# Estimulação transcraniana por corrente direta: uma alternativa promissora para o tratamento da depressão maior?

# Transcranial direct current stimulation: a promising alternative for the treatment of major depression?

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*Abstract*

***Objective:*** *In recent years, a number of new somatic (non-pharmacological treatments) have been developed for the treatment of major depression and other neuropsychiatric disorders. Among these, one of the most promising is transcranial direct current stimulation.* ***Method:*** *For the present literature review we searched the PubMed between January 1985 and February 2009. To be included, articles should have been published in English and should address general principles of transcranial direct current stimulation and its use in major depression.* ***Discussion****: Current protocols for the treatment of major depression with transcranial direct current stimulation usually involve the application of two sponge-electrodes in the scalp. In general, the positive electrode is applied in the region above the left dorsolateral prefrontal cortex (i.e., F3 region of the 10/20 International System for EEG) and the negative electrode is applied in the region above the right supra-orbital area. A direct electrical current of 1-2 mA is then applied between the electrodes for about 20 minutes, with sessions being daily performed for one to two weeks. Initial studies (including a randomized, double-blind, placebo-controlled clinical trial) showed that transcranial direct current stimulation is effective for the treatment of non-complicated major depression and that this technique, when used in depressed patients, is associated with improvement in cognitive performance (including working memory). Finally, transcranial direct current stimulation is safe and well tolerated.* ***Conclusion****: Recent studies show that transcranial direct current stimulation is an important neuromodulatory method that may be useful for the treatment of depressed patients. However, further studies are needed to better clarify its precise role in the management of depressive disorders.*

***Descriptors:*** *Depression; Transcranial direct current stimulation; Brain; Mental disorders; Review literature as topic*

*Resumo*

***Objetivo:*** *Nos últimos anos, uma série de novos tratamentos somáticos não-farmacológicos vem sendo desenvolvida para o tratamento da depressão maior e de outros transtornos neuropsiquiátricos. Dentre esses, um dos mais promissores é a estimulação transcraniana por corrente direta.* ***Método:*** *Para a presente revisão da literatura consultou-se no PubMed a literatura publicada entre janeiro de 1985 e fevereiro de 2009. Os artigos deveriam ser publicados em língua inglesa e deveriam abordar princípios gerais da estimulação transcraniana por corrente direta e sua utilização na depressão maior.* ***Discussão:*** *Os protocolos atuais de estimulação transcraniana por corrente direta para o tratamento da depressão maior envolvem a aplicação de dois eletrodos-esponja no escalpo. Em geral, o eletrodo positivo é aplicado na região sobrejacente ao córtex pré-frontal dorsolateral esquerdo (região F3 do Sistema Internacional 10/20 para eletroencefalograma) e o eletrodo negativo é aplicado na região sobrejacente à área supra-orbital direita. Uma corrente elétrica direta de 1-2 mA é então aplicada entre os dois eletrodos por cerca de 20 minutos, sendo as sessões de estimulação transcraniana por corrente direta realizadas diariamente durante uma a duas semanas. Estudos iniciais (incluindo um ensaio clínico randomizado, duplo-cego e controlado por placebo) demonstraram que a estimulação transcraniana por corrente direta é efetiva no tratamento da depressão maior não-complicada e que essa técnica, quando utilizada em pacientes deprimidos, está associada com melhoras no desempenho cognitivo (incluindo a memória de trabalho). Por fim, a estimulação transcraniana por corrente direta é segura e bem tolerada.* ***Conclusão:*** *Investigações recentes demonstram que a estimulação transcraniana por corrente direta é um importante método neuromodulatório que pode ser útil no tratamento de pacientes deprimidos. Contudo, novos estudos são necessários para esclarecer seu real papel no manejo dos transtornos depressivos.*

***Descritores:*** *Depressão; Estimulação transcraniana por corrente direta; Encéfalo; Transtornos mentais; Literatura de revisão como assunto*

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### Neurostimulation: is it relevant in the treatment of neuropsychiatric disorders?

The therapeutics with neurostimulation techniques has been often used as an adjunct tool in the treatment of several neurological and psychiatric illnesses, especially when medications are not efficient.[1,2] Neurostimulation uses specific techniques according to the structure to be stimulated (e.g., spinal medulla, deep brain nuclei or cortical regions).[3]

Cortical stimulation is especially interesting, as it can be reached by both invasive (e.g., surgical implantation of electrodes and pulse generator) and non-invasive (e.g., magnetic or electric transcranial stimulation)[4] procedures. Non-invasive cortical stimulation was initially developed for the management of chronic pain[5] and only after had its use expanded to other diseases.

