

Transcranial direct current stimulation in psychiatric disorders

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Abstract

The interest in non-invasive brain stimulation techniques is increasing in recent years. Among these techniques, transcranial direct current stimulation (tDCS) has been the subject of great interest among researchers because of its easiness to use, low cost, benign profile of side effects and encouraging results of research in the field. This interest has generated several studies and randomized clinical trials, particularly in psychiatry. In this review, we provide a summary of the development of the technique and its mechanism of action as well as a review of the methodological aspects of randomized clinical trials in psychiatry, including studies in affective disorders, schizophrenia, obsessive compulsive disorder, child psychiatry and substance use disorder. Finally,

we provide an overview of tDCS use in cognitive enhancement as well as a discussion regarding its clinical use and regulatory and ethical issues. Although many promising results regarding tDCS efficacy were described, the total number of studies is still low, highlighting the need of further studies aiming to replicate these findings in larger samples as to provide a definite picture regarding tDCS efficacy in psychiatry.

Key words: Non-invasive brain stimulation; Transcranial direct current stimulation; Psychiatry disorders; Review

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Core tip: Transcranial direct current stimulation (tDCS) has been the subject of great interest among researchers because of its easiness to use, low cost, benign profile of side effects and encouraging results of research in the field. In this review, we provide a summary of the development of the technique and its mechanism of action as well as a review of the methodological aspects of randomized clinical trials in psychiatry and we provide an overview of tDCS use in cognitive enhancement as well as a discussion regarding its clinical use and regulatory and ethical issues.

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INTRODUCTION

The interest in the brain stimulation using electricity exists since the Roman Empire, when the physician Scribonius Largus described the application of the electric shocks from "torpedo fish" to relieve headache^[1,2]. In recent history, the first report of cortical stimulation occurred in 1802, when Giovanni Aldini described the electrical stimulation of exposed human cortex. He also reported the use of a voltaic pile to perform transcranial electrical stimulation to treat melancholia^[2,3]. In fact, the invention of the voltaic battery encouraged the application of electrotherapy for medical purposes and during the 19th and 20th centuries physicians started to use galvanic batteries to perform electric brain stimulation for the treatment of different mental disorders with heterogeneous, dubious results. Notably, these first interventions were largely empirical and uncontrolled. Only in the 1950s and the 1960s systematic research was conducted in animals models, studying the effects of direct current (DC) on changing cortical excitability, and in clinical trials, performing DC

stimulation for the treatment of depressive or manic symptoms^[2]. The interest on "brain polarization" (as transcranial DC stimulation was described at that time) declined during the 2nd half of the last century, with the social stigma related to electroconvulsotherapy and the "golden age" of psychopharmacology. Only in the last 15 years, the findings that weak, DC stimulation delivered transcranially (tDCS) could induce prolonged neuroplastic changes in cortical excitability^[4,5] with functional effects in healthy subjects^[6], contributed to a resurgence of the interest in this technique not only as research tool but also as a potential approach for the treatment of several psychiatric disorders, such major depressive disorder, schizophrenia, obsessive-compulsive disorder and also other psychiatric and neurological disorders^[7-11].

Technical aspects and mechanisms of action of tDCS

tDCS is described as a non-invasive form of brain stimulation that uses a low-intensity, constant current applied directly to the head through scalp electrodes^[12]. This form of brain stimulation can induce significant currents in superficial cortical areas (see The stimulated brain, Elsevier 2014, Chapter 2, for a review and further references) and, since the current used is sub threshold, it can modulate neuronal excitability without triggering action potentials^[13], by facilitation or inhibition of spontaneous neural activity according to the polarity of the electrodes^[14]. Generally, anodal stimulation induces an increase of cortical excitability, whereas cathodal stimulation decreases cortical excitability, effects that may last beyond the stimulation period^[4,5], up to 30-120 min^[15]. In fact, the polarity-dependent effects are more complex and also dependent of the spatial organization of the cells: inward current flow at the cortex (anodal tDCS) generates hyperpolarization of apical dendritic regions of pyramidal cortical neurons and depolarization of somatic regions, whereas outward current flow (cathodal tDCS) results in somatic hyperpolarization and apical dendrite depolarization of pyramidal cortical neurons^[16].

The effects of tDCS are not only determined by the polarity of the electrodes, but also with the dose^[16]. This involves the current intensity (usually ranging between 0.5 to 2 mA)^[12], the duration of stimulation (usually ranging between 5 to 40 min)^[7] and the size of the electrodes that varies from 3 to 100 cm²^[17]. These variables determine the current density (in A/m²) and the total charge (in Coulombs) applied. Notwithstanding, the actual current delivered to the cortex is also influenced by several other uncontrollable factors such as the impedance of the cephalic structures^[7].

