Clinical use of transcranial direct current stimulation in depressive disorders: the state of the art

Utilizzo clinico della stimolazione transcranica con corrente diretta nei disturbi dell'umore: lo stato dell'arte

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Summary

Transcranial direct current stimulation (tDCS) is a noninvasive neuromodulation technique that modifies cortical excitability in a polarity-dependent way that has been increasingly investigated for the treatment of major depression (MD) during recent years. Stimulation for few minutes can induce plastic alterations of cortical excitability and improve cognitive performance. Even if the available evidence, including randomized clinical trials, has generally reported encouraging results in treatment of major depression and treatment-resistant depression, the use of tDCS in mood disorders should still be considered experimental. In fact, further research is needed to better define the optimal stimulation parameters, duration of treatment, durability of clinical effect and predictors of response. Nevertheless, to date, tDCS has shown a favourable tolerability profile, is easy to apply, portable and inexpensive. Taken together, increased use of the technique in the treatment of depressive disorders may be expected in the near future.

Key words

Transcranial direct current stimulation (tDCS) • Major depression (MD) • Treatment-resistant depression (TRD)

Introduction

Over the last decade, therapeutic brain stimulation interventions have been progressively implemented and, in light of the growing body of evidence, some techniques like transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS) and deep brain stimulation (DBS) have received specific approvals for the treatment of some psychiatric disorders. Even though the use of brain stimulation techniques is currently considered investigational in Italy and is subject to approval of the Ethical Committee and specific written informed consent [1], there is an increasing number of publications in this evolving field [2].

In this perspective, a novel neuromodulation technique, namely transcranial direct current stimulation (tDCS), has been investigated for the non-invasive and painless modulation of the human brain activity through the scalp, and in particular at the level of the dorso-lateral prefrontal cortex (DLPFC). The present article will provide a comprehensive and updated overview of the technique along with its main mechanisms of action, safety issues and clinical applications in major depression (MD).

Methods

We reviewed published data on tDCS searching Medline and Cochrane Library databases up to February 2011 using the following keywords: "transcranial direct current stimulation" and "tDCS", each individually matched with "major depression", "depressive disorders", "treatment-resistant depression" and "psychiatric disorders". The literature search for this narrative review was conducted by four independent reviewers (B.B., C.A., G.C. and C.D.). The publications reviewed included meta-analyses, randomized clinical trials, naturalistic and retrospective studies and clinical reviews, as well as descriptive publications on the mechanism of action of the technique. Furthermore, a manual-search for relevant articles was conducted by examining the cited references of retrieved publications. In particular, retrieved articles were used to review the following arguments: 1) introduction to tDCS; 2) historical background of the technique; 3) rational and putative mechanisms of action; 4) differences between tDCS and electroconvulsant therapy (ECT); 5) clinical use of tDCS; 6) clinical trials with tDCS in depressive disorders; and 7) safety issues.

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Results

1) What is tDCS?

Different from TMS which involves magnetic fields to induce electrical stimulating currents into the cerebral cortex, tDCS delivers weak direct currents (1-2 mA) through sponge electrodes on the scalp [3]. Part of the delivered current enters the skull thereby modulating the activity of cortical neurons and leading to polarity-dependent changes in cortical excitability. Two electrodes – an anode and a cathode – are generally placed on the scalp, allowing current to flow throughout the brain between the two sites, and polarization to occur over a relatively wide cortical area (Fig. 1). The current enters the brain from the anode, travels through neuronal tissue, and exits out of the cathode. Usually, researchers refer to this as either anodal or cathodal tDCS on the basis of which electrode is placed over the area that is being stimulated [4].

Even though focality of stimulation is lower with tDCS than TMS, the potential advantages of the former include its portability, safety and reduced costs. In addition, both cathodal and anodal tDCS – the two modalities of action of the technique – cannot be discriminated by the patient either from each other or *vs.* sham stimulation, which is of interest for planning sham-controlled trials [3 4].

2) Historic background

tDCS is the latest neuromodulation technique on the basis of available clinical trials conducted since 2006. Indeed, given that tDCS is perhaps the easiest way of focally stimulating the brain, it is not surprising to find techniques similar to tDCS practiced across Europe almost immediately after practical applications for electricity began to be developed in the late 1880s. Giovanni Aldini (1762-1834), nephew and assistant of Galvani, and Duchenne de Boulogne (1806-1875), resident and colleague of Charcot, were among the first physicians to study the applications of direct current to the body/brain [5 6]. Over subsequent years, due to lack of evident benefits, tDCS and its variants were largely dropped as therapies in Europe and US, but remained field of active research in Russia during the 1940's [4]. At that time, the technique was also referred to as "electrosleep therapy" [7], given that patients often went to sleep during treatment. More recently, a group from Gottingen has actively contributed to the initiation of a new phase of clinical research with tDCS [8] and, to date, the technique is the object of an increasing number of clinical trials in the field of neuropsychiatric disorders.

