

Novel neurotherapeutics in psychiatry: use and rationale of transcranial direct current stimulation in major depressive disorder

Novas neuroterapêuticas em psiquiatria: racional e uso da estimulação transcraniana por corrente contínua no transtorno depressivo maior

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Abstract

Background: Transcranial direct current stimulation (tDCS) is a novel non-pharmacological intervention being investigated for the treatment of major depressive disorder (MDD). **Objective:** To perform an updated review of tDCS for MDD. **Method:** Systematic review in Medline/PubMed and other databases of all clinical studies evaluating the clinical efficacy of tDCS in MDD, from the first date available to December/2013. **Results:** Out of 55 articles, 24 were included, being 6 open-label studies; 8 randomized, double-blind, sham-controlled trials; 2 follow-up studies; 2 meta-analyses and 6 case reports. We observed an improvement of 20-40% in depressive symptoms, being slightly better in open studies. Five randomized clinical trials displayed positive results. The meta-analyses presented mixed results; although none included the study of Brunoni *et al.* (2013) that represents almost 50% of the evaluated sample. Open-label studies and case reports also investigated tDCS in bipolar depression, post-stroke depression and employed different parameters of stimulation. **Discussion:** TDCS is a novel, promising treatment for MDD. Definite evidence from large, ongoing clinical trials will be available in the next years.

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Keywords: Transcranial direct current stimulation, major depressive disorder, systematic review, non invasive neuromodulation, interventional psychiatry, neurotherapeutics.

Resumo

Contexto: A estimulação transcraniana por corrente contínua (ETCC) é uma nova intervenção não farmacológica investigada como tratamento no transtorno depressivo maior (TDM). **Objetivo:** Apresentar uma revisão atualizada da ETCC no TDM. **Método:** Revisão sistemática no banco de dados Medline/PubMed e outros de todos os estudos clínicos publicados avaliando a eficácia da ETCC no TDM, da primeira data disponível a dezembro/2013. **Resultados:** De 55 artigos, 24 foram incluídos, sendo 6 estudos abertos; 8 ensaios clínicos randomizados, duplo-cego, placebo controlados; 2 estudos de seguimento; 2 metanálises e 6 relatos de caso. Observa-se uma melhora de 20-40% nos sintomas depressivos, sendo ligeiramente maior nos estudos abertos. Entre os ensaios controlados, 5 demonstraram eficácia da técnica. As metanálises divergiram quanto aos resultados, mostrando presença e ausência de eficácia e ausência da ETCC. Porém, nenhuma incluiu o estudo de Brunoni *et al.* (2013), que representa quase 50% da população estudada. Estudos abertos e relatos de caso também investigaram o uso da ETCC na depressão bipolar, na depressão pós-AVC e usaram variações nos parâmetros de estimulação. **Conclusões:** A ETCC é uma técnica promissora no tratamento da TDM. Evidências definitivas devem estar disponíveis nos próximos anos, com a divulgação de resultados de grandes ensaios clínicos em andamento.

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Palavras-chave: Estimulação transcraniana por corrente contínua, transtorno depressivo maior, revisão sistemática, neuromodulação não invasiva, psiquiatria intervencionista, neuroterapêuticas.

Introduction

The use of electricity as a clinical treatment is not novel in medical literature. For instance, there are reports of using the “torpedo-fish” to treat pain since the Ancient times¹. Nonetheless, the controlled use of electric currents for medical disorders only begun in the 18th century, with the development of the voltaic pile – even though, the application of electric currents over one’s scalp was still erratic and poorly executed². In 1960s and 1970s there are reports of a method of non-invasive brain stimulation named “brain polarization”, quite similar to modern transcranial direct current stimulation (tDCS), which could enhance mood and alertness in healthy volunteers³ and treat depression^{4,5}. Later on, this method was largely abandoned, possibly due to the advancement of psychopharmacology⁶ and the social stigma of electroconvulsive therapy (ECT) that hindered the development of other forms of non-invasive brain stimulation.

In fact, tDCS was only reappraised as a neuromodulatory tool in the turn of the 21st century, with the seminal works of Priori *et al.*⁷ and Nitsche and Paulus⁸ who 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. Notwithstanding its exact mechanisms of action being still elusive, tDCS probably operates by inducing small changes (< 1mV) in the membrane potential⁹, thus acting in the frequency of spike timing and modifying net cortical excitability¹⁰. The mechanisms of action of tDCS occur also at the synaptic level. For instance, glutamate antagonists abolish tDCS after-effects, while NMDA-agonists enhance them¹¹.

