could allow all stimulation parameters (i.e., current intensity, duration and number of sessions) to be pre-programmed. This would allow clinicians to ensure that the stimulation applied is kept within standard protocols that are known to be safe and prevents patients from using the device beyond their prescribed course.

When adhering to standard stimulation parameters—typically no more than 2.5 mA and 30 min duration—repeated sessions of tDCS are known to have a benign side effects profile and are well tolerated [5–7] (also see Chap. 22 of this book that discusses safety aspects of tDCS). The most commonly reported side effects are mild to moderate tingling, itching and/or a burning but not painful sensation at the electrode sites [8] that do not normally last beyond the stimulation period. Headache, light-headedness or fatigue may occasionally be reported during or after a session but are also usually mild to moderate, transient and rarely require medication. Provided that patients follow standard operation, are made aware of common side effects, and reporting procedures and instructions for seeking help are in place should an adverse event arise, tDCS administered at home should be as safe and well tolerated as tDCS administered in research/clinical centres.

Costs of tDCS operation and equipment also compare favourably to other brain stimulation techniques. As tDCS as envisaged for home use can be self-administered, there are no costs associated with clinic staff or facilities nor costs of travelling to and from a treatment centre, which usually involves attending every weekday for at least 2 weeks. Home-based tDCS would also afford greater accessibility for patients living in remote areas or patients who are less mobile or home bound, thereby encouraging better treatment adherence. Moreover, with the cost of a home-based tDCS device and consumables not exceeding a few hundred dollars, its affordability will make it a viable option for a greater number of people as a treatment that can be purchased outright and used as needed under a clinician's supervision.

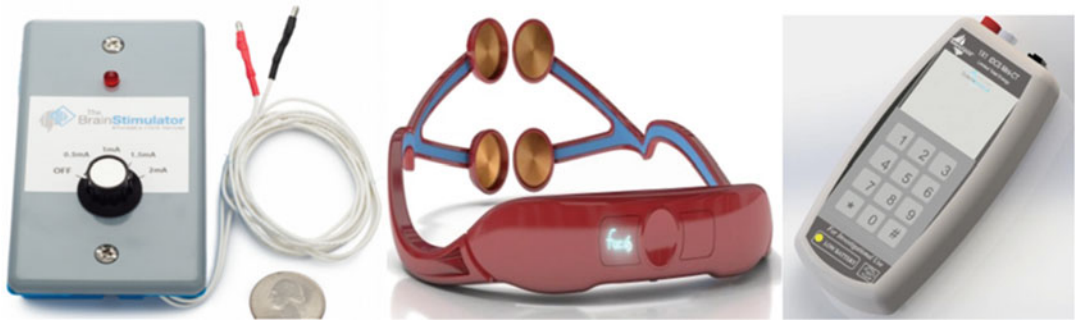

Fig. 23.1 Examples of tDCS devices developed for self-administration either autonomously or under clinical supervision

Device and Equipment Design

Until recently, tDCS devices have been primarily designed for clinician-administered stimulation within the context of a medical or research setting. However, the rapidly growing interest in home use necessitates devices that lend themselves to self-administration and take into consideration practical design issues as well as additional safety features.

All devices should meet regulatory requirements for commercial medical devices as a compromise in quality standards could lead to reduced overall safety and unanticipated side effects. Maintenance of these standards should also provide assurance that findings from clinical studies may be applicable to at-home use. Device safety features should include measures to restrict use within prescribed limits; that is, manual alterations of the intended stimulation parameters should be prevented by, for instance, locking devices to specific stimulation parameters (e.g. current intensity, duration, number of sessions) with devices programmed to deliver a stimulation session only when a single-use code is entered.

In terms of design, devices should feature large, clearly labelled buttons and cable slots for easy operation, and be accompanied by plainly written but comprehensive directions for use. The device interface should include an easily readable screen to monitor device performance with helpful readouts such as the stimulation time remaining, current intensity and impedance in real time. A dynamic impedance readout in particular will allow the user to be continuously aware of their "dose" quality and if in case of any irregularities, discontinue stimulation or make adjustments according to prescribed guidelines. For safety, it would be necessary to have a clear abort feature so that the stimulation can be safely terminated at any point by the user. As an additional safety feature, devices could also be designed to either be paused or automatically power down if abnormalities in impedance are detected. To preserve battery charge, devices should automatically shut off after a specific period of inactivity.

Headset design and electrode placement is an equally important consideration for at-home administration. Electrode placement is one of the critical determinants in achieving behavioral results [9]. If incorrectly positioned, unanticipated negative side effects may occur, including the reversing of polarity that could lead to unintentional disturbance of certain functions [10]. Headsets need to be uniform for standardised placement and adjustable for individual differences in head size and shape. Clear labels and markers on the headset can help guide correct placement.

Also important for headset design is the electrode montage to be used. Some montages would be more readily self-administered than others such as a bifrontal montage in which the user can directly see the electrode positioning in a mirror and make adjustments as needed. A montage in which electrodes need to be placed on the occipital area would be more difficult to directly check, though not impossible with, for example, the use

of a second mirror to enable a rear view. However, the electrode placement process for any montage could be facilitated by having a headset specifically designed for the montage to be used where electrodes can be fastened onto the headset at particular sites possibly standardised according to the 10–20 EEG system. Training users to identify key anatomical landmarks such as the nasion and inion as additional reference points should also assist in the relative positioning of the headset and electrodes.

Regarding electrode preparation, it would be important to have a standardised procedure for moistening the electrode sponges with saline as the recommended conducting solution. Electrode sponges that are too dry could lead to poor conductance or skin discomfort at the electrode sites while excessive moisture could lead to the current being shunted away from the intended target or unintentional weakening of the current intensity by being diffused over a wider area. To facilitate adequate moisture, sponges could be provided pre-moistened with saline and in sealed plastic until opened for use, or at the very least, the saline could be premeasured via syringe. Sponges could also be designed to indicate (e.g. by change of colour), when optimal saturation has been reached.

tDCS has a growing do-it-yourself community with many instructions for the design and use of devices already available on the Internet. These devices can be purchased directly without a prescription, training, or supervision. The potential safety concerns are apparent and their unsupervised use is not advisable given that there is an absence of safety standards with regard to prevention of device malfunction, governance to prevent overuse, and sanitary practices [11]. Some devices on the market may meet minimal manufacturing standards and/or include safety features (e.g. meters to prevent overuse) but little is known concerning their design and safety apart from information provided by the companies. Any claims for benefit are made independent of any governing oversight as there is no regulation of these devices or any certification process. The United States Federal Drug Agency does not approve or regulate the devices and it also does not verify any stated therapeutic use. For the two companies currently marketing tDCS devices directly to consumers for self-administration (i.e. the Brain Stimulator and foc.us), only one (a foc.us device) has been included in a clinical study. In this study, 24 college students were administered one session of active (1.5 mA) or sham stimulation for 20 min [12]. The active condition was well-tolerated overall but associated with significantly more uncomfortable sensations at the electrode sites (e.g. burning, tingling) than sham. Other than this initial study, the safety and tolerability of the use of these devices, and especially any clinical benefit, remains largely unknown.

Patient Selection and Contraindications

tDCS is now being trialled to treat a number of psychiatric and neurological conditions including depression [5, 13], stroke recovery [14, 15], neuropathic pain [16, 17] and auditory hallucinations in schizophrenia [18, 19] although very few studies have done so using home-based tDCS. While patient and condition specific criteria such as symptom profile, severity and comorbid conditions will determine the suitability of home-based tDCS, there are a number of common criteria that should be considered when assessing patient suitability.

The most practical consideration is the likelihood of the patient adhering to the prescribed course and capacity to self-administer or receive tDCS from a carer as failure to meet basic treatment requirements would result in suboptimal, if not ineffectual, treatment at best. Of greater concern, while there are few absolute contraindications that would preclude a patient from receiving tDCS, there should be particular note of conditions that could interfere with the normal current flow or affect the conductance. The presence of metal or implanted medical devices in the head are widely accepted as absolute contraindications as their conductivity can affect current concentrations and shunt the current away from the intended target. History of serious brain injury or neurological surgery would be considered more on a case-by-case basis depending on the location and

extent of anatomical changes as the size of skull defects could influence the distribution of peak cortical fields [20]. Other conditions such as history of headache or migraine, stroke or seizure would not necessarily be considered as absolute contraindications but may be application specific as such conditions may themselves be the target for treatment in some clinical trials of tDCS.

Special attention should also be given to any existing skin disorder and the condition of the scalp particularly at the intended electrode sites as skin burns can result from multiple tDCS sessions applied to the same scalp area if skin integrity is compromised [21, 22]. tDCS should not be applied if there are skin breakages, lesions, cuts, rashes, acne, pitting or excessive sensitivity and dryness at the electrode sites as the current may become focalised around the damaged area and potentially result in skin burns. Even using a lower current intensity to that originally intended would not be advisable as there is no guarantee that this will prevent further damage. However, as there is some degree of latitude with tDCS to slightly adjust electrode positioning without drastically changing the resultant stimulated cortical area, the electrodes could be moved if appropriate to avoid directly stimulating the affected skin.

There are no medications that are contraindicated for use with tDCS although effects of certain medications should be considered when assessing the likelihood of tDCS benefitting a patient. Benzodiazepines have been associated with a worse outcome in depressed patients receiving tDCS [23] although the exact mechanism by which they modulate tDCS effects have not been fully elucidated and could depend on a combination of factors such as their effect on GABA receptors and downstream modulation of remote cortical and subcortical areas [24]. Carbamazepine and flunarizine have been found to selectively eliminate the excitatory effects of anodal tDCS while dextromethorphane prevented induction of prolonged effects of tDCS irrespective of polarity [25]. These results suggest that any medications that affect neuroplasticity via actions on sodium and calcium channels as well as NMDA receptors, could modulate tDCS effects. However, whether or not concurrent use of such medications is permitted would depend on the intended use of tDCS as selectively eliminating or potentiating effects of anodal or cathodal tDCS could have specific beneficial applications.

Training and Credentialing

In clinical trials of tDCS, operators require training sessions with experienced staff before reaching competency in tDCS administration with most training usually focused on ensuring correct electrode placement and scalp contact. While tDCS devices developed for home-use have been designed to make electrode placement as simple and reliable a process as possible via headbands or caps to fasten the electrodes, it is nonetheless recommended that patients at least attend an initial training and credentialing session before being approved to take home a tDCS device. The purpose of such a visit would not only be to ensure that a patient can competently operate a tDCS device and safely administer tDCS but also to give the patient a working knowledge of tDCS principles and safety as well as giving an opportunity for the overseeing clinician to address aspects of the tDCS procedure and technique that may be specific to the patient.

Patients should first be given a demonstration of how the tDCS device is set up and operated, familiarising them with the device features and interface as well as use and maintenance of the associated equipment (i.e. headband, cable leads, electrodes, sponge sleeves and conducting solution). This would also include checking the equipment for wear that could affect stimulation quality such as oxidation and residue forming on the leads and tears or scratches on the electrodes.

Demonstration of the actual tDCS procedure should cover routine preparation for tDCS such as checking the scalp sites for any skin irritation or breakage, gently swabbing the skin with alcohol swabs to remove surface oils or dirt, and preparing the sponge electrodes in the conducting solution (usually saline). Correct electrode and headband placement should then be shown with particular attention on ensuring consistent positioning of the electrodes as well as maintaining firm and even

contact between the entire sponge electrode surface area and the scalp. As tDCS devices are designed to automatically run pre-programmed parameters once started, the only routine procedures for patients to follow during tDCS would be to periodically add saline to the sponge electrodes to avoid drying and maintain conductance, wipe dry any excess saline dripping from the sponge electrodes, and check the stimulation contact quality (if available via the device readout).

