

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

B. Dell'Osso*, F. Castellano*, C. Arici*, B. Benatti*, C. Dobrea*, G. Camuri*, A. Priori**, A.C. Altamura*

* Department of Psychiatry, University of Milan, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy; ** Center of Neurostimulation, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, University of Milan, Italy

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 experi-

mental. 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 consent¹, there is an increasing number of publications in this evolving field².

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.

Correspondence

Bernardo Dell'Osso, Department of Psychiatry, University of Milano, Fondazione IRCCS Ca' Grande, Ospedale Maggiore Policlinico, via Francesco Sforza 35, 20122 Milano, Italy • Tel. +39 02-55035994 • Fax: +39 02-50320310 • E-mail: bernardo.dellosso@unimi.it

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 scalp³. 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 stimulated⁴. 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's⁴. 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 Göttingen has actively contributed to the initiation of a new phase of clinical research with tDCS⁸ 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 seizure⁴. 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 emo-

tional functions has been investigated in healthy subjects, neurologic conditions (including stroke rehabilitation¹⁴, fluent aphasia¹⁵, migraine¹⁶, Parkinson's Disease¹⁷, 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 excitability¹⁹⁻²¹, 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 TRD²². 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 the active stimulation compared to 10% in the sham group²³. In terms of safety, tDCS was well tolerated with minor side-effects. More recently, the same group con-

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 1 st week of follow-up



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

ducted 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 treatment²⁴. A subsequent case-report showed only modest improvement of depressive symptoms with 4 weeks of augmentative anodal tDCS over DLPFC in a patient with TRD²⁵. 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 risk²⁶. 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 detected²⁷. 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

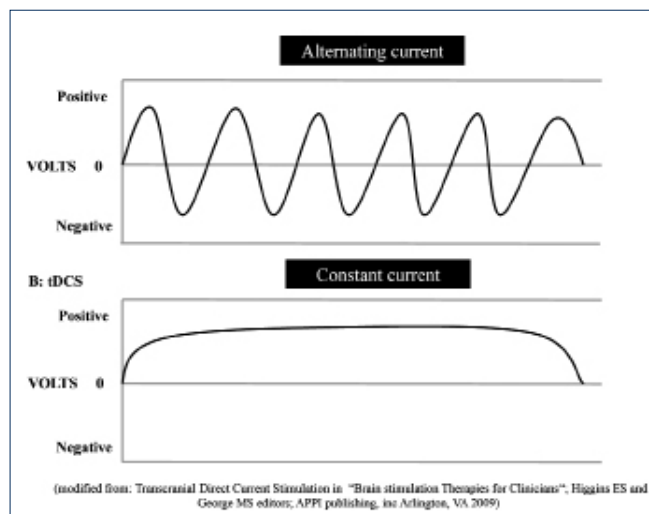


FIGURE 2. Differences in electrical currents between tDCS and ECT. *A: ECT B: tDCS. Differenze fra le correnti elettriche di tDCS ed ECT. A: ECT, B: tDCS.*

cortex and cathodal on the right cortical area – found similar rates of improvement in both groups with no adverse effects²⁸. 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 MD²⁹.

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 tDCS³² 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 frontoextracranial configuration³³.

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 progress³⁴. The potential to combine tDCS with other brain stimulation techniques like TMS is also under investigation³⁵. Nevertheless, the implementation of novel neuromodulatory techniques with minimal levels of invasiveness and minor side effects – like tDCS – in the field of psychiatric treatments³⁶ 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).

Other Authors do not have any direct or indirect financial or personal relationships, interests, and affiliations relevant to the subject matter of the manuscript which might imply any conflict of interest.