The electrode placement on the scalp is usually determined using the international Electroencephalogram (EEG) 10-20 System^[17]. Commonly, the active electrode is placed on the scalp, whereas the reference electrode can be placed on either another cephalic location (bipolar or bicephalic montage) or an extracephalic

location (unipolar or monocephalic montage), usually the shoulder or upper arm. The electric current enters the brain through the anode, passes through the scalp and skull before reaching cortical and subcortical regions and finally leaves through the cathode (The stimulated brain, Elsevier 2014, Chapter 2). The current flow produced reaches deep structures and, when using extracephalic electrodes, the midbrain and spinal cord as well. Importantly, the conventional montages used in tDCS present low precision - *i.e.*, the current flow produced is not restricted to the area under the electrodes but in fact spreads out to other cortical regions between and around the electrodes^[18].

The long-term effects of tDCS appear to operate through bidirectional modifications of post-synaptic connections similar to long-term potentiation (LTP) and long-term depression (LTD), occurring through NMDA-dependent mechanisms^[19]. Indeed, repeated tDCS sessions might further increase the duration of long-term effects on behavioral outcomes^[20].

Methodological aspects in clinical tDCS research

Over the past years, tDCS has been increasingly used in clinical research, from basic neuroscience research to a tool in the treatment of various neurologic and psychiatric disorders^[21,22]. In order to identify whether the effects of tDCS are non-specific or random, the use of a placebo (sham) group is mandatory in clinical trials. Indeed, the use of placebo is a standard method to blind participants and health care providers in randomized, controlled trials^[23]. Within this context, the development of reliable methods of sham stimulation is challenging^[24], as blinding failure can compromise evaluations, resulting in biased assessment of intervention effects.

The sham stimulation, method validated by Gandiga and colleagues^[25], is currently used in almost all tDCS clinical trials. The procedure involves short-lasting manual or automatic increase and decrease of current delivered during the first moments (30-60 s) of the stimulation session in order to simulate the same skin sensations of the verum stimulation^[25-27]. Palm and colleagues^[28] reported that using this blinding method the subjects were not able to distinguish between active and sham stimulation applied on prefrontal areas. However, in this study, the investigators were able to identify between active vs sham stimulation group based on the skin redness provoked by the active stimulation. In another research, Ambrus and colleagues suggested that this method of blinding is effective, not because the sham fade-out phase mimics the presumed disappearance of the sensations in the verum stimulation conditions, but because, the cutaneous sensations associated with the sham stimulation persist after the ramp-down phase^[29].

Another concern of tDCS detection involves current dose, which seems to be associated with active tDCS detection^[28] since it is related to immediate adverse

effect, especially discomfort sensation. In a randomized double blind crossover trial with 100 healthy volunteers, O'Connell *et al.*^[30] suggest that blinding in studies using tDCS at intensities of 2 mA is inadequate once the participants correctly judged the stimulation condition.

Furthermore, some authors suggest that longer ramp-in phases are preferable for blinding purposes, especially when daily tDCS sessions are applied^[24,31]. In fact, randomized clinical trials (RCTs) tDCS trials, which use parallel designs, might provide a more adequate blinding. In a recent RCT for major depression with a factorial design and two active interventions (sertraline/placebo and 2 mA active/sham tDCS), blinding assessment of the pharmacological and non-pharmacological interventions was comparable, with correctly blinding guessing primarily associated with clinical improvement and adverse effects and not blinding failure^[24].

Skin redness and discomfort are common adverse effects that can harm tDCS blinding, and some studies have been performed in order to control them. Guarienti *et al.*^[32] found that topical pre-treatment with ketoprofen 2% significantly attenuated the tDCS-induced erythema, with a medium effect as compared to placebo. Moreover, the unblinding of this adverse effect can be managed by avoiding the awareness of participants (for instance, looking at the mirror or contacting peers following stimulation) and raters (for instance, by adopting a rest period between tDCS session and the clinical interview). McFadden *et al.*^[33] reported the reduction of pain and discomfort associated with tDCS by using local anesthetics. A recent report showed that pretreatment with benzocaine 6%, a topical numbing agent, can decrease the discomfort in subjects during the stimulation using high definition (HD) electrode design, which can enhance the efficiency of the sham controlled studies^[34].

Adverse effects and safety

The general impression is that tDCS is a safe technique with mild and transient adverse effects (AEs). Human data on safety and tolerability are largely provided from single-session studies in healthy volunteers. In a meta-analysis, Brunoni and colleagues^[31] showed that tDCS presents a benign profile of side effects when used in 1-2 sessions for healthy volunteers; however, they referred that only 56% of all reviewed studies reported the presence/absence of AEs, concluding that AEs are being insufficiently reported during tDCS clinical research.

According to this meta-analysis, the most common adverse effects are detected in the active group, among which itching, tingling, headache, burning sensation and discomfort (Table 1).

Although well investigated in adults, there is no specific guidance for tDCS dosage in children. The few studies investigating tDCS among the pediatric population indicated that adverse effects were similar

Table 1 Adverse effects associated with transcranial direct current stimulation

Adverse effects	Active ¹	Sham ¹
Itching	46 (39.3%)	27 (32.9%)
Tingling	26 (22.2%)	15 (18.3%)
Headache	17 (14.8%)	13 (16.2%)
Burning	10 (8.7%)	8 (10%)
Discomfort	12 (10.4%)	11 (13.4%)

¹Number of subjects reporting adverse symptom (% in the sample). Adapted from Brunoni *et al.*^[31], 2011. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation.

to adults, restricted to itching or tingling sensations at the stimulation site and without the reporting of any serious side effects^[35]. A naturalistic study in 14 children with language disorders showed that 10 sessions of tDCS were well tolerated and the main side effect detected was irritability, followed by acute mood changes, tingling and itching^[36].