In theory, any psychiatric or neurological disorder that involves primary or secondary cortical dysfunction may be a good indication for cortical stimulation. In a simplified view, the therapeutic effects of cortical stimulation can be achieved by reactivating hypoactive neuronal structures or inhibiting hyperactive ones.[3] More specifically, the changes induced by cortical stimulation may affect neuronal excitability (as demonstrated by cortical excitability studies, using single and paired magnetic pulses), regional brain activity (demonstrated by functional neuroimaging methods) or else behavior and symptoms (as demonstrated by clinical and neurocognitive evaluations).[3,6]

In the last years, several neurostimulation techniques have been developed for the management of non-complicated major depressive disorder and, especially, of treatment-resistant depression[2] (whose prevalence ranges from 10-15% of the depressed patients[7]). Among these new techniques are included transcranial magnetic stimulation,[8] deep brain stimulation,[9] vagal nerve stimulation[10] and direct current transcranial stimulation.[11] The latter is currently considered one of the most promising neurostimulation techniques and, owing to this, will be the focus of this review.

### Methodology of the literature review

For this literature review we have consulted PubMed for studies published between January 1985 and February 2009. Articles should have been published in English and in peer-reviewed journals. The searching syntaxes used contained combinations of the following words in the title and/or in the abstract "*depress*", "antidepress*", "tDCS", "direct current", "stimulation", "transcranial" and "cortical".* Besides this, the references of the identified articles were visually inspected.

### Transcranial direct current stimulation (TDCS)

#### 1. General aspects

Up to recently, the TDCS technique was mainly used in animal experiments. Most studies with humans were performed in the 1960's[12-14] and new studies related to it have started being published specially since the 1990's.

TDCS studies on the treatment of major depression and schizophrenia were carried out in the 1960's and 1970's and showed inconclusive results[15,16] (for an in depth review about these pioneering investigations, please consult Murphy et al.[11]). The negative findings of some of these studies could be attributed to the use of different methodologies. Actually, more recent studies which used different sizes and positions of electrodes, besides different stimulation parameters, showed that TDCS is a method capable of modulating the cortical activity[12,17] and, therefore, could be useful in the treatment of major depression.[18,19]

TDCS has important advantages when compared to other neuromodulatory techniques: it is easily administered, its equipment may be easily transported, it is a relatively cheap, non-invasive, painless and safe therapeutic alternative, and its simulated form (*sham*) can be efficiently used in double-blind studies.[1,6,20]

Current TDCS protocols for the treatment of major depression generally involve the application of two surface sponge electrodes (non-metallic) of 25-35 $cm^2$ (bathed in water or NaCl solution) to the scalp, one serving as an anode (positive pole) and the other as a cathode (negative pole or reference electrode). A direct electric current of 1-2 mA (produced by a constant current stimulator, fed by an ordinary battery) is applied between these two electrodes, for approximately 20 minutes[6,11,21] (for further information about TDCS equipment, please consult Wagner et al.[22]). The current flow from the cathode towards anode is deviated through the scalp and moves towards the cerebral cortex, leading to an increase or a decrease in the cortical excitability that depends on the stimulation polarity.[1,11] More specifically, anodic stimulation increases the cortical excitability and cathodic stimulation decreases it.[17,23]

This way, in TDCS, a weak direct electric current is applied on the scalp's surface, resulting in a polarity-dependent modulation of the cerebral activity. The current density produced by present TDCS protocols ranges between 0.029 and 0.08 $mA/cm^2$.[1,4,11]

In order to mount the electrodes on the depressed patients' scalp, the 10/20 International System for electroencephalogram (EEG) is generally used, in which F3 corresponds to the left dorsolateral pre-frontal cortex (LDLP).[4] The positive electrode (anode) is placed above F3, and the negative electrode (cathode) is placed on the right supra-orbital area[11] (for a visual representation of the mounting of the electrodes, please consult Murphy et al.[11]). Normally, the scalp's skin is "prepared" by using an abrasive solution whose objective is to reduce the resistance and improve the homogeneity of the electric field.