3) Rational and putative mechanisms of action

Given that, similar to repetitive TMS, the anatomic target of tDCS is the DLPFC, and it is noteworthy to mention the main pathophysiological models linking the pathogenesis of MD to this specific area. Current models, in fact, suggest that 2 major groups of brain regions – a "dorsal" and "ventral" network – account for the formation and modulation of the varied symptoms of affective illness [9 10]. Within this theoretical framework, depression is hypothesized to involve concomitant hypoactivation of dorsal prefrontal regions and hyperactivation of ventral prefrontal regions, particularly in the left hemisphere. Therefore, remission of symptoms may require facilitation of hypoactive dorsal brain regions and inhibition of hyperactive ventral areas [9 10]. Nevertheless, alternative treatments that affect other cortical or subcortical regions that project to the dorsal and ventral systems could also initiate the requisite compensatory changes. For instance, the rostral subdivision of the cingulate cortex, in particular, is postulated to play a key role in treatment response because of its reciprocal connectivity and putative regulatory relationship with the aforementioned dorsal and ventral networks [9-11]. Ultimately, transcranial neuromodulatory techniques like TMS and tDCS are believed to restore physiologic intra- and inter-hemispheric functional balance.

In terms of mechanisms of action, electrophysiological data suggest that tDCS may strengthen synaptic connections through a mechanism similar to long-term potentiation, modulate neurotransmitter systems and promote brain derived neurotrophic factor-dependent synaptic plasticity [3 12]. In addition, changes in resting membrane potential, spontaneous neuronal firing rates, cerebral blood flow and metabolism have been reported [3 12 13].

4) tDCS and ECT: what differences?

Despite sharing the common feature of applying electrical current to the brain, there are significant differences between tDCS and ECT. In tDCS, in fact, small currents are utilized in a typical session of 20-30 min, allowing the brain to acclimatize to this constant and soft current. On the other hand, in ECT, a short and powerful bidirectional current is applied, preventing the brain from adapting to the stimulus and inducing, consequently, a seizure [4]. Waveforms of both techniques are shown in Figure 2. It is noteworthy to highlight that the total amount of electricity used in a session of tDCS does not significantly differ from a session of ECT, meaning that the brain reacts differently on the basis of specific characteristics (e.g., duration of application and type of electric current) of the applied stimulus.

5) Clinical applications of tDCS

Given that the modulatory effects of tDCS over the cortex can be long-lasting, its action on cognitive and emotional functions has been investigated in healthy subjects, neurologic conditions (including stroke rehabilitation [14], fluent aphasia [15], migraine [16], Parkinson's Disease [17], etc.) and psychiatric disorders (i.e., MD and TRD) [18]. Despite encouraging preliminary results in the field of depressive disorders, it needs to be stressed that tDCS is currently considered an investigational therapy with no formal approval for the treatment of these conditions by either the Food and Drug Administration or European Medicines Agency, and there are no guidelines defining the optimal parameters of stimulation in terms of safety and efficacy.

With respect to clinical applications of tDCS in depressive disorders, it is noteworthy to highlight that MD has been associated with alterations of cortical activity and excitability [19-21], particularly in prefrontal areas, as already mentioned. Therefore, it is reasonable to hypothesize that altering this pathological state with techniques of brain stimulation or modulation, such as tDCS, may provide a therapeutic target.

6) Clinical trials with tDCS in depressive disorders

Taken as a whole, relatively few studies with tDCS have been published in the treatment of MD and TRD [22]. Three studies have examined the effects of the technique in a double-blind sham-controlled design in depressed patients, while the remainder have assessed patients with TRD in open-label conditions (Table I).

A pivotal, two-week, double-blind, sham-controlled tDCS trial in major depressive disorder, with the anodal modality over the DLPFC, 2 mA current for 20 min, reported a mean symptoms improvement of 40% for

TABLE I.
Published clinical trials with tDCS in Major Depression. *Studi clinici pubblicati sull'utilizzo della tDCS nel trattamento della depressione maggiore.*