However, due to anatomical and neurophysiological differences in the developing brain (*i.e.*, skull thickness, cerebrospinal fluid volume, white and gray matter volumes) the dose parameters considered safe and efficacious for the use in adults should be adjusted to achieve comparable results in children^[37].

Recently, Kessler *et al.*^[37] conducted a study in order to evaluate the safety aspects of tDCS in children. Using magnetic resonance imaging (MRI), they derived head individual models by two neurologically normal children and by three adults with different head sizes and circumferences; their analyses showed an overlap of sensitivity between adults with smaller head size and children aged between 8 and 12 years. Moreover, they highlighted to pay of caution in applying current intensities of 2 mA or greater in pediatric populations, due to the fact that the average of the dose of current over the cortical surface after the tDCS stimulation after might be higher in children than adults.

USE OF TDCS IN PSYCHIATRIC DISORDERS

As a neuromodulatory tool, tDCS was reappraised in the turn of the 21st century, with the seminal works of Priori^[38], followed by Nitsche *et al.*^[4]. They showed that the induction of a weak, direct current through electrodes placed over the scalp could increase (anode) and decrease (cathode) cortical excitability beyond the period of stimulation. Its exact mechanisms of action are still being elucidated but it probably operates by inducing small changes (< 1 mV) in the membrane potential^[39], thus acting in the frequency of spike timing and modifying net cortical excitability^[40]. The mechanisms of action of tDCS occur also at the synaptic level. For instance, glutamate antagonists abolish tDCS after-effects, while NMDA-agonists

enhance them^[41].

Compared to repetitive transcranial magnetic stimulation (rTMS), tDCS is a relatively cheaper, easier to use, more portable technique with even less adverse effects. Such appealing characteristics motivated the research of using tDCS for the treatment of neuropsychiatric disorders (for a review see^[11]), and, among them, tDCS has been showing particularly positive results in major depression.

Major depressive disorder

Major depressive disorder is a severe psychiatric disorder, chronic and prevalent, showing a life prevalence between 6% and 12% and yearly between 3% and 11% in the whole world^[42]. Besides that, proximately 80% of the patients present a recrudescence of depressive symptoms after one year of treatment with antidepressant drugs and up to 33% do not achieve complete remission after the use of 2 or 3 medication trials, which characterizes the treatment resistant depression^[43]. In view of its complexity and heterogeneity, with variations in its etiology, symptoms, course and response to the treatment, further investigation aiming to refine the knowledge underlying neurobiology is needed, with the goal to identify circuits and brain areas connected with this pathology.

An important body of evidence coming from neuroimaging studies suggests that depression is a result of impairment in activity of neural circuits that connects the dorsolateral prefrontal cortex (DLPFC) and the limbic system to other subcortical structures^[44]. The current neural models of depression propose that the emotional deregulation is due to abnormalities in the dorsal neural system (cognitive control system) and the ventral neural system (emotional evaluation system)^[45]. The dorsal system, which comprehends the DLPFC, dorsomedial PFC, the anterior dorsal cingulate gyrus and the hippocampus, is involved both in the cognitive processing of emotional input as much as the voluntary regulation of emotion. The ventral system, which comprehends the amygdala, insula, the ventral striate, dorsal cingulate gyrus and ventral PFC is critic for the identification of the emotional meaning from both internal or external stimuli, for the automatic generation and regulation (regulation without any conscious effort) of affective states, mediation of automatic response, dependent of the stimuli and context that results in the production of the affective states. It was proposed that increase of ventral neural system activity and decrease of the dorsal neural system activity can result mainly in attention impairment, in the identification of negative emotions and in other cognitive and vegetative symptoms of the depressive disorder^[46].

tDCS in the major depressive disorder

In depression, the rationale of the montage with the anode positioned over the left DLPFC and the cathode over the right DLPFC, the right supraorbital area or in

an extra-cephalic position^[7] rests on: (1) the prefrontal asymmetry theory of depression, with relative hypoactivity over the left and relative hyperactivity over the right^[47,48]; (2) the improvement in working memory and affective processing observed after one-single tDCS session in depressed patients^[49-51]; (3) the top-down, neuromodulatory effects of tDCS, possibly reversing the imbalance between hypoactive cortical areas and hyperactive subcortical areas^[48]; and (4) the clinical effects observed in rTMS using either rapid, facilitatory stimulation over the left DLPFC and slow, inhibitory stimulation over the right DLPFC^[52,53].