Moreover, tDCS presents a low rate of adverse effects and is a safe technique when used according to the standard procedures. In a recent systematic review of clinical studies, our group¹² observed the lack of serious adverse effects associated with tDCS; with the excep-

tion of one case of skin burn¹³. In an animal study of safety, Liebetanz *et al.*¹⁴ showed, in an animal study of safety, that cathodal-induced brain lesions only occurred when the stimulation intensities almost one hundred times higher than used in clinical studies. In addition, tDCS does not adversely affect brain and heart activity, respectively measured using EEG and EKG records¹⁵⁻¹⁷. In fact, the only adverse effect particularly associated with tDCS is skin redness¹⁸ – even though, this effect is mild and does not seem to compromise blinding in sham-controlled tDCS trials¹⁹, which consist in turning off the device after < 30-60 seconds of stimulation, remaining turned off until the end of the session²⁰. Finally, tDCS is, compared to repetitive transcranial magnetic stimulation (rTMS), 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 see²¹), and, among them, tDCS has been showing particularly positive results in major depression, with the anode positioned over the left dorsolateral prefrontal cortex (DLPFC) and the cathode over the right DLPFC, the right supraorbital area or in an extra-cephalic position². The rationale for using this montage in depression rests on: (1) the prefrontal asymmetry theory of depression, with relative hypoactivity over the left and relative hyperactivity over the right^{22,23}; (2) the improvement in working memory and affective processing observed after one-single tDCS session in depressed patients²⁴⁻²⁶; (3) the top-down, neuromodulatory effects of tDCS, possibly reversing the imbalance between hypoactive cortical areas and hyperactive subcortical areas^{23,25}, (4) the clinical effects observed in rTMS using either rapid, facilitatory stimulation over the left DLPFC and slow, inhibitory stimulation over the right DLPFC^{27,28}.

The purpose of this review is, therefore, to summarize the findings of all clinical studies using tDCS in depression hitherto, as well as to discuss future challenges and perspectives for using tDCS as a novel intervention in the therapeutic arsenal of major depression.

Methods

We performed a literature review in PubMed/Medline, Scopus and Web of Science databases from English-written articles from 1998 to December 2013. The key search terms in PubMed were: “transcranial direct current stimulation” OR “transcranial electric stimulation” AND “depressive disorder”. We did not include editorials or articles reporting duplicated data. For the purposes of this review, meta-analyses evaluating the efficacy of tDCS in depression were also included.

Results

Out of 55 articles, 23 fulfilled our eligibility criteria. According to the study design, retrieved articles could be further classified in five types, as described below:

Open-label studies

Rigonatti *et al.*²⁹ compared the clinical effects of active prefrontal tDCS vs. a six-week treatment protocol with 20 mg/day fluoxetine, finding that the effects of both therapies were similar. Ferrucci *et al.*³⁰ used tDCS in 14 patients with severe depression using 2mA per day, twice a day for 5 consecutive days, demonstrating an improvement of about 30% on depressive symptoms. In another study, Ferrucci *et al.*³¹ evaluated 32 patients, finding that tDCS improvement was bolder in severe depression (50%) than those in mild/moderate depression (10%). Brunoni *et al.*³² used anodal tDCS over the left DLPFC in 31 patients (14 with bipolar and 17 with unipolar depression). Depressive symptoms in both study groups improved immediately after the 5th session. The beneficial effect persisted after one week and one month. Another recent open study³³ demonstrated the efficacy of tDCS in 23 patients with refractory depression, with a mean reduction in symptoms of 25%. Martin *et al.*³⁴ performed tDCS sessions consecutively for 20 days, with 2mA for 20 minutes, in 11 patients

with depression. In this open study, which placed the cathode on the right deltoid muscle, there was also a significant reduction in symptoms of about 44%. Finally, in the largest open-label sample to date, Brunoni *et al.*³⁵, in 82 patients with unipolar and bipolar depression, found that five days of twice daily tDCS significantly improved depression symptoms. This study also showed that the effects of tDCS are enhanced when associated with antidepressants and decreased with benzodiazepines (Table 1).