To formalise the training process and ensure consistent standards, a credentialing process may then be conducted to assess the patient's demonstrated competence against specific criteria, which may include items outlined below.

Skin and electrode preparation

- Parting hair to expose stimulation area and gently swabbing the skin with alcohol swabs.
- Checking skin for irritation and breakage.
- Checking equipment for wear and tear.
- Preparing sponge electrodes with the appropriate amount of conducting solution.
- Attaching the sponge electrodes onto the headband.
- Placing and securing the band on the head with the electrodes in the correct position and orientation.
- Adjusting band placement and tightness as needed.

Machine preparation

- Connecting the cable leads to the tDCS device.
- Connecting the leads to the electrodes.
- Understanding the electrode contact quality readout (if available) and adjusting the electrode and headband set-up accordingly.
- Entering the activation code to initiate stimulation.

During tDCS

- Monitoring contact quality.
- Adding appropriate amount of saline at designated intervals.
- Drying excess saline from scalp and face.

After stimulation

- Removing the headband and electrodes.
- Rinsing and cleaning electrodes.

Following satisfactory completion of training and credentialing, patients may also be supplied with a treatment diary to record the day/time of their treatment sessions and any side effects experienced. The diary should also include a procedural checklist that patients must follow and check off in sequence as they self-administer tDCS. Clinicians may also want to consider having the patient undergo their first tDCS session at the initial training/credentialing visit so that the patient is familiarised with the typical sensations of tDCS (e.g. tingling, itching) and issues relating to side effects can be immediately addressed.

Ongoing Monitoring and Oversight

Ideally, patients should continue to be under the supervision of a clinician during a course of home-based tDCS. This oversight is important for technical and safety reasons. For patients inexperienced with tDCS, even when credentialed to take a device home, there will be an ongoing learning process to streamline the placement of the tDCS headset and electrodes. Oversight and coaching via real-time monitoring can greatly assist in this learning process especially during the first few home-based tDCS sessions while ensuring the device continues to be operated correctly in the patient's home environment.

Periodic monitoring by a clinician during the tDCS course is also important to check for adverse or unintended effects of the stimulation and other possible changes in the patient's status where continued stimulation may not be advisable. Further, as stimulation may also be administered concurrently with other treatments, the monitoring process should include checking for potential unexpected interactions (e.g. with a medication) [13].

In addition to the safety issues, monitoring is recommended to determine the efficacy of stimulation. However, it may be difficult for an

individual to objectively evaluate whether their stimulation is leading to the intended effect. For example, change in mood or cognitive functioning may be difficult to determine without objective measures administered prior to starting a course and then repeated following course completion.

Patient Safety

The primary safety considerations with home-use tDCS relate to ensuring the safe administration of tDCS in the patient's home environment and their health and welfare during the treatment course. When approved to use a tDCS device at home, patients should be given a list of standard safety precautions to minimise any risk of harming themselves or damaging the tDCS device. Such a list may include the following:

- When administering tDCS, the rubber electrodes must always be covered by the sponges and never directly in contact with the scalp as this could lead to skin burns. Typical tDCS side effects such as tingling or itching should never be painful. If you feel any pain concentrated in one area, immediately abort stimulation. Remove the headband and check the skin for any redness or discolouration. Notify your treating team before proceeding any further.
- tDCS will automatically stop if the contact quality between the sponge electrodes and scalp drops to a critical level. The current intensity will quickly drop to zero and you may feel some transient light-headedness or even see a phosphene flash. These symptoms are not unusual but you must contact your treating team so that they can investigate the cause of the poor contact quality.
- Over repeated use or after rough handling of the rubber electrodes while inserting into or taking out of the sponge sleeves, the rubber electrodes may start to scratch or tear. This can lead to poor contact quality with tDCS not being able to start. At the start of each session, check the rubber electrodes for any tears and notify the treating team if any are present before proceeding any further. When inserting or removing the electrodes, always hold between the fingers and not the fingernails.
- Avoid spilling any liquids on the tDCS device. Do not use the device if it has been exposed to any liquids or is wet. Notify the treating team if this occurs.
- Ensure that the tDCS device is kept on a flat, secure surface during tDCS and avoid any sudden head movements as this could lead to pulling on the cables and causing the tDCS device to fall onto the floor.
- Do not administer tDCS over skin that is irritated or damaged including any cuts, scars, scratches or pimples as this could lead to the current becoming concentrated in one area and causing skin burns. You must notify the treating team if any of these are present at the electrode sites.

As part of the patient's treatment diary, a structured questionnaire checking for typical side effects that may arise during or after tDCS should be included with patients instructed to record the presence/absence of each side effect as well as the severity and duration. Any side effect that is rated as severe or atypical of tDCS, regardless of whether the patient feels it is related to the tDCS treatment, should be reported and assessed by the treating team before any further tDCS sessions are administered.

tDCS is a low risk procedure and is not expected to cause serious adverse events. However, guidelines that help patients to identify and document adverse events may be useful in managing any potential risks. An adverse event may be defined as any untoward medical occurrence that is temporally associated with the use of tDCS regardless of whether or not it results in the patient's hospitalisation. Any worsening of a pre-existing condition may also be considered an adverse event. Occurrence of any adverse event should be reported by the patient to the treating team and assessed before any further sessions are conducted. As patients will be receiving tDCS as a treatment for an existing psychiatric, neurological or other health condition, clear instructions should be communicated

to patients, their families and/or carers in case of an emergency. While the exact safety plan may be specific to the patient's condition, information regarding an emergency contact number and contact details for the nearest clinic or hospital should be provided in the event that the patient may not be able to obtain immediate help from their treating doctor.

Home-Based tDCS Studies

No study to date has investigated the relative efficacy of tDCS administered in a clinical setting compared to home use. Notably however, there are now a few initial studies of home-based tDCS that can potentially inform on the viability of differing approaches to how tDCS should be provided and supervised. One option is to simply provide participants with devices and directions for self-administration without ongoing training procedures or monitoring in real-time of any adverse events. One trial has reported results with this approach, using a 2-week crossover design (1.0 mA or sham) for the treatment of trigeminal neuralgia [3]. While results ($n = 17$) were promising in terms of clinical benefit (pain reduction), and no adverse events were reported, there was a high dropout rate ($n = 7$), due in part to difficulties with device use.

A second option is to study continued tDCS use after a treatment period in a clinic setting to either sustain or increase an initial clinical response. This option has less potential for safety concerns given that it would almost always be an individualized approach working directly with a clinician and repeated sessions for continuous therapy have been found to be safe [7], although on the other hand such an approach could increase dropout rates. As an example of this approach, one case study has reported spanning at least 100 sessions for the treatment of hallucinations in schizophrenia. The patient experienced initial improvement in a clinic, with doses ranging between 1 and 3 mA and was continued with once or twice daily sessions nearing 3 years to sustain benefit. No adverse events were reported [1]. For this approach, the tolerability would be established and the participant would have extensive experience with the procedures for stimulation. At-home use to extend clinical benefit may also be appropriate for managing transient symptoms as they occur. Future applications may include situational uses such as promoting wakefulness [26], managing an emerging mood state [27], or enhancing an aspect of performance (e.g. to increase or sustain attentional vigilance) [26, 27].

A third and most structured approach to the study of tDCS home use is to apply structured training procedures and real-time supervision. Standards and guidelines have been proposed by a working group of diverse clinical investigators interested in studying tDCS administered by patients or their carers [2]. Central to these recommendations is specially designed equipment that both carefully regulates and records use. Extensive training procedures and safety checks at each step overseen by a study technician can guide safe application to ensure the safest and most tolerable use. A protocol following these guidelines has been developed for at-home use of tDCS in a currently ongoing study of multiple sclerosis (MS) patients [28]. After a period of training, all stimulation sessions are provided under real-time supervision using a telemedicine platform. The device used is a pre-programmed device (Soterix Mini-CT) dependent on a code to "unlock" delivery of only one stimulation (or sham) session at a time. A study technician only provides the unlock code once a series of safety and tolerability checks have been met, including correct headset placement. With this protocol, targeting 10 sessions over 2 weeks, 20 participants have completed a total of 192 sessions without any adverse event or discontinuation of any session. There has been high tolerability and compliance, suggesting that the best model for providing home-based tDCS may be one that incorporates comprehensive training and ongoing supervision of patients during the treatment course.

Further Approaches Using Home-Based tDCS

Whilst there is growing evidence that tDCS as a stand-alone treatment is efficacious for some conditions such as depression [29], home-based tDCS has further potential as an adjunct treatment. For example, the past decade has seen a dissemination of psychological therapies via computer or Internet-based programs with a growing number of studies indicating that such therapies delivered in this way can be an efficacious treatment for depression [30–32]. Along with these developments, researchers have also begun investigating ways to further enhance the antidepressant effects of brain stimulation techniques such as tDCS and TMS by combining them with either a psychological therapy such as cognitive behaviour therapy or a cognitive training task [33–35]. The rationale is that by administering a cognitive activity that engages the same brain regions targeted by transcranial stimulation, synergistic antidepressant effects may result. Home-based tDCS has the potential to facilitate these developments by enabling completely decentralised treatment delivery with patients self-administering tDCS while carrying out a cognitive intervention via computer. Although there is promising preliminary evidence for such a treatment combination, the first randomised, controlled trial to investigate its feasibility and efficacy has yet to be conducted.

A recent case series of six patients has also investigated whether TMS could be a viable substitute for maintenance electroconvulsive therapy (ECT) especially for patients who are unable or unwilling to continue ECT or who do not experience a sustained benefit [36]. Self-report scores indicated all patients, following response to a course of ECT, maintained or improved their clinical state up to at least 6 months with maintenance TMS although two patients had relapsed by 9 months. To date, no trial has directly compared the relative efficacy of TMS and tDCS, nor have there been further trials of maintenance TMS following an ECT course. However, if found to be comparable, tDCS, as a maintenance treatment, can offer the added advantage of a more affordable, easily accessible alternative to TMS due to it being more amenable for home use. Moreover, having a home-based device may afford a clinician greater agility in adjusting their patient's tDCS "dose" (specifically, the frequency of tDCS sessions) in response to any symptom fluctuations as treatment would not depend on the patient's ability to travel to a treatment centre nor on the availability of clinic staff.

In summary, among brain stimulation techniques currently available, tDCS is the best positioned to be made available as a home-based, self-administered treatment option. Provided that tDCS devices intended for home-use can be designed to ensure reliable and consistent delivery of stimulation in a less controlled, non-clinical environment, tDCS has the potential to be an easily accessible and affordable treatment for a broad range of patients who may be limited from accessing other clinic-based treatments due to distance, cost or time constraints. Given these prospects and the burgeoning interest from consumers, the first randomised, controlled trials of take-home tDCS are greatly anticipated.