In the beginning of this century, some RCTs investigating the efficacy of tDCS for treating depression have showed promising results. Fregni *et al.*^[54] ($n = 10$, tDCS given at 1 mA, 20 min per session, 5 sessions on alternate days) and Boggio *et al.*^[55] ($n = 40$, 2 mA, 20 min, 10 sessions on consecutive weekdays) both found tDCS more effective than a sham control. Negative results were found in the study conducted by Loo *et al.*^[56] ($n = 40$, 1 mA, 20 min, 5 sessions on alternate days followed by 5 further active treatments) clinically meaningful improvement was seen with active tDCS over 10 sessions of treatment, but differences failed to reach statistical significance over the initial 5-session sham-controlled comparison period.

Although a variety of studies have found promising results in the reduction of depressive symptoms treated with tDCS protocols, two recent meta-analyses found different results. While Kalu *et al.*^[57] conducted a meta-analysis that found improvement in the depressive symptoms in the active group compared with the sham tDCS group, Berlim *et al.*^[58] did not find significant differences in the rates of response between the active and the sham treated groups, although it is important to emphasize that those meta-analyses considered distinct outcomes. Kalu *et al.*^[57] considered the size of the effect based on the depression classification scores while Berlim *et al.*^[58] focused on the rates of remission and response. 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, *etc.*) and different depression characteristics (regarding refractoriness, severity, mean age, unipolar vs bipolar depression and concomitant use of pharmacotherapy) in the sample. In fact, a more recent meta-analysis^[8] found that active vs sham tDCS had greater efficacy considering depression improvement as well as response and remission rates.

The largest controlled study so far about the application of tDCS in depression was recently published by Brunoni *et al.*^[59]. The authors made a controlled trial with 120 patients with depression. The results of this factorial study in which patients were randomly assigned to receive active tDCS/sham tDCS and verum sertraline/placebo showed a significant improvement on the depressive symptoms for the ones that took only active tDCS or in combination with sertraline.

Nonetheless, further randomized clinical trials

are necessary and, in fact, several trials evaluating the clinical efficacy of tDCS in depression are being currently performed worldwide. Therefore, in the next years a definite answer regarding the role of tDCS in the therapeutic arsenal of depression is expected.

Bipolar disorder

The etiopathogenic and physiopathological mechanisms of bipolar depression are not yet completely known. One important factor, however, seems to be the "hereditary-genetic". While the general risk to develop the bipolar disorder in the general population is between 1% and 2%, it goes up to 9% in first degree relatives of a Bipolar "carrier". The conformity between homozygous twins varies between 40% and 50% and the heritability (proportion of disease risk in the population due to genetic variation) can reach 80%-85%^[60].

From the neuroimaging point of view, several studies indicate the commitment of some structures involved in the affective regulation, such as PFC, anterior cingulate gyrus and amygdala. Neurophysiologic studies in bipolar patients, in turn, indicate executive and attention deficits, corroborating the idea of a commitment of the PFC^[61].

TDCS in bipolar depression

A recent study enrolling 31 patients (14 with bipolar depression and 17 with unipolar depression) had all the subjects submitted to a specific protocol: 5 sessions of tDCS with 20 min each, using anodic stimulation over the left DLPFC. The treatment was well tolerated by all and no significant adverse effects were observed. After the fifth tDCS session, depressive symptoms decreased in both groups and the beneficial effects lasted for a month^[62].

Loo *et al.*^[63], in which eight patients with bipolar depression (four in each group) were recruited, did not show important results in RCT phase, however on follow up approach the outcomes were more expressive. Thus, new studies are needed to reinforce the rationale of use in order to validate this technique in this illness.

Schizophrenia

Schizophrenia is a mental disorder that occurs in 0.5%-1.5% of the population^[64]. The clinical symptomatology of the disorder can be divided in three groups of symptoms: positive, negative and cognitive. The positive symptoms are characterized by hallucinations, delusions, thought disorders and movement disorders. Negative symptoms involve blunted affect, lethargy, and social withdrawal. Traditional antipsychotic medications have limited efficacy in treating these chronic, often refractory, symptoms^[65]. It is appraised that patients treated with antipsychotics remit in 30% of cases, respond partially in 30% and do not respond in about 40%^[66]. The best pharmacological option is clozapine, which is the first-line drug for patients with treatment-resistant schizophrenia, defined as the failure

of two adequate antipsychotic trials^[67]. About 30% of patients treated with clozapine responds partially and these cases are described as super-refractory^[67]. These patients are treated of different ways. Even if the evidence regarding non- pharmacological therapies is still limited, a recent meta-analyses have shown promising results in the application of rTMS in the treatment of auditory verbal hallucinations and negative symptoms^[68,69]. Neuroimaging studies have highlighted that these symptoms might be linked to abnormal brain activities within large dysfunctional brain networks. Auditory verbal hallucinations have been linked to fronto-temporal abnormalities with an hyperactivity in the left temporo-parietal junction^[70] and negative symptoms have been linked to hypoactivity in the right and left prefrontal cortex^[71].