Randomized, sham-controlled trials

Fregni *et al.*³⁶ in the first sham-controlled, randomized clinical trial, found a significant decrease in the Hamilton Depression Rating Scale and Beck Depression Inventory after 5 days of active stimulation with 1mA for 20 min once daily in 10 patients, with a mean reduction in depression scores of 60-70% for active tDCS group relative to baseline. Similar results were demonstrated in a further study in antidepressant-free patients with recurrent major depressive episodes after 5 days of active tDCS stimulation³⁷ with 18 patients. Boggio *et al.*³⁸ recruited 40 patients with moderate to severe depression, evaluating depression improvement after 30 days of stimulation (patients received 10 tDCS sessions). Only prefrontal tDCS reduced depressive symptoms significantly.

After these positive results, three other studies reported negative findings. Loo *et al.*³⁹ recruited 40 patients to receive active vs. sham tDCS and did not find significant differences between these groups. However, treatment was provided for only five treatment sessions, 3 days per week. This study also did not exclude patients with personality disorders. Palm *et al.*⁴⁰ recruited 22 patients with depression and randomized them to receive 1mA stimulation, 2mA stimulation or sham tDCS in a cross-over design. Active and placebo tDCS was applied for 2 weeks, but no differences in depression improvement were found. Finally, Blumberger *et al.*⁴¹ did not find significant differences between active vs. sham tDCS in a tertiary sample of 24 refractory patients. All these studies acknowledged methodological limitations (notably small sample sizes) that could have undermined the efficacy of tDCS.

In fact, two larger, recent tDCS trials observed that tDCS was an effective treatment for depression. Loo *et al.*⁴² randomized 64 patients to receive active or sham tDCS (2 mA, 15 sessions over 3 weeks), followed by a 3-week open-label active treatment phase. Mood and neuropsychological effects were assessed. There was significantly greater improvement in mood after active than sham treatment. Attention and working memory improved after a single session of active but not sham tDCS. There was no decline in neuropsychological functioning after 3-6 weeks of active stimulation. Finally, our group⁴³ enrolled 120 antidepressant-free patients with moderate and severe depression who were randomized in four arms (2x2 design): sham tDCS and placebo pill, sham tDCS and sertraline, active tDCS and placebo pill and active tDCS and sertraline (the study name was Sertraline vs. Electric Current Therapy to Treat Depression Clinical Trial – SELECT-TDCS; its design is described in⁴⁴). The tDCS parameters were 2mA per 30 minutes/day, for 2 weeks and 2 extra tDCS sessions every other week until week 6 (study endpoint); the dose of sertraline was fixed (50 mg/day). Our main findings were that: (1) the combined tDCS/sertraline was significantly more effective than in the other treatment groups in reducing depressive symptoms; (2) tDCS and sertraline efficacy did not differ; (3) active tDCS as a monotherapy was also more effective than the placebo group. Of note, we also found (1) no decline in cognitive improvement after tDCS or sertraline treatment; (2) 5 cases of hypomanic/manic episodes in the combined treatment group vs. one case in tDCS-only, one case in sertraline-only and no cases in the placebo arm (although this difference was not statistically significant); (3) use of benzodiazepines and treatment-resistant depression were both predictors of lower response; (4) treatment was well-tolerated with mild adverse effects, which were of similar frequency in both arms, except for skin redness that was more prevalent in the active group. Biological markers were also evaluated (some of them are discussed below) (Table 2).

Table 1. Open-label tDCS studies

Author	Sample (n)	Anode	Cathode	Intensity (A/m ²)	Number of sessions	Depression improvement
Rigonatti <i>et al.</i> , 2008 ²⁹	42	F3	R SO	0.57	10 (1x/day)	36.20%
Ferrucci <i>et al.</i> , 2009 ³⁰	14	F3	F4	0.57	10 (2x/day)	32.1%
Ferrucci <i>et al.</i> , 2009 ³¹	32	F3	F4	0.57	10 (2x/day)	27.70%
Brunoni <i>et al.</i> , 2011 ³²	31	F3	F4	0.57	10 (2x/day)	45.2%
Martin <i>et al.</i> , 2011 ³⁴	11	F3	R arm	0.57	20 (1x/day)	42.80%
Dell'Osso <i>et al.</i> , 2012 ³³	23	F3	F4	0.57	10 (2x/day)	31.30%
Brunoni <i>et al.</i> , 2013 ³⁵	82	F3	F4	0.57	10 (2x/day)	18%

F3: left dorsolateral prefrontal cortex; F4: right dorsolateral prefrontal cortex; R arm: right arm; R SO: right supraorbital area; tDCS: transcranial direct current stimulation. Depression improvement is the score change in from baseline to endpoint, for each study.