Study	Methods	Sample	Stimulation Parameters	Outcome
Fregni et al., 2006 [23]	Double-blind, sham-controlled; 2 weeks	20 patients with Major Depression	Anodal modality over the DLPFC, 2 mA for 20 minutes	Mean symptom improvement of 40% compared to 10% in the sham group. Overall good tolerability
Boggio et al., 2008 [24]	Parallel-group, double-blind, sham-controlled; 2 weeks	40 drug-free patients with Major Depression	Active stimulation over the DLPFC	Active stimulation was significantly better than sham. Overall good tolerability
Palm et al., 2009 [25]	Open-label single case report, augmentative tDCS, 4 weeks	1 patient with Treatment Resistant Depression	Anodal tDCS over DLPFC	Only modest improvement of depressive symptoms
Ferrucci et al., 2009 [26]	Open-label trial; 1 week	14 patients with Treatment Resistant Depression and high suicide risk	Active stimulation over the DLPFC	Significant improvement of depressive symptoms with favourable tolerability
Loo et al., 2010 [27]	Double-blind sham-controlled; 2 weeks	40 patients with Major Depression	Anodal stimulation over the left DLPFC, cathode on the lateral side of the contralateral orbit	Significant improvement of depression scores despite no between-group difference in the 5-session, sham-controlled phase. Minor side-effects
Brunoni et al., 2011 [28]	Open-label trial; 2 sessions/day, 1 week	14 unipolar and 14 bipolar subjects with Major Depression	Anodal electrode placed on the DLPFC and cathodal on the right	Similar rates of improvement in both groups with no adverse effects
Dell'Osso et al., 2011 [29]	Blind-rater, 2 sessions/day, augmentative tDCS, 1 week + 1 week follow-up	23 patients with poor responder Major Depression	Active stimulation over the DLPFC	Significant efficacy and good tolerability of tDCS with clinical benefit being progressive and extended to the 1st week of follow-up

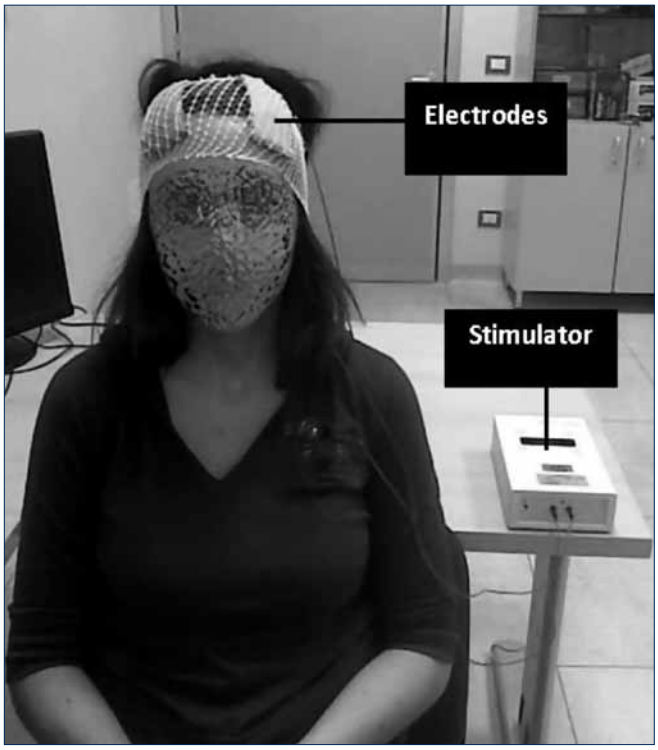

FIGURE 1.
Representation of the main tDCS components. *Rappresentazione dei principali componenti della tDCS.*

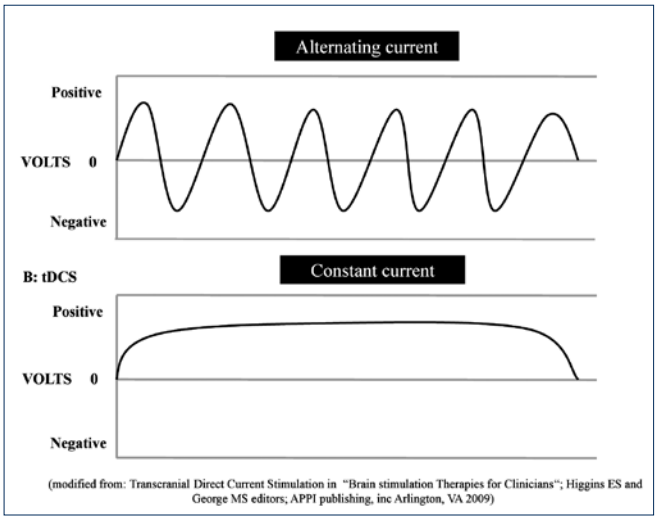

FIGURE 2.
Differences in electrical currents between tDCS and ECT. *A: ECT, B: tDCS. Differenze fra le correnti elettriche di tDCS ed ECT. A: ECT, B: tDCS.*