Thanks to the excitatory effect of the anode and the inhibitory effect of the cathode described in the neurophysiological studies investigating the effect of tDCS on motor cortex excitability, it has been hypothesized that anodal tDCS applied over the left prefrontal cortex (hypoactive) combined with cathodal tDCS applied over the left temporo-parietal junction (hyperactive) could alleviate auditory hallucinations in patients with schizophrenia (for a review see Mondino^[72]). In the same way, bifrontal tDCS with the anode placed over the left prefrontal region and the cathode over its right homologue or the right supraorbital region is assumed to decrease negative symptoms. Based on these hypotheses, several studies have investigated the clinical effects of tDCS in these two indications in schizophrenia. Current was set at an intensity of 2 mA and delivered during 20 min. The electrodes were placed over the scalp of the subjects according to the 10/20 EEG international system. The center of the electrode was placed on a point situated midway between T3 and P3 to stimulate the left temporo-parietal junction and on F3 (F4) or between F3 and FP1 (F4 and FP2) to stimulate the left (right) prefrontal region.

Another study evaluated 20 patients with predominant negative symptoms and stable medication (> 3 wk) and they were randomized to active or sham stimulation groups^[73]. Anode was placed over the left DLPFC and cathode over the right supraorbital area; tDCS was delivered once a day for 10 d. The active group showed significant amelioration in The Positive and Negative Syndrome Scale two weeks after the end of stimulation.

Regarding bifrontal tDCS, only some case-studies have highlighted the potential interest of tDCS to reduce resistant negative symptoms^[74,75] and catatonic symptoms^[76].

Regarding safety, on the total amount reported in world literature of about 50 schizophrenic patients that have received tDCS, the technique appears to be remarkable safe in the short and medium-terms^[77]. Regarding adverse effects, some reviews described only mild adverse effects associated to tDCS such as

tingling, itching and fatigue, similarly as observed in literature^[78,79].

Of note, two recent case studies have reported the clinical interest of original stimulation parameters using transcranial random noise stimulation. This kind of stimulation can be of interest to enhance clinical efficacy of transcranial stimulation^[80,81]. Finally, in the literature there are only few studies that have investigated the clinical efficacy of tDCS in schizophrenia. Promising results have been reported but replication studies with larger samples are needed before any conclusion.

Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) has a 2% lifetime prevalence in the general population^[82,83]. Commonly, OCD symptoms begin during childhood and have a chronic course, causing severe impairments in both interpersonal and occupational functioning^[84-86]. In addition, pharmacotherapy is only effective in 40%-60% of patients^[87], and cognitive-behavior therapy (CBT), which has been reported as the most effective treatment for OCD^[88], is not readily available to the majority of patients. Overall, 30% of OCD patients are refractory to any first or second line treatments^[89]. Thus, the search for a clearer understanding of disease etiology and the need for new approaches to treatment-resistant patients are paramount.

It has been proposed that OCD results from malfunctioning 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, orbitofrontal cortex (OFC), and basal ganglia^[90]. This model informed neurosurgical approaches to OCD, and resulted in effective invasive treatments as evidenced by the FDA humanitarian use approval for high frequency deep brain stimulation (DBS) in treatment-resistant cases^[91]. 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 SMA and to the OFC^[92], tDCS has been less investigated for the treatment of OCD. Therefore, questions about which areas should be targeted and which parameters should be used still need to be addressed. In one case report, tDCS resulted ineffective when applied to the DLPFC^[10], whereas a 30% reduction in the Yale-Brown Obsessive Compulsive Severity Scale was found in a case of treatment-resistant OCD after cathodal tDCS to the pre-SMA^[93]. Furthermore, D'Urso *et al*^[94] reported, in a randomized cross-over trial of anodal vs cathodal tDCS to the pre-SMA, that the cathodal application was significantly superior to anodal tDCS in reducing OCD symptoms. The results of this study are in line with findings of clinical efficacy of inhibitory rTMS to pre-SMA^[95], demonstrated to be hyperactive in OCD patients during performance of cognitive tasks related to attentional aspects of action control^[96,97].

The evidence deriving from the clinical efficacy of inhibitory rTMS and tDCS and from neurophysiological measures of altered motor cortex excitability in OCD^[91], that normalized after 1-Hz rTMS to the pre-SMA^[98], suggests that the pre-motor/motor system is abnormally hyperactive in OCD, and that there is a pathophysiological link between such hyperexcitability and OCD symptoms.

In this context, to optimize the effect of cathodal tDCS in OCD, simulated predictions of electric flow models would be an extremely useful strategy for the design of future tDCS trials. By applying this model, Senco *et al.*^[99] found that the application of the active electrode (cathode) over the pre-SMA, with the reference electrode (anode) positioned on 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 randomized controlled trial testing the clinical and neurobiological effects of tDCS in OCD is underway.

TDCS in child psychiatry

The first onset of a variety of mental disorders diagnosed in adults occurs in childhood or adolescence, as for instance, impulse-control disorders, attention deficit hyperactivity disorder (ADHD), phobias, separation anxiety disorder and substance use disorder^[100]. Earlier onset is associated with treatment delay, longer duration of illness and poorer clinical and functional outcomes, being an important cause of burden during this period of life^[101,102]. In this sense, the use of novel treatments such as tDCS, should also be considered for children and adolescents, and might constitute a promising therapeutic and diagnostic tool, as the capacity for brain plasticity is greater during this period of life^[103]. tDCS would be also an interesting tool to explore which brain areas are particularly important in each stage of development both in healthy and pathological conditions^[7]. Nevertheless, the scope of literature in child and adolescent psychiatry is still very limited, with the majority of studies being case reports and open label studies.