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Ethical Aspects of tDCS Use in Neuropsychiatry and the Risk of Misuse

24

Rachel P. Wurzman and Roy H. Hamilton

Abstract

There is growing enthusiasm about the potential of tDCS to be of value to clinical treatment and cognitive enhancement in neuropsychiatry. Yet despite its promise, the use of tDCS in clinical and nonclinical contexts faces several scientific and ethical challenges, which must be considered to protect against unanticipated or even adverse effects on individuals and groups in society. Scientific challenges include the lack of precise understanding of tDCS mechanisms, the present unreliability of predictions for the magnitude and nature of an individual's response to stimulation, the need for tDCS research to better capture dynamic effects in highly heterogeneous populations in whom comorbid diagnoses and the concurrent use of (multiple) medications may interact independently and interactively to affect tDCS response. Ethical challenges include issues of safety, character, justice, and autonomy. These considerations prompt a need to anticipate the trajectories of current and potential future use of tDCS both within and outside of clinical contexts, as there are likely to be evolving social and cultural consequences of tDCS use within neuropsychiatry. Likewise, neuroethical consequences from nonclinically oriented tDCS use are likely to have an impact on the way tDCS is used—and sought out—in clinical contexts. The accessibility of tDCS and its likelihood for broad use outside of medical contexts make it especially important to consider the promises, potential perils, and likely trajectories of tDCS use in multiple contexts from the outset. In this chapter, we reflect upon the way that the present degree of scientific understanding of tDCS motivates, justifies, and sometimes cautions against tDCS use.

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Introduction: Is tDCS Hope or Hype?

There is growing enthusiasm about the potential of transcranial direct current stimulation (tDCS) to be of value for clinical and cognitive enhancement purposes. With headlines like "Got a problem—put your electric thinking cap on" or "Trying a 9-volt shortcut to expertise," hundreds of enthusiastic print media articles have been published in the last few years [1–3]. The majority of media attention to tDCS has been optimistic and has praised the putative benefits of the technology [2]. However, while the tone of such coverage speaks in part to the considerable therapeutic potential of tDCS for disorders of cognition and mood, it also highlights the need to distinguish hope from hype. More than that, the science of tDCS and its potential applications present practical and ethical obstacles that warrant serious contemplation.

In many ways, practical and ethical considerations for tDCS mirror those of other forms of brain stimulation or neural interventions more broadly, but there are a few key features about tDCS that set it apart. Compared with other forms of noninvasive brain stimulation such as transcranial magnetic stimulation (TMS), tDCS is cheap, accessible, and portable. These factors multiply the contexts and applications for tDCS, some of which could present ethical, legal, and social problems if tDCS use were to become more widespread. At the same time, its very high level of accessibility also limits the range of potential actions that can be taken to prevent potentially problematic developments. Its low cost and relative technological simplicity make tDCS applicable to a broader set of contexts than other forms of invasive or even noninvasive brain stimulation, as it doesn't require surgery and can be easily self-administered. Consequently, tDCS is highly amenable to direct-to-consumer product development and marketing, as well as to increased use in so-called para-clinical contexts for enhancing cognitive and behavioral abilities, such as in the workplace, on the battlefield, or as a cosmetic enhancement in daily life. This potential for broad use both inside and outside of medical contexts calls for special consideration of the promises, potential perils, and implications for tDCS in the field of neuropsychiatry—both in how it is practiced as well as how it is perceived.

This chapter starts by exploring the promise of tDCS, first as a tool in cognitive neuroscience research, then as a clinical intervention, and finally as a technology to enhance normal cognition. Next, the scientific and ethical perils of tDCS are discussed in terms of the current state of the science, and how that informs the ways we think about the ethical challenges that tDCS poses with respect to safety, justice, character, and autonomy. For example, how can and should (or should not) knowledge learned in controlled research contexts be translated for potential safe and effective tDCS administration to complex real-world patients with multiple diagnoses, often on multiple medications? If cognitive self-enhancement becomes a social norm, what effects will that have on social structures, personal development, perhaps even clinical norms for what is considered normal versus pathological? Finally, we consider the ways in which tDCS presents specific advantages as well as challenges to neuropsychiatry and its role in society.

The field and scope of tDCS use (and other noninvasive brain stimulation and cognitive enhancement interventions) may already be developing at a rate that exceeds the pace of our scientific understanding [4]. One needs only to look at the recent and upcoming products released by the companies Thync (*Thync*, *Los Gatos*, *CA*) and Halo neuroscience (*Halo Neuroscience*, *San Fransisco*, *CA*)—not to mention their marketing

approaches—to glimpse the future role that tDCS could come to play in daily life. We may not be able to predict the rate at which the potential pitfalls may develop, but we can be sure that if tDCS continues to develop along its present trajectory, ethical, legal, and social issues will eventually arise. It is therefore important to consider these issues now, so that we can take proactive steps to mitigate against potentially unintended and undesirable consequences.

The Promise of tDCS

tDCS as a Cognitive Neuroscience Tool

Noninvasive brain stimulation (NIBS) methods are highly useful to cognitive neuroscience, in that they are used to modulate activity in brain regions or networks with varying degrees of anatomical selectivity and functional specificity. In general, NIBS add significant inferential strength to the ability of cognitive neuroscience to decipher causal brain region-function and network-function relationships. Following stimulation, subsequent changes in cortical activity, measured directly or indirectly by probing sensorimotor or cognitive behavioral functions, afford improved understanding of how brain activity in one region contributes to cognition and behavior. In recent years, tDCS has seen increasing use in the cognitive neuroscience community, with the number of publications published per year increasing over fivefold since 2010 [2]. TDCS has been applied to a variety of cognitive domains, including but not limited to skill learning, memory, executive functions, creativity, language, spatial processing, and social cognition [5]. This section provides a brief partial review of studies in which tDCS has been shown to manipulate cognition in informative ways, some of which have possible clinical applications.

With respect to learning and memory, acquisition and retention of new procedural skills has been experimentally enhanced using tDCS. One study found that, compared to sham stimulation, increased motor cortex excitability and enhanced learning of motor movements resulted when simple repetitive practice was paired with anodal tDCS [6]. Similarly, tDCS delivered over 5 days paired with training on a complex motor task resulted in increased improvement between daily stimulation sessions and persistent superior skill retention 3 months after stimulation [7]. The implications of this are that repeated administration of tDCS may have "off-line" effects that consolidate skill acquisition, effectively enhancing the long-term effects of rehearsal on performance. Declarative verbal memory has also been investigated using tDCS. For example, stimulation applied to the left dorsolateral prefrontal cortex had the effect of increasing the rate of verbal learning [8]. Consistent with this, another study found that tDCS delivered to the same site but with the opposite polarity had an inhibitory effect on verbal learning [9].

Various executive functions such as cognitive and behavioral impulse control and working memory have also been investigated with tDCS. One study found that orbitofrontal cortex stimulation with tDCS enhanced decision making and improved cognitive impulse control, without any concurrent effects on attention, mood, or motor impulse control [10]. In another study, tDCS improved response inhibition, which refers to the ability to inhibit an action once initiated [11]. For working memory (WM) and related functions, tDCS-induced improvements of performance on some tasks appear to depend in part on the level of cognitive demand of the tasks. For example, one group found that stimulation over the right cerebellum or left DLPFC increased accuracy and decreased response times for an arithmetic task that was more difficult and attentionally demanding, but not for an easier arithmetic task [12, 13]. Similarly, Gill and colleagues (2015) found that stimulation effects were readily observed when a more cognitively demanding working memory task was used during stimulation, but not when the task was less challenging [14]. Importantly, these effects also required that domain-specific cognitive behaviors be engaged during stimulation; stimulation-induced improvements were absent when tDCS was not paired with a relevant behavioral task [14, 15]. In other work, cathodal tDCS was used to enhance aspects of cognitive flexibility, presumably by inhibiting certain frontal lobe functions. This research,

which found that subjects could come up with more uncommon uses for everyday objects with inhibitory stimulation of the left, but not right, prefrontal cortex, suggests that creativity could be enhanced by stimulation that increases the influence of unfiltered bottom-up information [16].

It may be possible to significantly enhance the ability to learn new languages using tDCS. For example, anodal tDCS over language regions of cortex enhanced new vocabulary learning in healthy young adults [17]. Even without a reference object to associate with a novel "nonword," tDCS facilitated the acquisition of the phonological form of the nonwords into long-term memory, beyond the stimulation session [18]. Reading skills may also be enhanced using tDCS. Compared with sham stimulation, subjects receiving real tDCS subjects exhibited significantly better nonword reading efficiency. Curiously, this seemed only to apply consistently to below-average readers in the cohort; subjects who were more efficient readers to begin with saw much more variable changes in reading performance during real tDCS [19].

TDCS has been used to manipulate and enhance aspects of visuospatial processing. For example, we showed [20] that anodal tDCS over the right posterior parietal cortex could be used to selectively enhance detection of left-sided allocentric targets, which is to say that stimulated subjects were better able to detect the left side of visual targets independent of where the targets were in the subjects' visual fields. Interestingly, tDCS has also been used to manipulate how spatial and temporal processing contribute to higher order mental representations, such as the perception of cause and effect. In a study by Woods and colleagues [21], subjects were asked to make judgments about the causal relationship between two virtual objects (i.e., did one object cause the other to move by striking it), while the spatial and temporal features of the objects' motions were manipulated. Consistent with the role of the parietal cortex in spatial processing, the authors found that parietal tDCS selectively influenced how sensitive subjects were to spatial manipulation as it related to their perception of causality. On the other hand, frontal cortex stimulation influenced both spatial and temporal judgments with respect to causality, consistent with the overarching role of the frontal cortex in cause-and-effect reasoning [22].

Brain stimulation has also been used to alter social cognition and behaviors, including those that affect moral decision making that balances self-interest with social values. For example, individuals will often reject an offer that they perceive as highly unfair, although accepting the offer would still be to their benefit, as reciprocal punishment for the perceived unfairness (a concept know as "altruistic punishment"). Noninvasive inhibitory stimulation of the right DLPFC makes people less likely to reject marginally beneficial but unfair offers, even when consciously recognized as highly unfair, suggesting that direct current stimulation might also be used to calibrate the impact of economic self-interest on people's enforcement of social norms [23, 24]. In research on lie detection, tDCS has been demonstrated to alter individuals' deception skills in fairly specific ways, such as influencing someone's deceptive abilities when trying to conceal one's guilt or in situations such as card games. Early studies found that the act of lying increases cortical excitability on both sides of the brain [25]. People became better liars in a simulated interrogation task when cathodal tDCS was used to inhibit the anterior prefrontal cortex. Not only did stimulation make people better at concealing guilty knowledge, decreasing the kinds of signals that a polygraph detects when someone is lying, it also decreased their feelings of guilt over deceiving the experimenter [26]. On the other hand, anodal excitation of the dorsolateral prefrontal cortex made people worse at pretending not to have knowledge about something true, like whether a particular card is in their hand; interestingly, this effect did not extend to subject's behavior when bluffing or telling the truth [27].