During a typical TDCS session the patient remains awaken and comfortably seated.[11]

#### 2. General parameters

The efficacy of TDCS to induce acute modifications in the polarity of the neuronal membrane depends on the density of the current (that determines the power of the induced electric field) and is determined by the ratio between the current power and the electrode size[1,14]. Besides, it was demonstrated in humans, that higher densities result in more significant cortical effects.[1,24,25]

Other important parameter of TDCS is the duration of stimulation. Considering a constant current density, the increase in the duration of the stimulation determines the occurrence and the maintenance of the post-stimulatory effects.[22] Besides, a crucial factor to determine the stimulated neuronal population is the orientation of the electric field, which is generally defined by the position of the electrodes on the scalp and by their polarity.[22]

The increase in the focalization of TDCS can be achieved, for example, by reducing the size of the electrode responsible for the cortical stimulation (keeping the current density constant), by reducing the current density in the reference electrode or else by using an extra-encephalic reference electrode.[1]

As the increase in the density of the electric current provokes an increase in the cutaneous feeling of pain and affects different neuronal populations (due to a higher penetration of the effective electric field), it is recommended, in general, the increase in the duration of stimulation and not in the current density to prolong the effects of TDCS.[22]

For repeated applications of TDCS, it is suggested a sufficiently large interval between the sessions in order to avoid undesired cumulative effects. The duration of this interval depends on the stimulation procedure. If the objective is to induce stable changes in the cortical function, daily TDCS sessions may be adequate.[11,22] However, new studies are needed to establish more precisely the ideal interval between TDCS sessions.

Lastly, for studies involving simulated (sham) TDCS, the best results are obtained by gradually increasing and decreasing the electric current in the beginning and in the end of the stimulation session, respectively.[20] Nevertheless, some patients succeed in discerning real from sham stimulation and, therefore, the utilization of post-stimulation questionnaires is important in order to verify the efficacy of blind studies.[1]

### 3. Mechanism of action

During the stimulation of the motor and visual cortex, anodic TDCS is associated with an increase in the cortical excitability, being the effect the opposite of that observed during the application of cathodic TDCS.[26] The effects of cortical inhibition suggest that TDCS modulates the excitability of both the inhibitory inter-neurons and excitatory neurons.[6]

Pharmacological studies offer some clues about the neurophysiological mechanism of TDCS.[6] Especially, it was demonstrated that calcium and sodium channel blockers have eliminated the short- and long-term effects of anodic stimulation, whereas glutamate channels blockers have eliminated only the long-term effects.[27]

The effects produced by TDCS may induce synaptic neuroplastic processes (by means, for example, of long-term potentiation), being the duration of these effects dependent on the stimulation intensity. Besides, it was hypothesized that post-TDCS effects could be explained by the modulation of the activity of N-methyl-D-aspartic acid (NMDA) receptors.[27]

In summary, despite not being yet totally clear, the specific mechanism of action of TDCS seems to involve a combination of hyper- and depolarizing effects in the neuronal axons, as well as alterations in the synaptic function.[1,6] However, there is no direct evidence to date that TDCS influences neurotransmitters.[11]

### 4. Is it efficient in the treatment of major depression?

The first post-1970 research about the efficacy of TDCS in major depression was published in 2006 by Fregni et al.[18] This pilot study has investigated the efficacy of anodic stimulation of the left dorsolateral prefrontal (DLPF) cortex in depressed patients who were alternately randomized for active treatment and simulated stimulation *(sham)*. The approach used included 20-minute TDCS administrated every other day during five days with a 1-mA current. The results demonstrated that four out of five patients submitted to active stimulation showed a significant reduction of depressive symptoms [i.e., nearly 60% of reduction according to the Hamilton Depression Scale (HAM-D) and more than 70% according to the Beck Depression Inventory (BDI)], whereas the control group did not show clinical improvement.

Another study compared TDCS to pharmacological treatment with fluoxetine (20mg/day) in 42 depressed patients.[28] The parameters used were similar to those described by Boggio et al.[21] (see below). Even though patients had not been simultaneously assessed, the results showed a significant reduction in the depressive symptoms (according to the BDI)] two weeks after TDCS *versus* sham TDCS ($p = 0.0002$), and a similar reduction to that observed after six weeks of fluoxetine treatment ($p = 0.54$). More specifically, after two weeks of active TDCS it was observed a reduction of 43.1% (± 30.9) in the BDI scores *versus* 15% (± 35.2) after two weeks under fluoxetine. However, the improvement in the depressive symptoms was similar between both groups after six weeks with fluoxetine [i.e., 36.2% (± 38.9) and 38.1% (± 36.9), respectively]. The HAM-D scores demonstrated similar results. Thus, the antidepressant action of active TDCS was observed faster than that associated with fluoxetine.