An open study evaluating autistic patients with minimal verbal language have applied anodal tDCS over the Broca's area to improve language acquisition and the results showed that mean vocabulary scores were significantly higher after the intervention Schneider *et al.*^[104]. One double-blind, sham-controlled trial with 12 youths (age range from 10 to 17 years) with schizophrenia evaluated the tolerability of tDCS. The patients were assigned to anodal or cathodal stimulation and both groups were stimulated for 20 min per day during 10 d. Although no clinical improvement was

observed, this protocol was well tolerated, without reports of serious side effects Mattal^[105]. No study has assessed so far the effect of tDCS for the treatment of major depression in children and adolescents.

Attention deficit hyperactivity disorder is a behavioral diagnosis of early childhood where children often have changes in motor control development, and studies with adults suggested that anodal tDCS in the DLPFC may be associated with enhancement of cognitive performance^[106]. Currently, there are an increasing number of studies investigating TMS as an evaluation and therapeutic tool in ADHD, but no studies regarding tDCS in children and adolescents with this diagnose.

During childhood and adolescence the developing brain is probably more sensitive to interventions. This might lead to better results comparing to adults, but also to an increased risk of side effects, related to possible negative or maladaptive plasticity^[35]. For this reason, the application of tDCS in developmental age should be considered only after convincing evidence has been collected on adult populations, even when dealing with disorders usually first diagnosed in infancy, childhood, or adolescence. In the case of Autism, despite two reports of positive findings about the use of cathodal tDCS over the DLPFC for the treatment of some autism-related core behavioral symptoms D'Urso^[107] no study has involved so far autistic patients in the developmental age. Nonetheless, neuroplasticity in important brain areas can hardly be controlled in RCT even when using widely accepted and traditional treatments as psychotropic medication, so that the only available way to gather adequate data on efficacy and side effects is testing directly the specific target population^[2]. Indeed, a recently published review of literature regarding non invasive brain stimulation in childhood and adolescence highlighted the importance of systematic research in dose-finding, with sham-controlled, double-blinded studies that are capable to provide important information not available from open label studies^[35].

Substance use disorders

The treatment of substance use disorders is usually difficult and challenging. The central reward pathway, critical in the mechanism of dependences, comprises the dopaminergic system including the mesolimbic cortical ventral tegmental area and projections to the nucleus accumbens and the prefrontal cortex^[108,109]. Neuroimaging studies showed the important function of the prefrontal cortex in substance use disorders, being an important cortical structure in working memory and executive functions, two cognitive domains that are usually damaged in chemical dependencies^[110]. In literature, only few studies have investigated the application of tDCS for the treatment of chemical dependencies. Nonetheless, these studies have shown a possible role of this technique for the treatment of these conditions, especially by stimulating the activity

of the prefrontal cortex. Thus, the efficacy of tDCS in treating substance use disorders deserves further investigation, as shown below.

Cocaine: Goriniet *et al.*^[111] used tDCS over the DLPFC in two samples of subjects (18 cocaine dependent users and 18 control subjects) to investigate the effects of increasing cortical excitability after right or left anodal stimulation. The subjects were randomized to receive left-anodal/right-cathodal stimulation, right-anodal/left-cathodal stimulation, or sham (placebo) stimulation; each session was delivered at least 48 h apart. The results showed that the activation of the DLPFC (left and right) results in the reduction of risky behaviors in both, patients and control subjects, in cocaine dependent users. The authors concluded that in the future tDCS could represent a valuable tool for intervention in users of cocaine.

Alcohol: A randomized sham-controlled study in which 13 subjects received three different types of bilateral stimulation of DLPFC with tDCS: (1) active anodal left and cathodal right tDCS; (2) active anodal right and cathodal left tDCS; and (3) sham tDCS, have shown a reduction of craving for alcohol in both active groups compared to the sham group^[112].

Moreover, Klausset *et al.*^[113] studied 35 subjects randomized to receive active bilateral (left cathodal/right anodal over the DLPFC) repetitive (five consecutive days) tDCS (2 mA, 35 cm², two times daily stimulation for 13 min with a 20-min interval) or sham-tDCS. They observed that bilateral tDCS over DLPFC reduced relapse probability in severe alcoholic subjects and improved perception of quality of life.

Nicotine: Fregni *et al.*^[114] have investigated 24 patients, who received three different condition of a single tDCS session in a randomized order: sham stimulation, anode on the right DLPFC and anode the left DLPFC. The authors observed a reduction of craving in both active groups compared to the sham group.

Another study evaluated the effects of five consecutive sessions of tDCS on DLPFC. Twenty seven patients were randomized into two distinct groups: left anode and sham stimulation. The results showed a small but significant reduction in cigarette consumption and craving in active vs sham groups^[115].