One of the advantages of NIBS compared to classical methods in cognitive neuroscience and cognitive neurology like lesion studies is that these technologies can be used both to interfere with and enhance cognitive functions, at least temporarily. For example, the aforementioned studies on executive function and creativity illustrate how inverting the polarity of stimulation over brain regions responsible for cognitive control can either result

in favoring of cognitive abilities that require heavy filtering of extraneous information, such as sustained attention and working memory, or in favoring cognitive abilities that benefit from unfiltered intrusion of extraneous information, such as divergent thinking and creativity [10–16]. While enhancing aspects of cognition using such manipulation is a powerful tool for making inferences about brain function, it also opens the door to considering whether technologies like tDCS could be used to facilitate cognitive processes in patients with neurologic or psychiatric disorders of cognition, as well as in cognitively healthy individuals. For example, the ability of tDCS to manipulate perception of cause and effect could have implications for understanding and treatment of psychiatric disorders such as schizophrenia and obsessive compulsive disorder (OCD), where abnormal causal perceptions can contribute to symptoms [28, 29]. Moreover, the enhancement of allocentric spatial processing found by Medina and colleagues (2013) could have important implications for the treatment of spatial neglect in stroke patients [22], and studies related to executive function could lead to applications in a wide range of neurologic and psychiatric disorders [10–15]. Further research will be required so that group-level results from cognitive neuroscience studies, which are principally designed to reveal brain function, can be translated to clinical applications in which the goal is to alter specific functions in single individuals.

tDCS as a Clinical Intervention

With respect to clinical contexts, a growing body of literature suggests that tDCS is a potentially effective therapy for a wide variety of neuropsychiatric syndromes and symptoms, as well as other neurologic conditions affecting cognition [30, 31]. Depression and chronic pain in particular are two areas in which a substantial number of clinical trials support the utility of tDCS to alleviate symptoms [32, 33]. For depression, tDCS to the prefrontal cortex has shown promise as a treatment and medication adjunct to improve therapeutic outcomes [34–41]. With respect to tDCS as a treatment for pain, clinical trials for tDCS have been performed for chronic lower back pain [42, 43], chronic pain in the elderly [44], chronic temporomandibular disorders [45, 46], chronic pain in irritable bowel syndrome [47], neuropathic pain [48] such as in fibromyalgia [49, 50], or multiple sclerosis [51], and chronic pain associated with CNS damage from spinal cord injury [52] or stroke [53]. Although the results of clinical trials have in some cases been mixed [54], the potential utility of tDCS for clinical pain applications has been demonstrated in studies that show tDCS can affect aspects of nociception, pain thresholds, and affective (i.e., emotional) components of pain processing in healthy individuals [55–59]. Other neuropsychiatric conditions in which tDCS has been investigated include attention deficit hyperactivity disorder (ADHD) [60], schizophrenia [61–65], Alzheimer's disease [66] and mild cognitive impairment (MCI) [67], tinnitus [68], obsessive-compulsive disorder (OCD) [69], and generalized anxiety disorder [70]. TDCS is also being considered for PTSD, based on observed effects in fear extinction [71] and attentional bias for threat in anxiety [72, 73].

Other clinical applications for tDCS include disorders characterized by problematic behaviors related to abnormal executive function, including addictions and risk-taking behaviors [74, 75]. Studies have shown that tDCS may be useful for decreasing cigarette cravings and smoking behavior [76–80]. Interestingly, study of risk-taking behavior in smokers versus non-smokers found that tDCS was associated with personality-dependent effects [75], which emphasizes that existing cognitive patterns influence the specific nature of tDCS effects. Cravings and substance abuse in alcoholism [81–84] and drug addiction to methamphetamine [85] and crack cocaine [86–88] were also responsive to tDCS. Preliminary clinical studies of tDCS applied to DLPFC to intervene in obesity and disordered eating behavior have seen positive results. These have mostly examined acute tDCS effects on subjective reports of food craving, and attentional bias for food as probed with eye tracking following a single session of stimulation [89–93]. One 8-day, randomized, sham-controlled, crossover study found that anodal DLPFC stimulation decreased specific and nonspecific subjective

appetite and was associated with a decrease in calorie consumption at a standardized multi-choice test buffet by 14%, with a specific reductions in consumed carbohydrates [94].

Substantial promise has been found for tDCS in post-stroke neurorehabilitation. Following stroke, tDCS has been shown to assist in upper motor limb recovery from paresis [95, 96]. Similarly, anodal tDCS to the posterior parietal cortex mitigated unilateral visuospatial neglect [97] in one study, and in another study the response to prism-adaptation therapy was improved when therapy was paired with tDCS [98]. Anodal tDCS to the right premotor cortex also mitigated one patient's anosognosia for hemiplegia during stimulation [99], and in another case study, cognitive neglect therapy paired with biparietal tDCS, but not sham stimulation, enhanced the patient's response to therapeutic cognitive training [100]. Additionally, multiple studies have shown that when tDCS is paired with speech and language therapy, naming ability can be improved in stroke patients with aphasia [101–110]. Another neurorehabilitation application may be to post-stroke attentional decline, as anodal tDCS to the left DLPFC also improved attention in stroke patients, resulting in increased accuracy on a cognitive task of executive function [111]. Finally, tDCS is also being explored as enhancement to learning and memory in normal aging and in states of cognitive impairment [112–115].

Not coincidentally, tDCS has been explored clinically in many areas where the underlying impaired cognitive constructs have been shown in cognitive neuroscience research to be manipulable using stimulation. For example, cognitive neuroscience studies showing effective tDCS modulation on decision-making, including risk-taking, reward-seeking, impulsivity, and fairness consideration are considered as promising for addictive disorders, in which the hallmarks of clinical symptomatology are compromises in such decision-making capacities [116].

There are many practical reasons to favor tDCS in clinical settings. In addition to being small and portable, tDCS is inexpensive compared to other neuromodulation technologies like TMS. As currently used tDCS protocols are also safe, tDCS is an ideal form of neuromodulation to pair with existing therapies, and could potentially be self-administered by patients who may benefit from repeated stimulation on a regular basis.

tDCS to Enhance Normal Cognition

In addition to clinical applications and cognitive neuroscience studies designed to elucidate brain function (described above), there has been growing interest in explicitly enhancing normal cognition. In particular, tDCS joins a variety of neuroscience tools applied to so-called neuroergonomic purposes, referring to applications intended to aid human operators in the performance of their work duties [20]. Academic investigations for this purpose include—and in many cases expand upon—cognitive neuroscience studies of effects on isolated cognitive abilities, by examining tDCS effects on the performance of more complex tasks. Frequently, these experiments involve more naturalistic paradigms with clear applications to specific occupational functions, and assess improvements in the cognitive functions of implicit memory (e.g., procedural and motor learning; probabilistic learning), explicit learning and memory (e.g., declarative memory encoding with retrieval), working memory, attention, and perception [117]. For example, tasks in which tDCS has shown accelerated learning, enhanced performance, and/or prolonged training effects include threat detection in virtual-reality simulated urban warfare scenes [118–120], simulated air traffic controller games [121], a complex multi-task game "Space Fortress" [122], and an image analysis task in which target objects must be identified from synthetic aperture radar images of terrain with buildings and vehicles [123]. Not surprisingly, much of this research has been funded by the US Department of Defense [124].

On the other end of the spectrum from defense and security organizations, a community of individual "do-it-yourself" (DIY) tDCS users are also actively pursuing cognitive self-improvement [125]. The practices of this community were recently described in detail by Wexler [126]. The DIY community refers collectively to tDCS use outside of professional or academic settings, and can be subdivided

into those who seek to enhance their cognition and those who intend to alleviate clinical symptoms of neuropsychiatric disorders [126].

A burgeoning wearables market is also emerging, producing tDCS products controlled by companion apps for cognition and athletic performance enhancement, in both healthy individuals and clinical populations. Two of these companies supply direct-to-consumer devices for recreational and lifestyle indications (Thync and Foc.us), and another has a stimulator intended for healthy and "impaired" populations in a well-funded development pipeline (Halo Neuroscience; http://halo-neuro.com/#science) [124]. These companies are at the forefront of trends that could potentially to lead to widespread, if not ubiquitous, use of neuromodulatory technologies in daily life.

However, at present the effects of tDCS are far from established. Despite growing excitement about the possibility of using tDCS for enhancement of otherwise normal cognition, caution is warranted before extrapolating observations and lessons learned in cognitive neuroscience and clinical contexts to cognitive enhancement in healthy individuals due to fundamental differences in the theoretical, practical, and ethical issues related to each (as will be discussed in the next section).

The Perils of tDCS

Despite its promise, the use of tDCS in cognitive neuroscience, clinical research, and para-clinical applications faces several scientific and ethical challenges, which must be considered to protect against unanticipated or even adverse effects on the bio-psycho-social health of individuals and communities. It is especially important to accurately assess the state of the science, and reflect upon the way that the present degree of scientific understanding of tDCS motivates, justifies, and sometimes cautions against tDCS use.

Scientific Challenges

Scientific challenges stem from the fact that there is much that we do not yet understand about the underlying neural mechanisms of tDCS. Our incomplete understanding of tDCS mechanisms is underscored by data that indicates that the effects of stimulation on brain function are neither monotonic nor invariant. The initial dogma based on studies in motor cortex, which attributed enhancement or diminishment of cortical excitability to anodal or cathodal stimulation, respectively, often conflicts with experimental results. On the contrary, dose-response relationships are still poorly understood. For example, one study found that 1 mA cathodal stimulation diminished motor cortex excitability, but 2 mA cathodal stimulation enhanced it [127]. Similarly, doubling the time of stimulation can reverse the behavioral and cortical excitability effects [128, 129]. Moreover, the "anodal-facilitation versus cathodal-disruption" schema is a clear oversimplification; particularly beyond motor cortex, anodal and cathodal stimulation does not have equal and opposite effects on behavior. In cognitive studies, anodal and cathodal stimulation is sometimes found to have the same net facilitative effect on behavior, or only one stimulation polarity over the target will be found to influence a given behavior [11].

More broadly, we know that stimulation parameters matter a lot, but we are limited in our knowledge of what difference they actually make. For example, finite element models of tDCS-induced electrical current flow tell us that the size and location of the "reference" electrode strongly influences the effects of stimulation [130, 131]. Small changes in electrode position and individual head shapes can also greatly modify current flow patterns [132, 133]. However, the results of these models vary considerably based on model assumptions [134]. In other words, the best tools we have for understanding what stimulation is doing are themselves quite limited.

Other unknown variables when considering the perils of broader applications of tDCS to enhance cognition are the interactions that brain stimulation may have with comorbid diagnoses and the concurrent use of medications. The interaction of brain stimulation with agents that act on different neurotransmitters is of special concern in neuropsychiatry, since many (or perhaps most) people who suffer from these problems are taking

one or more such medications. Some drugs have been found to have profound, complex and varied influences on tDCS-induced neuromodulation [135–137]. In one very large clinical study of tDCS and depression, an additional naturalistic study systematically evaluated how tDCS responses were affected by concurrent treatment with psychiatric medications, including benzodiazepines, serotonin-noradrenergic reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), first- and second-generation antipsychotics, and mood stabilizers, and found that medication-stimulation interactions are significant considerations [138]. Specifically, they confirmed that antidepressants generally increased tDCS effects, but found that taking benzodiazepines actually worsened outcomes. They also found that tDCS did not interact with non-benzodiazepine anticonvulsants and antipsychotics, which are frequently used as mood stabilizers in patients with depression. Considering that there have been reports of hypomanic switches after tDCS in depression patients [139, 140], including an episode of manic psychosis in a stimulated patient taking sertraline [36], these findings warrant further investigation in order to develop safety guidelines for treating mood disorders with tDCS [141].

In sum, we have an incomplete understanding of how stimulation parameters and other dose variables act on the brain or interact with medications. This lack of precise mechanistic understanding limits our ability to predict the effects of tDCS in individuals. It is essential that clinicians and self-applicators of tDCS temper their enthusiasm with an understanding of these limitations. There are ethical and pragmatic obligations to resolve these uncertainties and to seek a more detailed mechanistic understanding of tDCS.

Ethical Challenges

The potential for tDCS use to become widespread raises a number of social and existential risks that must be carefully weighed against its benefits. By their nature, the effects of tDCS on cognition and affect blur the distinctions between treatment and enhancement. Moreover, its accessibility makes its use especially difficult to confine within the bounds of clinical medicine. Thus, ethical issues raised by tDCS cannot be viewed solely through a clinical ethics lens. Like pharmacological treatments that also have the potential to be used for enhancement purposes, the use of tDCS has not and will not remain in the medical realm. However, there is much still unknown about cognitive enhancement [4], both in terms of the science and in terms of its broader effects in ethical, legal, and social spheres. As discussed below, the ethical issues surrounding tDCS can be broadly categorized into concerns regarding *safety*, *justice*, *character*, and *autonomy*. The latter three concerns deal with potential trajectories of tDCS technology development and use patterns that are, at present, still speculative. However, it is important to consider the ethical implications of possibilities so that the negative consequences can be anticipated, and if possible, avoided.