The main study about TDCS in the treatment of major depression was a randomized double-blind placebo-controlled clinical trial published in 2008 by Boggio et al.[21] Its main objective was to determine the short-term efficacy of anodic active stimulation of the left DLPF cortex, when compared to both a sham controlled stimulation and an active controlled stimulation of the occipital cortex. This active control was employed to exclude the possibility that the cathodic stimulation of the right supra-orbital region could have any relevant clinical effect (as during TDCS both anodic and cathodic stimulation occur). In this trial, 40 patients with a diagnosis of major depressive disorder without pharmacological treatment for at least two months were included. The TDCS protocol involved daily sessions (for 20 minutes) for a period of two weeks with a 2-mA current. The results were encouraging: the active anodic stimulation of the DLPF cortex was associated with a significant reduction in the depressive symptoms assessed both by the HAM-D ($p = 0.0018$ *versus* sham ETCD and $p = 0.009$ *versus* occipital TDCS) and by the BDI ($p = 0.0045$ *versus* sham TDCS). Besides, active TDCS was associated with higher rates of response to treatment (defined as a $\geq 50\%$ reduction in the HAM-D score; $p = 0.019$) and clinical remission (defined as a score of $\leq 7$ in the HAM-D; $p = 0.02$). The clinical improvement remained significant for at least 30 days after the end of treatment.

However, a recent pilot study (double-blind, randomized, and placebo-controlled) involving 10 patients with treatment-resistant depression (i.e., absence of response to at least two antidepressants in the current episode) was not able to demonstrate a significant difference between active and simulated (sham) TDCS.[29] Nevertheless, despite using a disposition of electrodes similar to that described by Boggio et al.,[21] the current employed was of only 1 mA and this fact (added to the small number of participants) might explain the negative results found.

### 5. Adverse effects

The accumulated experience in the last four decades has demonstrated that TDCS is associated with only mild and transient side-effects (both in normal volunteers and in individuals with varied neuropsychiatric disorders).[30,31] However, the safe limits of current duration and intensity are not yet fully clear.[1]

The adverse effects most commonly associated with the treatment of major depression by TDCS include mild transient headache (with a duration of less than one hour) and mild transient pruritus and erythema in the stimulation site (the latter with a duration of less than 40 minutes).[18,21,28] Other less prevalent side-effects include nausea, difficulty of concentration, visual fosphenes and vertigo.[11]

Lastly, the secondary side-effects of TDCS can be usually minimized by means of a gradual increase and decrease of the electric current during the beginning and the end of the session, respectively.[1,4]

### 6. Cognitive effects in major depression

A recent study has assessed the neurocognitive impact of TDCS

in major depression.[32] For that, 26 depressed patients were randomized to receive alternatively anodic TDCS in the left DLPF cortex, anodic TDCS in the occipital cortex and simulated (sham) TDCS (with mounting and parameters similar to those used by Boggio et al.[21]). For the assessment of their cognitive function, patients were submitted to an affective "*go-no-go*" task just before and after TDCS (for more information about this task, please consult Murphy et al.[33]). Post-hoc analyses have demonstrated that a single *post-hoc* active TDCS session was associated with a significant improvement in the performance of depressed patients (in terms of the number of correct answers; $p = 0.005$). Besides, this effect was specific to figures with positive emotional valence. However, this performance change occurred only regarding the accuracy (and not the performance speed) and was not correlated to mood alterations observed after 10 days of TDCS.

In a previous randomized study, Fregni et al. assessed the cognitive performance of 18 depressed patients before and after five sessions of active TDCS (administered on the DLPF cortex) or simulated TDCS.[34] For that, they used a series of neuropsychological tests associated with the pre-frontal cortex function. Statistical analyses demonstrated a significant improvement in working memory (according to two specific tests) only after active TDCS ($p = 0.009$ and $p = 0.048$, respectively).

## Conclusion

TDCS is currently one of the most promising neuromodulation techniques. Recent studies have shown that it can be useful in the treatment of major depression and several other neuropsychiatric disorders. Nevertheless, new studies (with larger samples and in distinct populations) are needed to confirm the usefulness of TDCS in depression and determine, among other things, which are the optimal stimulation parameters and the most efficient and well tolerated mounting of the electrodes. Besides, the combination of TDCS with different forms of psychotherapy, medication and somatic interventions might significantly expand the available arsenal for the treatment of the depressive disorders. The use of specific research tools (e.g., neuroimaging), in turn, might help explain the mechanisms of action underlying this neuromodulatory technique.

Lastly, TDCS can be considered a potentially useful therapeutic alternative for developing nations like Brazil,[35] as the equipment needed is simple, relatively cheap (it may cost less than U$ 200,00) and reusable.

## Disclosures

| Writting group member | Employment | Research grant[1] | Other research grant or medical continuous education[2] | Speaker's honoraria | Ownership interest | Consultant/ Advisory board | Other[3] |
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| Gustavo Turecki | McGill | CIHR*** | - | - | - | RBP | - |

** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
*Note: CIHR = Canadian Institutes of Health Research; RBP = Revista Brasileira de Psiquiatria.*
*For more information, see Instructions for authors.*

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