A more recent study showed that anodal stimulation over the left DLPFC improved smoking-related negative affect, but did not improve the fissure. The authors studied 24 smokers who received one real session and one sham session of tDCS after overnight abstinence from smoking in two different days. They applied anodal tDCS to the left dorsolateral prefrontal cortex and cathode to the right supra-orbital area for 20 min with a current intensity of 2.0 mA^[116].

Fecteau *et al.*^[117] rated two five-day tDCS regimens (active or sham). Stimulation was delivered over the right DLPFC at a 2 mA during 30 min in twelve

adults. The main finding was a significant reduction in the number of cigarettes smoked when participants received active as compared to sham stimulation.

Food: Fregni *et al.*^[118] conducted a study on healthy subjects who reported frequent food cravings. They designed a sham controlled crossover study, applying one session of tDCS stimulation (2 mA, 20 min) in three different conditions: anodal-left/cathodal-right DLPFC, cathodal-right/anodal-left DLPFC and placebo. They observed a reduction of cue-induced food craving when comparing active anodal left/cathodal right DLPFC over the other groups and a lower caloric ingestion when comparing active (both configurations) to sham group.

Goldman *et al.*^[119] applied 1 session of tDCS (2 mA, 20 min, anodal prefrontal dorsolateral cortex right) in healthy subjects that reporting food craving. The study showed a reduction of craving in both sham and active tDCS conditions. Moreover, the results indicated decreased ratings for specific food items when comparing active to sham tDCS.

Cannabis: Boggio *et al.*^[120] studied the effect of tDCS on cannabis dependence. Twenty-five patients were divided into three distinct groups: anode left/cathode right, anode right/cathode left and sham stimulation. The results showed a significantly decrease of the craving for marijuana in the anodal right stimulation group.

USE OF TDCS IN COGNITION

Results from several studies regarding the effects of tDCS stimulation suggest that it could induce clinical gains in major depressive disorder, schizophrenia and substance use disorders^[121]. In many studies, researchers have noticed improvement in cognitive aspects of patients, such as working memory, attention, executive functions and processing speed^[122]. Furthermore, reports have demonstrated its utility in the facilitation of several cognitive domains, such as implicit motor learning and visuo-motor learning^[123,124], indicating its potential effectiveness on the modulation of behavior through the modulation of neurotransmitter-dependent plasticity on the network level.

The results of some studies in patients with major depression suggest improvement in performance Digits Test^[125], increasing of correct responses in affective Go-no-go^[51], improving of attention and working memory^[49,63,126], cognitive control^[127] and processing speed^[126]. Some studies in patients with Alzheimer's disease showed improvement in recognition memory^[127] and visual recognition memory Boggio *et al.*^[128,129] after stimulation with tDCS. One study reported an improvement in learning probabilistic membership functions in schizophrenic patients after tDCS^[130]. Another study in 18 schizophrenic patients showed an improvement in working memory^[131]. Finally, a study of alcoholic subjects showed that after five

weeks of stimulation, the subjects showed significant improvement in executive functions^[132].

With the same logic that the effects of tDCS showed cognitive improvement in psychiatric and neurological patients, studies with healthy subjects have shown that tDCS can promote changes in cognitive function after only one session or even after a series of sessions^[6]. Several studies have demonstrated the effects of tDCS on different cognitive functions in healthy subjects^[133]. In order to study further the relationship between tDCS and cognition, some researchers have decided to study neural underpinning effects on cognition. Supported by the observation that anodal tDCS over the left DLPFC could improve naming performance in healthy participants^[134] investigated the putative neurophysiological mechanisms underpinning language production. The authors found the reduction of semantic interference after anodal stimulation. Other studies have been conducted to explore the inhibitory effect of the technique^[133].

This area of study may contribute in the future in the investigation of the application of tDCS as an important non-invasive tool for the rehabilitation of cognitive functions. However, the studies so far available suggest that the changes in cognitive performance observed after tDCS stimulation are short-lived; this warrants more studies to better explore the development of the application of tDCS in patients with neurocognitive disorders.

REGULATORY ISSUES

There are over 1200 tDCS publications in Pubmed, with more than 200 being clinical trials for multiple clinical disorders. The potential of tDCS for clinical practice has been demonstrated for psychiatric and cognitive disorders, as described above, for psychiatric conditions associated with neurologic disorders, such as depression in Parkinson diseases and stroke, but also for tinnitus, chronic pain and motor deficit due to different neurological diseases.

An interesting aspect of tDCS is that it has a low risk; it is simple to operate, being portable and having a relatively low cost. On the other hand these same characteristics increases the chance of misuse, such as enhancement application, recreational using and using without supervision (as discussed below in ethical issues), which increases the need for regulations concerning the use of tDCS.

A worldwide implementation of tDCS regulation is not straightforward, since each country follows its own medical, sanitary and legislative rules. Commonly, the use of tDCS devices in research requires an approval by the local ethics committee, which, in several countries follows, at least partially, the World Medical Association-Declaration of Helsinki^[135].