Safety

In most traditional ways of thinking about safety, tDCS is of low concern; all current evidence indicates that tDCS delivery by currently applied protocols is very safe. While there are some recognized minor risks associated with tDCS such as mild headache and a mild itching or burning sensation under the electrodes [142], the risk of obvious physical injury from tDCS is extremely low. The most severe recognized potential medical risks associated with tDCS are burns to the skin and complications resulting from electrical equipment failures [143–145], but these are very rare and more likely to result from DIY systems than commercially manufactured stimulators.

The main potential concern with safety is that tDCS may alter cognition in unintended ways [146, 147]. Evidence suggests that stimulation at different sites may benefit some cognitive abilities but impair others [148]. Additionally, inhibiting or exciting the same region of brain can elicit different types of benefits. For example, anodal stimulation to the

lateral prefrontal cortex not only improved working memory, but also related fronto-executive functions that require a high degree of cognitive control, such as selective attention and set-switching. However, some aspects of cognitive flexibility and divergent thinking could be more consistent with a loosening of cognitive control, resulting in less "top-down" regulatory filtering of low-level information. Accordingly, cathodal stimulation to lateral prefrontal cortex has been shown to enhance cognitive flexibility in tool use [16]. Viewed together, these studies raise theoretical concerns that stimulation delivered with the intent of enhancing attention or working memory could have detrimental tradeoffs for cognition associated with creativity.

These kinds of tDCS-induced mental tradeoffs have been demonstrated for other aspects of cognition [148]. For instance, Iulcano and Kadosh (2013) recently explored how tDCS affected two dissociable aspects of learning that were relevant to mastery of a novel mathematical task: skill acquisition rate, and skill automaticity whereby tasks are performed quickly, effortlessly, and without conscious intention. Using tDCS to brain regions associated with learning (posterior parietal cortex; PPC) or automaticity (DLPFC) the investigators demonstrated a double dissociation wherein tDCS to the PPC enhanced learning rate but impaired automaticity while tDCS of the DLPFC enhanced automaticity at the expense of learning rate [148].

The nature of stimulation benefits may be specific to certain traits or states. For example, tDCS improved arithmetic decision making efficiency in healthy subjects who had high levels of pre-existing math anxiety, but it slowed reaction times in healthy subjects who had low-math anxiety, whose arithmetic efficiency was already unimpaired [149]. In several studies, state-dependent tDCS effects were linked to one's starting level of ability, with factors that lead to better performance at baseline associated with less improvement, and potentially impairment [114, 150, 151]. In a related fashion, the effects of tDCS on learning and memory task may depend on the stage of training [152].

In some cases where tDCS is associated with worse outcomes, stimulation does not directly cause cognitive degradation, but rather may block typical improvement by factors such as practice. One group discovered this while looking at the effects of tDCS on repeated IQ testing, employed as a means to simultaneously assess multiple domains for cognition. The study found that practice-related improvements for subtests of fluid intelligence (e.g., perceptual reasoning) were specifically attenuated when right, left, *or* bilateral anodal tDCS was delivered before retesting [153]. While in retrospect these results are consistent with expected effects of frontal anodal tDCS on cognitive flexibility, the authors initially hypothesized that tDCS would improve IQ test performance because previous studies had found that other types of task performance were improved by such stimulation. Such evidence highlights that tDCS is not a panacea, and further suggests that perhaps we should consider a more nuanced notion than "cognitive enhancement" for framing tDCS applications.

One of the challenges in understanding the risks, benefits, and trade-offs of using tDCS to enhance cognition is that, while many in the DIY stimulation community and elsewhere look toward the cognitive neuroscience community to inform how stimulation for enhancement could be pursued, the fundamental approach taken by most cognitive neuroscience studies does not adequately address the "cognitive safety" of enhancement with tDCS in at least two ways. First, the scientific methodology used in most cognitive neuroscience studies of tDCS only test one or a very limited number of cognitive functions in order to test specific hypotheses about the relationships between the brain areas stimulated and those specific mental operations. They do not test to make sure there are no deleterious effects on every other intellectual function. Second, cognitive neuroscience studies generally do not test for the durations that one might consider relevant if one was trying to make long-term changes in cognition. We simply do not know what the effects of increased frequencies and durations of stimulation are for individuals with healthy cognition. While this is not terribly relevant for basic

cognitive neuroscience studies, it is extremely relevant for cognitive enhancement studies, due to the increased likelihood of repeated and potentially prolonged stimulation sessions in the latter. Similarly patient studies do not wholly inform what the likely effects of neural enhancement with brain stimulation are because the brains in which therapeutic stimulation is being applied have already been altered by disease. Thus, safety considerations for tDCS underscore that the science has yet to support the technical application of tDCS for unmitigated cognitive enhancement.

Justice

Distributive justice refers to the equitable distribution of benefits. The development of "cosmetic" tDCS as a boutique service for cognitive remediation or enhancement could exacerbate social disparities by introducing a new type of "cognitive" privilege for those who can afford to exogenously treat or augment their own intellect [154]. Moreover, if boutiqued cognitive enhancement becomes a norm that is taken for granted, expectations regarding a "normal" range of cognitive abilities could become distorted to the point where unaugmented cognition is perceived as pathological. This could result in (further) medicalization of systemic disadvantage, which may introduce further obstacles to the remediation of social inequality, since access to education, medical care, and nutrition are already inequitable. Thus, explicit "cognitive health" disparities might further entrench systems of privilege and socioeconomic inequality. In many ways, this problem is not new or unique to enhancement with NIBS, but is symptomatic of the already vast separation in privilege between the haves and the have-nots.

On the other hand, compared with other technologies (including pharmaceutical agents) with utility as treatments or enhancements, justice may arguably constitute less of an issue for tDCS than other neurotechnologies, because it is relatively inexpensive and easy to create and employ with only modest technical training [155]. Noninvasive brain stimulation in healthcare is currently inequitable; if tDCS could confer comparable benefits while requiring less medical or technological infrastructure, it could increase justice in medically oriented neurostimulation [156].

Character

Issues of character relate to our essential humanity and how we find meaning in life. Ethical issues of character with brain simulation are those that impact our experience of personhood [157]. With its potential to alter our experience of behavior and cognition, brain stimulation raises two key questions. The first question is about identity and the integral core constellation of mental and behavioral characteristics that define us. It asks, "To what extent *can* and *should* we have the ability to change the core of who and what we are?" In part, the answers depend on the degree to which the core traits that distinguish us are considered to be stable, consistent, and integrated, and whether tDCS can disintegrate or change this subjective "core." The second question is about Self and the potential long-term consequences of self-enhancement on character building, as well as other more general aspects of psychosocial development, both within individuals and as a society. What sort of experiences are necessary for wisdom and maturity and virtue, and what are the consequences of avoiding them? These questions have already been deeply explored for neural interventions, in particular invasive deep brain stimulation (DBS) [158–162]. However, the scope of access to tDCS adds an additional dimension to such ethical consideration, as the potential effects on character development or change shifts from being an issue that affects select patients and their loved ones to something that could extend more directly to everyone.

Aspects of life experience that are not necessarily subjectively positive are integral to shaping a person's bearing, demeanor, and personality. It is a widely accepted social norm that adversity breeds character. If cognitive and emotional challenges can all be eased by exogenously stimulating the brain, how does that affect the resilience

and moral quality of a society in which this life of convenience is available? On the other hand, how much suffering is enough, and who gets to decide? After all, we do not consider it a moral failing if a person treats pain associated with childbirth or medical procedures. At what point, if any, does relief from difficult experiences diminish us? The consequence of tDCS on individual development ultimately affects society and culture in ways that are evolving and reciprocal, because social dynamics among individuals and groups influence, and are influenced by, the ambient culture. Thus, the adoption of widespread self-enhancement will bring questions about whether there should be limits to alter our fundamental nature to the forefront in formulating social and policy responses to growing use of tDCS.

Despite potential concerns, the effects of widespread tDCS use on character may not necessarily be negative. For instance, ongoing research is exploring the role of the brain in sports and fatigue (http://www.neuroelectrics.com/use-case/), and seeks to leverage this understanding to develop stimulation that could remove neural obstacles to maximum physical athletic performance. One could argue that removing obstacles to maximum performance *given maximum effort* is a categorically different type of enhancement than enhancement that makes something require *less* effort. In such a context, tDCS could be viewed as an *enabling* tool that could *enhance character*, rather than to act as a *substitute* for qualities that character would ordinarily supply to ensure success, such as commitment, patience, perseverance, and self-transcendence. This distinction is potentially relevant not only to athletics, but also to treatment in neuropsychiatry, wherein stimulation could potentially enable rather than rather than substitute for self-driven efforts to cultivate positive character traits. For example, enhancement of executive function in someone with ADHD to improve impulse control and the ability to sustain attention might *enable* such individuals to practice acts of high character, such as finishing what one has started or keeping commitments. The cardinal distinction applying to both situations is that high sustained effort is still required, and that absent the intervention, there are limits to the degree that such effort could affect performance. Assuming that the same amount of effort is exerted with or without tDCS, what is the true nature of the effect, if any, on the character of the athlete or individual with ADHD? These are all largely philosophical and psychological questions whose answers hinge on arguments about the relative influence afforded to *situational context* versus *personality* when assessing of character. Although this subject is beyond the scope this chapter, it is worth noting that a meaningful discussion of the impact of tDCS on character may require further consideration of a broader conceptual framework to address the daunting philosophical challenge of relating concepts such as identity and self to behavior and neurobiological functions.

Autonomy

Autonomy can be thought of as the right to one's own life, to make choices based on reasons and motivations that are not the product of manipulating or distorting external forces. In the context of tDCS, autonomy can be considered in terms of two types of freedom: (1) the freedom *not* to be stimulated, and (2) the freedom *to be* stimulated.

The freedom *from* stimulation can be threatened by hard or soft coercion. In hard coercion, the individual is forced into an activity for the perceived "good of society". Neuropsychological hard coercion is far from unheard of. Examples include psychopharmacologic agents given to soldiers to maintain battlefield performance and chemical castration to diminish the libido of imprisoned sex offenders [163, 164]. It is not all that hard to imagine cognitive enhancement with brain stimulation potentially following a similar course with similar vulnerable populations. With soft coercion, the individual feels societal pressure to keep up with norms and mores. As we know from many examples in professional sports, in high-stakes competitive environments, individuals turn readily to performance enhancers to give themselves a competitive edge. With respect to mental performance, we can see examples of

soft coercion currently in individuals who take pharmacologic cognitive agents in hopes of optimizing their performance at school or work. With respect to neuropsychology, the hazard of soft coercion again highlights that tDCS could potentially blur the distinctions between pathologically poor brain function and brain function that is normal but suboptimal for the tasks one desires to accomplish.

The freedom *to* be stimulated is unlikely to be overtly threatened given the accessibility of tDCS components. In this, lessons can be learned from other examples of cognitive self-enhancement, and cosmetic applications of medical technologies, including neuropharmacology. While it is important to remember that individuals are free to do as they see fit with respect to their own bodies and minds, inevitably, autonomy must necessarily be balanced with other ethical imperatives that arise from pragmatic or moral justifications, such as the need to consider the health of the community. Just as soft coercion can be used to encourage stimulation, social pressures can be exerted to influence the actions of those who would elect to use tDCS for medical or enhancement purposes. Given the complexity of the issues surrounding the use of tDCS for medical or enhancement, monolithic laws are unlikely to be helpful—or effective.