the active stimulation compared to 10% in the sham group [23]. In terms of safety, tDCS was well tolerated with minor side-effects. More recently, the same group conducted a two-week, parallel-group, double-blind, randomized clinical trial in 40 drug-free patients with MD. Study design included two active modalities of tDCS (DLPFC and occipital) *vs.* sham and the active stimulation over the DLPFC was found to be of largest benefit with overall good tolerability. Of note, antidepressant effects were maintained for one month after the end of treatment [24]. A subsequent case-report showed only modest improvement of depressive symptoms with 4 weeks of augmentative anodal tDCS over DLPFC in a patient with TRD [25]. Subsequently, however, an open-label trial with twice-daily tDCS over the DLPFC for five days found a significant improvement of depressive symptoms with favourable tolerability in 14 patients with TRD and high suicide risk [26]. A recent double-blind sham-controlled trial conducted with 40 depressed subjects reported a significant improvement of depression scores over 10 tDCS sessions (anodal stimulation centred over the left DLPFC, with the cathode placed on the lateral side of the contralateral orbit) with only minor side-effects. However, no between-group difference in the five-session, sham-controlled phase could be detected [27]. A recent study assessing differential efficacy of tDCS in unipolar (n = 14) *vs.* bipolar (n = 14) depressed subjects in a twice-daily, five-day open treatment – anodal electrode placed on the left prefrontal cortex and cathodal on the right cortical area – found similar rates of improvement in both groups with no adverse effects [28]. Finally, in a recent blind-rater trial, 23 patients with TRD were treated with augmentative tDCS for five days, two sessions per day. A significant reduction in rating scales scores was observed at study endpoint supporting the efficacy and good tolerability of tDCS with clinical benefits being progressive and extending to the first week of follow-up. Of clinical interest, among different outcome measures, tDCS showed significant improvement in melancholic symptoms which are considered the core symptoms of MD [29].

7) Safety issues with tDCS

To date, only a few studies on the safety of tDCS have been published [30,31], and safety information must be derived from the above-mentioned clinical trials which, taken as a whole, report a favourable tolerability, also in light of the minimum level of invasiveness of the technique. On one hand, it seems that the main reported problem may be a transient skin reaction below the stimulating electrode, which only rarely becomes a small burn. In addition, transient headache, skin itching and redness have been reported. On the other hand, safety concerns for the operator have not been described. In fact, a recent systematic review assessing adverse effects associated with tDCS [32] was published with 209 identified studies, among which

117 (56%) different adverse events. The most common were, for active *vs*. sham tDCS group, itching (39.3% *vs*. 32.9%), tingling (22.2% *vs*. 18.3%), headache (14.8% *vs*. 16.2%), burning sensation (8.7% *vs*. 10%, $p > 0.05$) and discomfort (10.4% *vs*. 13.4%). None of them, however, reached statistical significance and meta-analytical techniques, moreover, could be applied in only few studies. No definite conclusions could be withdrawn due to the heterogeneity of a low number of studies.

Finally, a case of hypomania induction with tDCS has been recently reported. A 33-year-old female with bipolar II disorder, on mood stabilizers who had previously participated in a study of tDCS for the treatment of MD with a bifrontal electrode modality of stimulation without any mood-switch, became hypomanic when she received a subsequent course of tDCS with a frontoextracephalic configuration [33].

Conclusions

Based on the above, there is not sufficient evidence to recommend tDCS as a therapeutic modality for depression. However, a growing body of evidence with double-blind sham-controlled trials, in particular, represent a first step in this direction and encourage further studies in this area. As for TMS, additional investigation is required to clarify the optimal parameters of stimulation (e.g., duration of treatment, electrode placement, etc.), clinical target (i.e., MD or TRD), treatment modality (i.e., monotherapy or augmentation), duration of benefit and patient characteristics that may respond to tDCS. In particular, unequivocal evidence about the potential antidepressant efficacy of tDCS is expected from large double-blind sham controlled trials currently in progress [34]. The potential to combine tDCS with other brain stimulation techniques like TMS is also under investigation [35]. Nevertheless, the implementation of novel neuromodulatory techniques with minimal levels of invasiveness and minor side effects – like tDCS – in the field of psychiatric treatments [36] provides a further confirmation of the pathophysiological acquisitions in this area and the presence of a "third way" of treatments in addition to psychotropic drugs and talk therapies.

Financial disclosure

Prof. Alberto Priori is president and is shareholder of the company Newronika Srl, Milan, and reports his patent pending "Process for reducing neuromuscular fatigue caused by exercise", Patent number: WO2008155114 (A1).

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