Follow-up studies

Two studies evaluated the efficacy of tDCS in the maintenance phase of the depressive episode. We⁴⁴ recruited 42 patients who were tDCS responders from the SELECT-TDCS trial and performed tDCS sessions every other week for 3 months and then every month for 3 additional months (tDCS sessions were interrupted earlier in case of relapse, characterizing failure treatment). In this follow-up study, we observed that treatment-resistant depression was significantly associated with an increased relapse rate (over 80% in 6 months). On the other hand, > 80% non-refractory patients sustained clinical response for at least 6 months. In this trial, the overall relapse rate in 6 months was around 50%, with most relapses occurring in the first 3 months. Another group⁴⁵ also followed patients previously recruited to a randomized clinical trial (n = 26) and performed weekly tDCS sessions for 3 months, followed by tDCS sessions every other week in the remaining 3 months. Similarly to our findings, a relapse rate around 50% in 6 months was observed. However, most relapses occurred after the 3 initial months, when tDCS sessions were spaced. Therefore, although the evidence is very preliminary, this trial suggests that an intensive continuation treatment (at least once a week tDCS session) during early follow-up might be recommended to sustain clinical improvement.

Case reports

The available case reports for tDCS in depression fall into three scenarios: (1) report of emergent hypomanic/manic symptoms following tDCS⁴⁶⁻⁴⁹; (2) description of tDCS use in a specific type of depression (post-stroke depression)⁵⁰ and (3) evaluation of clinical symptoms and EEG findings in a patients with treatment-resistant depression⁵¹ (Table 3).

Meta-analyses

The two published meta-analyses for tDCS in depression showed disparate results – interestingly, these meta-analyses evaluated the same randomized clinical trials described above (except for our factorial trial that was not published yet) as they used different outcome measures – i.e., Kalu *et al.*⁵² employed continuous outcomes (depression improvement) and Berlim *et al.*⁵³ dichotomic measures (response and remission) for estimating the effect size of the intervention. In an updated meta-analysis including data from our recent clinical trial, we found that active vs. sham tDCS was more effective using both continuous and categorical outcomes (Shiozawa *et al.*, study under review), with the effect being small to moderate.

Table 2. Randomized, controlled tDCS trials

Author	Sample (n)	Anode	Cathode	Intensity (A/m ²)	Number of sessions	Outcome (score improvement)
Fregni <i>et al.</i> , 2006 ³⁶	10	F3	R SO	0.28	5 (every other day)	60%
Fregni <i>et al.</i> , 2006 ³⁷	18	F3	R SO	0.28	5 (every other day)	58.50%
Boggio <i>et al.</i> , 2008 ³⁸	40	F3	F4	0.28	10 (1x/day)	40.40%
Loo <i>et al.</i> , 2010 ³⁹	40	F3	R SO	0.28	5 (every other day)	19.5%
Palm <i>et al.</i> , 2011 ⁴⁰	22	F3	R SO	0.28/0.57	10 (1x/day)	14.6%/16.7%
Blumberger <i>et al.</i> , 2012 ⁴¹	24	F3	F4	0.57	15 (1x/day)	24.50%
Loo <i>et al.</i> , 2012 ⁴²	64	F3	R SO	0.57	15 (1x/day)	28.40%
Brunoni <i>et al.</i> , 2013 ⁴³	120	F3	F4	0.8	10 (1x/day)	29.8 %/55.6%*

F3: left dorsolateral prefrontal cortex; F4: right dorsolateral prefrontal cortex; R arm: right arm; R SO: right supraorbital area; tDCS: transcranial direct current stimulation. Depression improvement is the score change in from baseline to endpoint, for each study. * Represents depression improvement in the active tDCS/placebo-pill and active tDCS/sertraline arms, respectively.

Table 3. TDCS case reports

Author	Sample (n)	Anode	Cathode	Intensity (A/m ²)	Number of sessions
Palm <i>et al.</i> , 2009 ⁵¹	1	F3	R SO	0.28	16
Baccaro <i>et al.</i> , 2010 ⁴⁶	1	F3	F4	0.57	5
Arul-Anandam <i>et al.</i> , 2010 ⁴⁸	1	F3	R SO	0.28	5
Brunoni <i>et al.</i> , 2011 ⁴⁷	1	F3	F4	0.57	5
Bueno <i>et al.</i> , 2011 ⁵⁰	1	F3	F4	0.57	10
Galvez <i>et al.</i> , 2011 ⁴⁹	1	F3	R arm	0.57	14

F3: left dorsolateral prefrontal cortex; F4: right dorsolateral prefrontal cortex; R arm: right arm; R SO: right supraorbital area; tDCS: transcranial direct current stimulation. Depression improvement is the score change in from baseline to endpoint, for each study.