Ethical Considerations Pertaining to Neuropsychiatry

It may be taken for granted that the principle ethical considerations for tDCS with respect to the practice of neuropsychiatry boil down to whether tDCS is an acceptable way to treat patients. To this end, it is important to keep in mind that the distinction between normal and pathological is indiscrete and often culturally determined. Importantly, individuals whose thoughts and behaviors may objectively deviate from typical behavioral norms do not always do so in a way that leads to suffering; the moral imperative to medically treat dysfunction depends on the qualitative impact it has on an individual's life rather than the mere presence of abnormality [165]. Indeed, neurodiversity is increasingly being recognized as an intrinsic and valuable part of the spectrum of human experience that confers value and vigor to our overall ability to cognitively adapt to social and environmental changes [166]. Medicalizing neurodiversity pressures individuals and professionals (to some extent) into enforcing conformity to sociocultural norms of what is considered a "valuable" life. Neuropsychiatry as a field should consider tDCS alongside other dilemmas involving neurodiversity that drive the overall societal disposition towards psychiatry. These are not necessarily different issues than those pertaining to medicating neuropsychiatric disorders, but the fact that one doesn't necessarily need a prescription to self-administer tDCS (in some form) could shape perspectives on whether neuropsychiatric therapeutic applications of tDCS are perceived as legitimate, relative to other contexts in which tDCS could be used for enhancement or recreation.

Neuropsychiatry as a field should also be aware of the ways that widespread and even non-medical use of tDCS could influence perceptions of normality versus pathology. It can, at times, be difficult to distinguish between true "diseases" of the mind and more mundane dissatisfaction with mental states. Psychological aspects of individuals that are considered to be symptoms can often be conceptualized as traits that vary along a continuous spectrum of expression, for example, from inattentiveness to an attention deficit, or from sadness or emotional exhaustion to depression. This slippery slope of spectrum is especially problematic considering the capacity of tDCS to alter intellectual performance or mood. While most neuroscientists would argue that we are still far from being able to reliably alter mental states on an individualized basis using tDCS, the marketing for products like Thync and subjective experiences reported by DIY users indicate that at least the *perception* that tDCS can be used to induce targeted changes to mood (for example) exists presently. Having the power to so easily remedy dissatisfaction with one's mental states using tDCS—or even just believing that one has that power—has the potential to further obscure boundaries between what is considered normal, sub-clinical, or pathological.

Clinical fields that purport to distinguish between normal and pathological mental functioning face special obstacles when clinical values conflict with sociocultural norms, such as individuality or self-reliance. This has implications for clinical uses of tDCS. It is already difficult to determine when it is ethical to use technology to intervene in one's mental functioning. Widespread use of neural enhancement technologies like tDCS could further pathologize aspects of cognitive performance that would otherwise be considered along a spectrum of normalcy. This distortion could have the effect of decreasing individual autonomy by exerting positive pressure on clinical professionals to treat patients using neurostimulation or on individuals to "treat" themselves. As with pharmacological self-enhancement, some individuals might seek neuropsychiatric treatment for the purpose of procuring access to such technology as opposed to alleviating the suffering caused by illness. Thus neuropsychiatrists run the theoretical risk of becoming dispensers of cognitive commodities in tDCS as well as neuropharmacology. On the other hand, if there is general cultural pushback to increasing use of NIBS for self-enhancement, the application of tDCS in neuropsychiatric contexts, even where therapeutically beneficial, could come to be seen as problematic. Consider, for example, the stigma that popular culture has placed on electroconvulsive therapy (ECT), a highly effective treatment for refractory and life-threatening cases of depression, and how that stigma has had a sustained negative influence on its acceptance and use as a therapy. If tDCS becomes similarly stigmatized, this could raise obstacles to the development effective treatments for a variety of neurologic and neuropsychiatric conditions.

Several points raised in this chapter also have ethical implications for clinician-patient encounters. Because tDCS is not yet approved for specific clinical indications, we will here consider concerns that apply primarily to users of DIY or direct-to-consumer products. As public use of these technologies becomes more widespread, patients may sometimes confide to their neurologists or psychiatrists that they are experimenting with tDCS for self-treatment. In this situation, it is important that patients understand the safety consequences tDCS, including possible unintentional alteration of cognition or emotions. It will also be important for patients to recognize the current limits of the scientific literature, which cannot reliably predict what effects tDCS will have in the context of polypharmacy or other concurrent treatments. Conversations about the state of tDCS science and what is and is not known about tDCS might help patients to make better-informed decisions for themselves. However, insofar as there is currently no compelling evidence of serious medical risk posed by tDCS, some patients may be inclined to disregard the advice of their clinician and continue to self-administer tDCS in ways that, at least theoretically, seem potentially deleterious. This raises ethical issues of how best to engage with the patients regarding the risk of tDCS misuse in the absence of clear evidence for or against long-term harms. The issue of clinical misuse or overuse is similarly likely to arise in the event that tDCS is approved for specific indications such as depression or pain. While there is no clear one-size-fits-all strategy for navigating this topic with patients, it is an issue that neurologists and psychiatrists should be aware and ask about in their patients, especially as awareness of the therapeutic potential of tDCS becomes much more widespread in the public sphere.

Conclusion

In sum, there are pragmatic considerations specific to the practice of neuropsychiatry that bear weight in assessing both the utility and risks of employing tDCS as therapy. As it is presently understood, the mechanism of tDCS effects may be of particular utility for disorders in which dysfunction coincident and overlapping neural circuits leads to a range of psychiatric and cognitive symptoms. Targeting those common neural substrates with tDCS may lead to a variety of salutary effects in patients with complex disorders of mood, affect, and cognition. However, stimulation of overlapping neural circuits may also give

rise to cognitive tradeoffs that should prompt caution, particularly when the intent is to use tDCS to enhance normal cognition as opposed to treat disease. It is important to consider what is known versus what is not known about tDCS when designing clinical and cognitive research studies, and even more so when developing public policy and communicating with potential tDCS users (both consumers and patients). Clinicians and neuroscientists alike have an ethical responsibility to ensure that the lay public can access accurate information about what is and is not known about the mechanisms, effects, and safety of tDCS. In some cases, this may mean tempering unbridled enthusiasm for tDCS expressed in media coverage. The benefits and risks of tDCS clearly vary according to the context of administration, both with respect to the research, clinical, and cosmetic purposes for stimulation, as well as the states and traits of individual recipients.

All these considerations prompt a need to anticipate the trajectories of current and potential future use of tDCS both within and outside of clinical contexts, as there are likely to be dynamic broader social and cultural consequences of tDCS use within neuropsychiatry. Likewise, neuroethical consequences from nonclinically oriented tDCS use are also likely to have an impact on the way tDCS is used and sought out by patients. Thus, the use of tDCS in neuropsychiatry may have profound impacts not only on the social-cultural milieu, but also on the perceptions and practices of neuropsychiatry as a field.

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Regulatory Aspects

25

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Abstract

The increased research on transcranial direct current stimulation (tDCS) around the world reflects its potential as a therapeutic tool for many neuropsychiatric disorders. The simple technology and positive results on safety and efficacy have led to its increased use in research and clinical practice. However, there is no current regulation of tDCS by the Food and Drug Administration (FDA) in the USA for clinical use. Most of tDCS studies are considered of minimal risk, requiring only the Internal Review Board (IRB) approval to conduct a research study. Uses other than research include off-label and compassionate treatments. Special considerations on patient selection and the application of tDCS must be taken into account to optimize the technique and guarantee a safe practice. Further knowledge of tDCS experience in other countries and their combined efforts can help to promote the appropriate and safe use of this technique.

Keywords

tDCS • Medical device • Regulatory • FDA • IRB • Off-label • Compassionate treatment • Nonsignificant risk device

Abbreviations

CE	Conformité Européene
CES	Cranial electrotherapy stimulation
FDA	Food and Drug Administration
HD-tDCS	High definition-transcranial direct current stimulation
IDE	Investigational device exemption
IRB	Institutional Review Board
NIBS	Noninvasive brain stimulation
NSR	Nonsignificant risk
PMA	Premarket approval
SR	Significant risk
tDCS	Transcranial direct current stimulation

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Introduction

The field of noninvasive brain stimulation (NIBS) has undergone considerable advances in the last decade. The increased research on transcranial direct current stimulation (tDCS) around the world reflects its potential as a therapeutic tool through the modulation of cortical excitability, and its safety and efficacy have motivated scientists to increase its use in several conditions such as stroke [1–4], chronic pain [5, 6] cognitive impairment [7–9], and neuropsychiatric disorders [10–13].

Compared to other NIBS techniques, the relatively ease of use, portability, and low cost of tDCS makes it an attractive technique that can be easily accessed and used without any supervision, including nonmedical reasons. Therefore, it is important to have regulatory guidelines regarding the use of tDCS in both research and clinical practice. Currently, there is no international consensus with well-defined regulations for the use and distribution of tDCS [14]. In this chapter, we provide an overview of the regulatory process, the current status of tDCS in the USA and other countries, tDCS devices, special considerations on patient selection, and the practical aspects involving the use of tDCS.

FDA Regulation of Medical Devices

The federal agency responsible for regulating medical devices in the USA is the Food and Drug Administration (FDA). This agency has defined a medical device as an "*instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or other similar or related article, including a component part, or accessory which is*:

- *Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,*
- *Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or*
- *Intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.*" [15].

Before receiving the permission by the FDA to be legally marketed, the medical device submission enters in a review process for premarket and postmarket approvals. In the first case, the FDA classifies the medical devices according to the risk they pose to the consumers. Class I Medical Devices include devices such as elastic bandages or examination gloves for which general controls provide sufficient evidence of safety and efficacy. Class II Medical Devices include devices posing moderate risk to the patients, such as infusion pumps for the treatment of pain. Finally, for Class III Medical Devices, there is insufficient information to assure their safety or efficacy. Examples that fall in this last category are heart replacement valves or deep brain stimulating electrodes [16, 17].

Additionally, this classification determines the regulatory requirements that the manufacturer must follow. A device classified as Class I is exempt from the premarket notification. In the case of moderate and high-risk devices, the clearance is carried out through a premarket approval (PMA) or Product Development Protocol Processes [16]. The PMA process is usually longer and consists of conducting clinical studies to provide evidence of safety and efficacy of the medical device; most Class III and novel devices pass through this process in order to receive the FDA approval.

Furthermore, the premarket submission of a 510 (k) notification must be done to demonstrate that the device is substantially equivalent to a device that is already in the market. This notification includes information regarding the design and characteristics of the device and its components, as well as the clinical or nonclinical studies that were done to support the performance of

the device. This is required to assess the quality of the new device and thus, be able to compare to the current available devices. Most Class I and II devices are exempt from this submission before their sale; they do however undergo further control requirements [18]. This 510 (k) notification is also required for already marketed devices when there have been changes in their technology or a new indication for their use is foreseen.

Once the FDA approves the medical device for marketing, the manufacturer must follow other postmarket requirements: labeling and advertising, manufacturing, postmarketing surveillance, device tracking, and adverse event reporting [16].