For clinical purposes, it is necessary the regulation of a new treatment according to the country's internal policies, which is based on ethical aspects, safety and

clinical evidence of effectiveness. To our knowledge, there is no country that regulated the use of tDCS in clinical practice as an on-label treatment, although the evidence of the benefit of tDCS is increasing. For instance, a recent meta-analysis found that active tDCS was statistically superior to sham for treatment of acute depression^[8]. The regulation in several countries tends to be very restrictive, since it is also used to determinate medical insurance coverage and public health politics. Moreover, in our opinion, tDCS device should be regulated as a medical device, since it fulfills the criteria for this, at least for the United States Foods and Drugs Administration^[136].

Frequently, the regulation for clinical use also defines the professional category that could perform the therapy. We advocate that tDCS should have similar regulation of the psychotropic medications, since it has direct effect in the brain. In our opinion, the stimulation could be applied by trained technicians, but always with medical indication and supervision, although this is not necessarily a consensus in scientific community.

Although it is still necessary a better understanding of the parameters of stimulation and the long terms effect of tDCS for therapy, it is being already used in some countries as off-label and compassionated treatment. The use in this situation is normally justified by the lack of conventional treatment for neurologic and psychiatric diseases.

ETHICAL ISSUES

As all medical interventions in clinical practice and research, tDCS raises general and specific ethical issues that must be promptly addressed. Wider ethical issues regarding tDCS encompass the pillars of bioethics, namely, the principles of non-maleficence, beneficence, autonomy and justice^[137]. Nonetheless, the definition and overall discussion of these paradigms surpass the scope of this section of the paper.

The specific ethical issues raised by the growing use of neuromodulation techniques, of which tDCS is a part, are plentiful. Topics particularly relevant are: the "cosmetic use" of tDCS as a cognitive-enhancement procedure (*i.e.*, for non-research or non-therapeutic objectives), the hypothetical long-term effects of tDCS on other mental faculties of its recipients, and the inappropriate assemblage and use of tDCS devices by nonmedical population, in nonclinical settings^[7,138,139].

There are several medical interventions (both pharmacological and non-pharmacological) aimed at improving cognitive faculties in some neuropsychiatric disorders. For instance, methylphenidate is medically approved to treat ADHD, and thereby improve the patient's ability to concentrate and appropriately conclude tasks. On the other hand, this drug is knowingly misused by healthy populations, who end up taking it to improve their performance in situations like academic presentations and exams. The same phenomenon

could occur with tDCS. Consequentially, an intervention initially devised to treat pathological conditions, such as major depressive disorder, and lead to recovery of secondary cognitive deficits, might mistakenly be used for cosmetic cognitive enhancement^[138].

The major concern about the indiscriminate use of tDCS, especially for cosmetic purposes, is that since it is a relatively novel method, and in many ways still in phases of research, its long-term side effects are not completely known. Despite its notorious short-term safety with minimal and benign side effects, there is preliminary evidence pointing to possible and unforeseen interference of tDCS with the individual's social cognition^[139], moral judgment^[140] and even the capacity to tell the truth or deceive others^[141]. While such effects might be of minimal clinical relevance when tDCS is applied correctly in clinical settings, with adequate monitoring of individual responses, the same cannot be said about its cosmetic use.

Finally, it is important to recognize that while the equipment necessary to perform other neuromodulatory techniques is expensive and not portable (rTMS, for instance), naturally limiting their use in nonclinical settings, the device used in tDCS is lightweight, portable and can be assembled inexpensively^[138]. Moreover, it can be used at home, and in fact, there are websites and open discussion groups aimed at instructing nonmedical population on how to independently apply tDCS on oneself.

Therefore, as the practice of tDCS becomes widespread, physicians and researchers need to be very attentive to its correct clinical use, its long-term effects on cognition, moral judgment and personality, and cooperate with governmental regulation regarding the manufacture and commercialization of its devices and apparel. Needless to mention, all to safeguard the appropriate autonomy of our patients, while helping them make the best decisions with regard to their mental and physical health.

CONCLUSION

We hereby presented an overview of tDCS use in psychiatry, from its history, through the mechanism of action, results in different fields of psychiatry, ethical considerations and methodological aspects were presented. The main point of emphasis, perhaps, for this conclusion is tDCS clinical research - particularly randomized controlled-trials, began to be researched in psychiatry only recently. Even being a technique that has a recent scientific and clinical interest, it has already demonstrated that it might be a promising tool in the therapeutic arsenal of psychiatric disorders.

The interest, both academic as of the lay public and the media around the tDCS has increased considerably in recent years^[142]. This interest will probably continue to increase, given the promising results that the technique has presented in psychiatry and also in other field, such

as neurology^[143]. Along with promising results, comes the excitement and interest of the media. The ethical aspects surrounding the tDCS is being intensively discussed. This is necessary to maintain scientific rigor in terms of the information that reaches the lay public^[142].

With the promising results found in different psychiatric disorders, further studies, with robust methodologies, should strive to replicate, expand and optimize the findings, perhaps testing larger, different samples and also varying tDCS parameters such as electrode size, dosage, reference electrode, length of sessions, number of days of application are still warranted in order to provide a definite picture regarding tDCS clinical efficacy in psychiatry.

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