Discussion

We reviewed 24 clinical studies (from case reports to randomized clinical trials) and two meta-analyses that evaluated the clinical efficacy of tDCS in major depression. The clinical improvement, considering changes in depression scores, ranged from 20-40% according to number of tDCS applications, sample characteristics (refractoriness, severity) and study design, with open-label trials showing discretely better results than the active arms of sham-controlled trials. Such improvement is in the same range of antidepressant drug treatment⁵⁴ and, in fact, two studies that directly compared tDCS vs. fluoxetine²⁹ and sertraline⁴³ found similar improvement rates in the pharmacological and non-pharmacological arms. This could suggest that tDCS might be a *substitute* for pharmacotherapy when its use is hindered, for instance, due to medical conditions⁵⁵. The advantages of substituting medicines to tDCS are that the latter is virtually absent of side effects and pharmacological interactions. On the other hand, the necessity of daily tDCS sessions requires that the patients daily return to the service, undermining adhesion. In this context, the development of portable, “home-use” tDCS devices could help in this issue, as the number of visits to the clinical center would be dramatically reduced.

Moreover, other reviewed studies evaluated the role of tDCS as an *augmentation* strategy for pharmacotherapy, showing that the combined therapy of tDCS with antidepressant drugs was associated with superior improvement and, interestingly, that tDCS combined with benzodiazepine drugs presented decreased efficacy^{35,43}. These findings might be explained by neurophysiological studies in healthy volunteers that evaluated motor evoked potential changes after taking a pharmacological agent (or placebo). Using this design, Nitsche *et al.*⁵⁶ observed that the effects of anodal tDCS are greatly enhanced by the SSRI citalopram, and also that the inhibitory effects of cathodal tDCS changes to excitatory after citalopram. In fact, in ancillary SELECT-TDCS studies we found that the 5-HTTLPR (serotonin transporter) polymorphism impacts on tDCS response⁵⁷ and that tDCS combined to sertraline was the only treatment effective for the core symptoms of depression (depressed mood and anhedonia)⁵⁸. Therefore, although the mechanistic foundations for the greater effects of the combined therapy remain elusive, one hypothesis is that these interventions have synergistic effects, one augmenting the other.

Another critical and unclear point is the optimal treatment protocol during the maintenance phase. Only two follow-up studies were carried out hitherto^{44,45} with relatively poor results, with a relapse rate of around 50% in six months. We propose that the same strategies under research for rTMS could be employed here, namely more frequent stimulation sessions and use of antidepressant drugs during the maintenance phase. Future studies should also explore whether patients who responded to tDCS and further relapse would again achieve clinical response after another tDCS trial.

Finally, it should be underscored that not all clinical trials yielded positive results and one meta-analysis failed to show superiority from active tDCS to sham treatment. Some reasons for these mixed findings include relatively small sample sizes, disparate treatment modalities (including number of sessions, cathode positioning, duration and intensity of the sessions etc.) and different depression characteristics (regarding refractoriness, severity, mean age, unipolar vs. bipolar depression and concomitant use of pharmacotherapy) in the sample. In our updated meta-analysis (currently under review) we found tDCS effects to be statistically significant, with the effect size of similar magnitude than observed in clinical trials⁵⁴. Nonetheless, further randomized clinical trials are necessary and, in fact, several trials are being currently performed worldwide – according to clinicaltrials.org (assessed online on November 27, 2013), there are 15 randomized clinical trials evaluating the clinical efficacy of tDCS in depression. Therefore, in the next years a definite answer regarding tDCS clinical efficacy is expected.

Conclusion

Transcranial direct current stimulation is a promising somatic therapy for the treatment of major depression. Low cost, easiness of use and absence of severe adverse effects are its main advantages. Further, the development of “home-use” tDCS devices might help in overcoming one of the main caveats in non-invasive neuromodulatory therapies, which is the need to perform daily visits to the clinic to have the stimulation sessions delivered. Although initial tDCS trials displayed mixed findings; recent, larger trials showed that tDCS was effective in depression treatment. Future ongoing studies will provide a definite answer regarding the role of tDCS in the therapeutic arsenal of depression.

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