Currently, there is no regulation of tDCS devices for therapeutic uses. The FDA regulates Cranial Electrotherapy Stimulation (CES) devices, but does not consider tDCS as a CES due to the use of direct current stimulation and the difference in electrode placement [19]. However, considering the FDA framework on medical devices as above discussed, tDCS could be contemplated and regulated as such, considering its intended use for the treatment of different medical conditions and its effects on brain function.

tDCS in Research

All clinical evaluations of investigational devices are under the Investigational Device Exemption (IDE) regulation [20, 21]. This exemption allows the new device to be used in clinical trials to provide information regarding its safety and effectiveness. Moreover, it distinguishes between significant and nonsignificant risk devices studies and, based upon this, the process for the study approval may vary. Clinical studies using devices classified as significant risk (SR) require both the FDA and the Institutional Review Board (IRB) approval before the initiation of the study, and in order to obtain the FDA approval, the investigator must submit the IDE application. Specific information including details about the sponsor, report of prior investigations and the investigational plan is required to apply. Furthermore, the sponsor must demonstrate that the potential risks to which the subjects may be exposed are reasonable in relation to the anticipated benefits and generation of scientific knowledge.

For studies involving nonsignificant risk (NSR) devices, only the IRB approval is required, and the sponsors' submission of the IDE is made directly to the IRB. The sponsors should also provide the study proposal and an explanation of why the device study should be considered as a NSR. If the IRB agrees, the study can begin without submission of an IDE application to the FDA. However, if the IRB determines it is a SR device, the sponsor has to report this decision to the FDA within a week (CFR Part 812.150(b)) [22, 23].

Finally, the approval of the proposed research by the IRB is based on the same criteria involving any FDA-regulated product; where the decision takes into account the risks and benefits of the investigational device and the contribution to science [24].

In the case of tDCS, these devices have been considered of NSR by the IRBs, so an IDE submission to the FDA is not required. Furthermore, its use has also been considered of minimal risk by some IRBs, which allows tDCS studies to be approved through an expedited review procedure [14, 22]. However, this is not indicative of its approval or the clearance by the FDA for the use of tDCS in scenarios other than research.

To date, the only companies having an IDE for tDCS devices by the FDA are Soterix Medical Inc. (tDCS and HD-tDCS) and NeuroConn [14]. The regulation of these devices has been subject to the FDA Quality System guidelines.

tDCS in Clinical Practice

Besides research, health care professionals in the USA can prescribe tDCS as an off-label treatment. This term refers to the use of a therapy that has proved to be safe within established parameters, for a purpose that has not been approved by the FDA. Considering that it is performed under the physician´s professional and ethical judgment, the FDA has developed Clinical Practical

Guidelines intended to help them make decisions regarding individual patient care [25]. Off-label uses of tDCS include motor recovery in stroke, improvement of balance and gait in cerebral palsy, and pain improvement in fibromyalgia.

Since the FDA has no legal authority to regulate clinical practice, unsupervised application of tDCS needs to be carefully reviewed for ethical and safety considerations. Off-label treatment should be applied according to the conventional protocols, with the approved devices and by trained personnel to guarantee safety and efficacy of the tDCS.

It is also important to consider that there is insufficient information regarding the long-term effects of stimulation, so this practice should be conducted with caution.

Furthermore, people who are not eligible to participate in a clinical trial may be able to get tDCS outside of a clinical trial through a "compassionate treatment." According to the FDA it can be considered as an option in patients with serious or life-threatening conditions that do not respond to currently approved treatments [26]. To date, this option has been accepted in most countries, considering the course of neuropsychiatric diseases and the limited treatment options [14].

The application of tDCS in either scenario must be ruled by ethical and legal considerations. Every medical research involving participation of human beings should be preceded by careful assessment of the benefit–risk ratio, an equitable selection of subjects and the obtainment of informed consent [27]. Especially for the latter, it is important to use simple and clear language to describe the tDCS procedure, as well as its potential benefits and adverse events.

TDCS Devices

The stimulation devices must meet safety requirements to be suitable for medical or scientific use. Generally, the use of battery driven devices is preferred because it prevents the delivery of dangerous high voltages and/or currents to the patient in case of technical problems. The device must be designed to indicate and allow adjustment of the parameters by the operator, specifically the output current, voltage, and duration of the stimulation. Furthermore, the protection of the patient must be enhanced through the presence of a gradual increase or decrease ("ramp-up" and "ramp-down" phase) of the desired current over a defined time interval (e.g., 30 s) at the beginning and the end of the stimulation, respectively. Moreover, the devices should have an accessible stop button to abort the stimulation in case of any adverse events.

Finally, it is recommended that an impedance monitoring system is included in these tDCS devices. The optimization of the technique might rely as well in the quality of the electrode preparation and the voltage demands to maintain the direct current magnitude [28, 29].

FDA-approved iontophoresis devices have been used by clinicians and researchers for tDCS in the off-label program. Iontophoresis devices use direct current stimulation (approximately $\leq$4 mA) to introduce ions of soluble salts or other drugs through the skin. These devices lack of many of the controlled elements mentioned previously, so its use as off-label treatment should be done with caution. In addition, they manage different doses and they were not designed to deliver current to the brain, and thus, they would not be ideal for performing tDCS [29].

Commercial devices claiming to have the same technology used for tDCS are already being sold to the public in the USA and other countries. Devices such as *foc.us* [30, 31] promoting the improvement of cognitive performance have raised concerns among health care professionals and researchers. In the first place, the company declares that as their product is not considered a medical device, no FDA regulation is required. In addition, these types of devices are usually designed with fixed stimulation parameters whose safety and/or efficacy have not been proved yet.

Indeed, a recent study in healthy volunteers assessed the effect of online and off-line foc.us tDCS applied over the prefrontal cortex on working memory. The authors showed that active stimulation (constant current of 1.5 mA during

20 min with a linear fade-in/fade-out of 15 s) with foc.us, compared to sham, significantly decreased the ability to monitor and update information in the working memory [31].

This device exemplifies that commercial devices may be sold without proper validation, that may result in inadequate use of the technique. In the case of foc.us, it has been presented as an alternative to "Conformité Européene" (CE) marked tDCS devices that have shown positive results on the working memory in healthy subjects [9, 32].

Furthermore, the media has encouraged programs such as Do-It-Yourself (DIY), where step-by-step tutorials on how to build a tDCS device and its application are widely available for untrained individual users [33]. Enthusiastic benefits of these devices are promoted without taking into account the population, parameters of stimulation, and medical background of the users. This reflects the need of regulation on devices that are being advertised in the media as potential tDCS devices carrying the risk of negative neuroplastic effects and misuse.

Considerations on Patient Selection

A careful patient selection is the core for an adequate tDCS intervention, and they evolve as daily publications define and refine the specific parameters of stimulation that maximize the benefits of the tDCS therapy and reduce the adverse events. However, the patient population, the medical illness, and the interaction between concomitant treatments are factors that must be taken into account before the application of tDCS.

tDCS Candidates

The identification of subjects who are appropriate candidates either for a study or an off-label program must be conducted carefully. Although specific inclusion criteria may vary according the specific study, certain considerations must be assessed in each patient to guarantee the safety and efficacy of tDCS:

- History of neurological and psychiatric conditions
- History of traumatic brain injury with loss of consciousness
- History of brain surgery or tumor
- History of seizures
- Presence of metallic plates in the head
- History of alcohol or substance abuse
- Use of psychopharmacological drugs
- Children
- Pregnancy

Ideally, tDCS should be adjusted in a patient-specific manner to select the best tDCS approach, reaching adequately the targeted region and avoiding safety concerns. As an example, skull defects or stroke related lesions might need modification of tDCS dose montages [28].

General exclusion criteria include the presence of unstable medical conditions (i.e., heart disease), intracranial metallic implantation or other conditions that may increase the risk of the stimulation [28].

In addition to the appropriate patient selection, it is important to assess and report adverse events/safety during and after tDCS. The following items are included in the proposed questionnaire by Brunoni et al. to survey tDCS adverse effects: headache, neck pain, scalp pain, tingling, itching, burning sensation, skin redness, sleepiness, trouble concentrating, acute mood changes and others. The subject should enter a value from 1 to 4 (1, absent; 2, mild; 3, moderate; 4, severe) to each item and, if present, assess if it is related to the tDCS [28, 34] (Also see Chap. 23 of this book for a discussion regarding safety).

tDCS in Pediatrics

There are limited reports of the use of tDCS in the pediatric population, mainly due to safety concerns that rise when adult studies with tDCS are extrapolated to children. To date, the optimal dose of tDCS for safety and efficacy in the pediatric population has not been well established. Studies reporting the use of tDCS in children have considered the following stimulation

parameters: duration of stimulation up to 20 min, current intensities from 1 to 2 mA, and bilateral (anodal and cathodal) or cathodal montages [26, 35, 36] in conditions such as refractory epilepsy, schizophrenia, and autism. Serious adverse events have not been reported yet, and the most common adverse events are tingling and itching at the electrode site [26]. Although published data suggest that the use of tDCS in children is well tolerated, special considerations have to be taken into account.

Previous modeling studies have shown that the potential variability in the tDCS efficacy between these populations may result from differences in brain size, neuroplasticity, development, and age-dependent anatomical features (i.e., skull thickness, and white and gray matter volumes) [37–40]. For example, the scalp brain distance increases with age due to increases in extra-axial CSF space and skull thickness. Considering that the bone conductivity is low and that the skull thickness in children is decreased compared to an adult, the transmission of the current would be higher. Furthermore, the decreased amount of extra axial CSF would provide less shunting of the current and more focal stimulation [37, 40, 41].

In the case of the white and gray matter proportion, is important to consider that after reaching the maximum brain volume by age 5, the gray matter volume decreases approximately 1.1 % per year and there is an estimated increase of 1.5 % in the white matter volume until 18 years of age [39, 42–44]. The differences in this proportion, reflecting maturation in the brain structure, influence the depth of the current penetration being higher in a pediatric patient.

Another important anatomical feature dependent on age and sex is the head circumference [37]. Approximately, the 98 % of the total head circumference growth occurs before age 18 years. After the greatest gains in head growth during the first year of life, the head circumference increases as a lower pace until adulthood. At the age 8 years, the mean head circumference for boys is 52 cm and for girls 51 cm. Once they reach the age 18 years the mean head circumferences are 56 and 55 cm for boys and girls, respectively [45]. This anatomical factor, as well as the size of the conventional tDCS electrodes, affect the focality of the stimulation. As the conventional tDCS protocol uses 5 cm by 5–7 cm sponges wrapped rubber electrodes, their use in a small head circumference would end up covering the majority of the scalp, thus losing focality [37].

Based on the empirical experience with tDCS in children and the considerations mentioned previously, tDCS given within the standard parameters is well tolerated. However, due to the limited safety studies and the lack of information about the neurophysiological effects with different parameters of stimulation, caution is warranted for pediatric populations. In fact, the benefits of tDCS must be clear before designing clinical trials, especially in children with very young age (≤7 years), taking into account the phases of brain development, tDCS potential of neuroplastic changes, and the risk of inducing maladaptive plasticity in these patients.

tDCS in Pregnancy

To our knowledge, few studies have been performed on tDCS in pregnant patients. In healthy subjects, a recent study showed that tDCS does not induce any significant changes in the autonomic function, ventilation rate or core body temperature [46–48]. These results, in addition to the localized nature of tDCS [49] and the low risk of seizures, suggest that tDCS is unlikely to cause any significant risk to the fetus. To date, a case report showed successful application of tDCS in a pregnant woman with schizophrenia, with no adverse events reported on the fetus [50]. Furthermore, a pilot study using tDCS for the treatment of major depression during pregnancy [51] provided a basis for the development of future larger multicenter studies including this population.