References

- 1 Rabins P, Appleby BS, Brandt J, et al. *Scientific and ethical issues related to deep brain stimulation for disorders of mood, behaviour, and thought*. Arch Gen Psychiatry 2009;66:931-7.
- 2 Dell’Osso B, Altamura AC. *Tecniche di brain stimulation in disturbi psichiatrici resistenti*. Rivista di Psichiatria 2006;41:289-300.
- 3 Priori A, Hallett M, Rothwell JC. *Repetitive transcranial magnetic stimulation or transcranial direct current stimulation?* Brain Stimul 2009;2:241-5.
- 4 Higgins ES, George MS. *Transcranial direct current stimulation in: Brain stimulation therapies for clinicians*. Arlington: American Psychiatric Publishing, Inc. 2009, pp. 147-56.
- 5 George MS. *Reanimating the face: early writings by Duchenne and Darwin on the neurology of facial emotion expression*. J Hist Neurosci 1994;3:21-33.
- 6 Parent A. *Giovanni Aldini: from animal electricity to human brain stimulation*. Can J Neurol Sci 2004;31:576-84.
- 7 Feighner JP. *Electrosleep therapy: current usage in psychiatry*. Calif Med 1971;115:44.
- 8 Rosenkranz K, Nitsche MA, Tergau F, et al. *Diminution of training-induced transient motor cortex plasticity by weak transcranial direct current stimulation in the human*. Neurosci Lett 2000;296:61-3.
- 9 Mayberg HS. *Limbic-cortical dysregulation: a proposed model of depression*. J Neuropsychiatry Clin Neurosci 1997;9:471-481.
- 10 Davidson RJ. *Anterior electrophysiological asymmetries, emotion, and depression: conceptual and methodological conundrums*. Psychophysiology 1998;35:607-14.
- 11 Blumberg HP, Stern E, Martinez D, et al. *Increased anterior cingulate and caudate activity in bipolar mania*. Biol Psychiatry 2000;48:1045-52.
- 12 Nitsche MA, Fricke K, Henschke U, et al. *Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans*. J Physiol 2003;553:293-301.
- 13 Fritsch B, Reis J, Martinowich K, et al. *Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning*. Neuron 2010;66:198-204.
- 14 Schlaug G, Renga V, Nair D. *Transcranial direct current stimulation in stroke recovery*. Arch Neurol 2008;65:1571-6.
- 15 Fridriksson J, Richardson JD, Baker JM, et al. *Transcranial direct current stimulation improves naming reaction time in fluent aphasia: a double-blind, sham-controlled study*. Stroke 2011;42:819-21.
- 16 Antal A, Kriener N, Lang N, et al. *Cathodal transcranial direct current stimulation of the visual cortex in the prophylactic treatment of migraine*. Cephalalgia 2011;31:820-8.
- 17 Benninger DH, Lomarev M, Lopez G, et al. *Transcranial direct current stimulation for the treatment of Parkinson’s disease*. J Neurol Neurosurg Psychiatry 2010;81:1105-11.
- 18 Nitsche MA. *Transcranial direct current stimulation: a new treatment for depression?* Bipolar Disord 2002;4(Suppl 1):98-9.
- 19 Schaffer CE, Davidson RJ, Saron C. *Frontal and parietal electroencephalogram asymmetry in depressed and nondepressed subjects*. Biol Psychiatry 1983;18:753-62.

- ²⁰ Shajahan PM, Glabus MF, Gooding PA, et al. *Reduced cortical excitability in depression. Impaired post-exercise motor facilitation with transcranial magnetic stimulation.* Br J Psychiatry 1999;174:449-54.
- ²¹ Bajbouj M, Lisanby SH, Lang UE, et al. *Evidence for impaired cortical inhibition in patients with unipolar major depression.* Biol Psychiatry 2006;59:395-400.
- ²² Dell'osso B, Priori A, Altamura AC. *Efficacy and safety of transcranial direct current stimulation in major depression.* Biol Psychiatry 2011;69:e23-4.
- ²³ Fregni F, Boggio PS, Nitsche MA, et al. *Treatment of major depression with transcranial direct current stimulation.* Bipolar Disord 2006;8:203-4.
- ²⁴ Boggio PS, Rigonatti SP, Ribeiro RB, et al. *A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression.* Int J Neuropsychopharmacol 2008;11:249-54.
- ²⁵ Palm U, Keeser D, Schiller C, et al. *Transcranial direct current stimulation in a patient with therapy-resistant major depression.* World J Biol Psychiatry 2009;10:632-5.
- ²⁶ Ferrucci R, Bortolomasi M, Vergari M, et al. *Transcranial direct current stimulation in severe, drug-resistant major depression.* J Affect Disord 2009;118:215-9.
- ²⁷ Loo CK, Sachdev P, Martin D, et al. *A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression.* Int J Neuropsychopharmacol 2010;13:61-9.
- ²⁸ Brunoni AR, Ferrucci R, Bortolomasi M, et al. *Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder.* Prog Neuropsychopharmacol Biol Psychiatry 2011;35:96-101.
- ²⁹ Dell'Osso B, Zanoni S, Castellano F, et al. *Transcranial direct current stimulation in patients with poor responder major depressive episode.* Eur Psychiatry 2011 May 27 [Epub ahead of print].
- ³⁰ Nitsche MA, Liebetanz D, Lang N, et al. *Safety criteria for transcranial direct current stimulation (tDCS) in humans.* Clin Neurophysiol 2003;114:2220-2.
- ³¹ Poreisz C, Boros K, Antal A, et al. *Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients.* Brain Res Bull 2007;72:208-14.
- ³² Brunoni AR, Valiengo L, Baccaro A, et al. *Sertraline vs. Electrical Current Therapy for Treating Depression Clinical Trial – SELECT TDCS: design, rationale and objectives.* Contemp Clin Trials 2011;32:90-8.
- ³³ Gálvez V, Alonzo A, Martin D, et al. *Hypomania Induction in a Patient With Bipolar II Disorder by Transcranial Direct Current Stimulation (tDCS).* J ECT 2011 Jan 4 [Epub ahead of print].
- ³⁴ Brunoni AR, Amadera J, Berbel B, et al. *A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation.* Int J Neuropsychopharmacol 2011 Feb. 15 [Epub ahead of print].
- ³⁵ Loo C, Martin D, Pigot M, et al. *Transcranial direct current stimulation priming of therapeutic repetitive transcranial magnetic stimulation: a pilot study.* J ECT 2009;25:256-60.
- ³⁶ Fox D. *Neuroscience: Brain buzz.* Nature. 2011;472:156-8.