Although further studies are required to have solid evidence of the safety profile of tDCS in pregnancy, a conservative therapeutic approach for future clinical trials and also potential off-label use appears to be justified in the case where a clear benefit for the patient is present.

Considerations on Application of tDCS

As clinical practice and research on tDCS advances, several practical aspects such as the setting and the person who should apply this technique turns relevant. For tDCS research studies, the IRBs usually do not require the principal investigator to be a licensed physician but an expert in the tDCS technique, its principles, neurophysiological changes and the potential side effects. Besides this, safety must be guaranteed defining a protocol for emergency response within the study protocols in case the subject has any unexpected adverse effect.

Even though there is no consensus regarding the training and the accreditation requirements for performing tDCS, it is important that the principal investigator guarantees proper training including basic knowledge of brain physiology, mechanisms of tDCS, potential risks, and the different protocols. Trained professionals may include MDs, technicians, psychologists, physiotherapists, and engineers, as in other techniques such as transcranial magnetic stimulation [52]. In our Neuromodulation Center at Spaulding Rehabilitation Hospital in Boston, the program includes twenty hours of theoretical and training sessions given by experts in the field, followed by the corresponding assessments and certification.

In the clinical practice, a licensed physician is responsible for prescribing tDCS as an off-label or compassionate treatment. During these sessions, the trained personnel must have full access to emergency and life-support equipment to manage any potential acute complication of the treatment.

TDCS Experience in Other Countries

For other countries leading tDCS research such as Brazil and Germany the regulations regarding the use of tDCS in research and the clinical practice depends on the local/governmental regulations. In addition, we include the example of South Korea where the experience with tDCS has been limited.

In Brazil, the regulatory considerations for tDCS are very similar to the USA. Clinical trials using tDCS require the approval by the local ethics committee (Comitê de Ética em Pesquisa, CEP). As the IRBs in the USA, the CEP bases the final decision on the statement of ethical principles from the World Medical Association-Declaration of Helsinki [24]. In addition, the National Ethics Committee (CONEP) may also be involved in the statutory regulation of basic and clinical tDCS research especially in the situation of international multicenter trials. Further regulatory assessment is the responsibility of the National Health Surveillance Agency (ANVISA), that is in charge of the supervision and administration of medical devices such as tDCS. Currently, the only device that has been registered by the ANVISA for the use of tDCS is provided by the company "NEUROCONN GMBH." Although the tDCS device has not been approved for clinical use, the off label and compassionate tDCS use are considered in specific situations [14].

In the case of Germany, clinical trials which may be initiated by the producer of the device require the approval of the local ethics committee and the Federal Institute for pharmaceutical and medical products (BfARM), which is the corresponding federal entity. In the case of nonclinical trials, the local ethics committee is free to assess the risk-benefit ratio of the study and its decision is sufficient to approve or not the study [14]. Besides research, off label and compassionate tDCS are provided in the context.

Finally, South Korea regulation on tDCS has shown to be very strict. To date, no tDCS device has been approved by the Korean Ministry of Food and Drug Safety (MFDS). TDCS has been considered to have a class II risk profile and thus, its approval requires preexistent evidence either from research studies performed in South Korea or abroad.

The application and regulation for the device approval are variable, some study protocols require approval just from the local IRB and others from the MFDS. In either case, this process is repeated for every single trial and the tDCS devices should be destroyed after the study [14]. Further uses of tDCS have not been reported.

Conclusion

We provide an overview of the regulatory aspects and special considerations for the use of tDCS in the USA. In the case of other countries leading tDCS research, the requirements for its use vary according to their local/federal laws. We consider that the involvement of the international community is crucial for the establishment of consistent tDCS regulatory aspects and the development of guidelines for its use in research and clinical practice. The active participation of the scientific community in this process of tDCS will be helpful to mitigate the potential risks of misuse and the uncertainty of long-term effects on the brain, which are not fully known.

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Clinical Research and Methodological Aspects for tDCS Research

26

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Abstract

Although transcranial direct current stimulation (tDCS) is seemingly simple and easy to apply, specific aspects of sound application and design must be taken into consideration to obtain reliable results in clinical and research settings. This chapter provides an overview of methodological, design, and application techniques important for technically sound application of tDCS. Topics covered in this chapter include: clinical/research trial design; patient/participant screening practices; electrode selection, preparation, and placement; montage selection; assessment for adverse events/safety, and functional effects monitoring. This chapter is intended: (1) to provide information for education of researchers and clinicians new to tDCS, (2) to provide a description of methodological details important for experienced tDCS researchers and clinicians attempting to replicate clinical and research outcomes, and (3) to highlight methodological details important for consideration in clinical and research applications of tDCS.

Keywords

Transcranial direct current stimulation • Methodology • Design • Application • Reproducibility • Technical guide • Safety • Patient and participant screening • Electrodes preparation • Montage selection

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Introduction

Transcranial direct current stimulation (tDCS) was reintroduced as a method for noninvasive brain stimulation (NIBS) in humans approximately 15 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 15 years. This variation, together with a lack of standardized reporting methods for the field, has 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 hypopolarzing 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. Unfortunately, studies often do not provide the level of methodological detail required to guide clinicians/researchers new to the field of tDCS or 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 education of a new generation of tDCS researchers and clinicians.

In this chapter, we 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.

Clinical/Research Trial Designs

Protocol Intensity/Duration/Repetition

When designing an experimental or intervention protocol it is important to choose tDCS parameters (i.e., stimulation intensity, 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. Whilst 1 mA stimulation intensity delivered over the left dorsolateral prefrontal cortex for 10 min improved working memory performance in healthy participants [8], 2 mA stimulation intensity for 20 min was necessary to produce similar effects in patients with schizophrenia [9].

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 out-

comes. 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 [10]. 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 [11]. The latter finding additionally highlights the potential role of metaplastic effects within the stimulated region on outcomes (i.e., when tDCS is administered again during the after effects of a previous tDCS administration).

Taken together these collective findings 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 clinical pilot. Such piloting can also be invaluable for informing future studies.

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 [12]. 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" [13]. 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 [14]. When evaluating outcomes in interventions involving repeated tDCS administrations these effects should also be considered, as "offline" effects or "aftereffects" 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 aftereffects have primarily been shown in the context of research studies [1, 15, 16], their impact should be carefully considered in multi-session 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 [17]. Further, the relative level of task-related activity has also been found to be relevant. Whilst performance of a slow motor task during anodal stimulation of 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 [18]. 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 [19].

As such, both the timing of task execution and 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 during and following stimulation.

Blinding, Sham, and Active Control

A relative advantage of tDCS compared to other noninvasive brain stimulation methods is the ability to implement effective blinding. 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. For 1 mA tDCS with an electrode size of 25 cm^2, this method has been shown to reliably blind subjects [20]. As stronger stimulation intensities induce larger sensations, providing a brief constant stimulation at the maximum intensity, however, may compromise blinding [21]. An alternative approach is to apply topical anesthetics to abolish skin sensations [22]. 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, a recent paper 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 [23]. Nonetheless, care should be taken when considering the use of topical anesthetics.

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 though can be reliably reduced by acetylsalicylate, or topical application of ketoprofen [24]. Having one experimenter record side effects following tDCS (e.g., skin reddening) while another one only assess efficacy measures can further blind the primary interventionist to study conditions. Hence, for reliable double blinding, several different approaches should be considered.

Alternatively, or in addition, 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 to 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) should be considered, as this enables better localisation the stimulation effects particularly for cortical regions [25–28]. 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.

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. 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 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 [29]. For neuropsychiatric conditions, this can be achieved using published formal structured interviews, for example, the Structured Clinical Interview for DSM-5 (SCID-5: [30]) or the M.I.N.I.6. International Neuropsychiatric Interview (M.I.N.I. 6.0: [31]). Potential neurological conditions can be screened either through either patient interview or self-report questionnaires (e.g., Transcranial magnetic stimulation Adult Safety Screen; TASS; [32]). 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, pacemaker, no stimulation over fissures, or cranial holes) are also typically implemented.

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 [33]. Other common medications, including selective serotonin reuptake inhibitors (SSRIs; [34]), mood stabilizers (i.e., sodium and calcium channel blockers; [6]), antipsychotics (i.e., dopamine antagonists; [35]), and common pain killers and sedatives (e.g., benzodiazepines; [36]), have also though been shown 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 [37].

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 [34, 38–41]. The tDCS electrode assembly most commonly comprises (1) a metal or conductive rubber (e.g., biocarbon) electrode, (2) an electrode sponge, and (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 [42], 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 [43]. 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 oversaturated, 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 alters the distribution of current delivered to the scalp and the brain [44, 45]. 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 [44, 45]. 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.

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, 27, 46]. 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, 27, 46]. Woods et al. [4] 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. 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 [47, 48], or another gross anatomical coordinate system [49], (2) neuronavigation systems (e.g., MRI guided), or (3) physiology-based placement (e.g., TMS generated MEPs). These methods can be used to consistently center each electrode on the head, accommodating varied head shape or size.

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 undertightened or overtightened, electrodes have a strong tendency to move 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 overtightened, 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 overtightening 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.

tDCS Stimulator Selection

A limited set of certified tDCS-stimulators are currently available (e.g., produced/distributed by Brainstim, Magstim, Neuroconn, Neuroelectrics, Newronika, and Soterix Medical). These devices are designed to deliver constant current through two or more electrodes [50, 51]. 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 (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. In contrast, many stimulation devices repurposed for tDCS (e.g., iontophoresis stimulators) provide the ability to deliver stimulation up to and beyond 1 Amp—a significant safety concern regarding skin lesions/burns. 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.

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. Whilst tolerability refers to the presence of uncomfortable and unintended effects (e.g., tingling, 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 [52]. The most frequently reported side effects are tingling and itching sensations under the electrodes, headache, and tiredness [41]. The sensation of phosphenes elicited by abrupt current onset 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 [53].

In relation to safety aspects, no structural damage of brain tissue as examined with diffusion-weighted and contrast enhanced MRI [54], or neural damage as assessed using neuron specific enolase [54, 55] have been reported using the modern protocols introduced by Nitsche and colleagues. 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 [56]. 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 [57]. Computer modeling of the use of an extracephalic electrode placed upon the shoulder suggests that cardiac or brainstem activities should not be affected [58, 59]. Data in healthy subjects suggests that using an extracephalic electrode reference does not modulate brainstem autonomic activity [60]. 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 [23, 61]. Risk to subjects, however, can be substantially ameliorated through the implementation of several previously outlined recommendations [37]. (1) Subjects should be screened for skin disease, irritation or lesions underneath where the electrodes will be placed to minimize focalisation 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 [61]. (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 (~3 mm) and should cover the electrode completely, preventing direct contact of the electrode with the skin. (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 [37, 62], to regularly assess subjects' skin condition and risk for burns.

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 [55, 63]. Another commonly used approach is to examine cognitive effects either during or following tDCS administration (for review see [64]).

Increasingly, investigators are additionally employing neuroimaging tools (e.g., EEG and fMRI) to further explore functional effects. EEG, whilst 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 [18]. Similarly 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 [25]. 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 [65].

Functional effects may further be investigated using magnetic resonance imaging (MRI), which incorporates several methods including Blood Oxygen Level Dependent (BOLD) fMRI [15, 66], Arterial Spin Labeling [12], as well as proton and non-proton MR Spectroscopy [67]. tDCS can be applied within the bore of the magnet, with the option of assessing effects either during "online" stimulation, and "offline," where subjects are removed from the scanner, have tDCS applied, and then are returned in the scanner. There are several methodological considerations in regard to the use of tDCS within the MR bore. 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 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.

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 to 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 [68], 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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