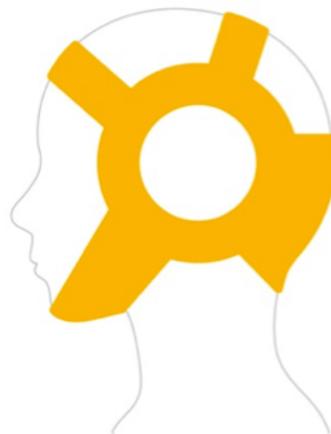


tDCS clinical research - highlights: Depression

Neuroelectrics White Paper WP201303

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Is transcranial current stimulation (tCS, including direct current, tDCS, alternating current, tACS, or random noise stimulation tRNS) effective for the treatment of depression? Under what conditions? With what montages? We focus here on a review of the recent literature on this topic. We have relied on Google Scholar and also [PubMed](#) to carry out the search, including the terms of tDCS, tACS, tRNS as well as Stroke (from March 2012 and till Sep 2013).

As you can read below, there quite a few encouraging results in this area, and study group sizes (the famous N) are moderately large. We try to indicate group size and the use of a sham-controlled, double-blind experimental technique. Most studies are careful about these crucial aspects. In addition, it is worth mentioning that there continues to be a lack of bad news from the safety point of view. This seems to be a common pattern of tDCS research (or tCS, in fact). I will discuss this further in a future post on an update on tCS Safety. **The typical target for treatment is anodal on the left DLPFC (F3 in the 10-20 EEG system) with the cathode over the contralateral orbit or, sometimes, over the right DLPFC.**

As in prior posts, in what follows I concentrate on relevant, study-oriented papers with patients, and leave reviews to the end. In order to make the reading lighter, I've edited the abstracts a bit (just click on the title link if you are interested in the paper).

In the case of Depression we've found no negative recent findings.

Overview

Major depression is a common psychiatric disease with a lifetime prevalence of about 15% and a 12-month prevalence of about 7% that generates a large socio-economic burden (Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., Rush, A.J., Walters, E.E., Wang, P.S., National Comorbidity Survey Replication, 2003. [The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication](#) (NCS-R). JAMA 289, 3095–3105). Although antidepressant drug treatment has improved during the last decades, symptoms in about 20% of the patients are not in remission two years after initiation of pharmacological intervention. Thus alternative or adjunctive therapies are needed, and in this context, brain stimulation approaches may play a prominent role [M. A. Nitsche, P. S. Boggio, F. Fregni, and A. Pascual-Leone, "[Treatment of depression with transcranial direct current stimulation \(tDCS\): a review](#)," Exp Neurol, vol. 219, pp. 14-9, Sep 2009].

Major depressive disorder is associated with alterations in prefrontal cortical activity. For example, fMRI and PET studies have shown reduced blood flow in prefrontal cortex, particularly on the left, in depressed patients relative to controls [W. C. Drevets, "[Functional neuroimaging studies of depression: the anatomy of melancholia](#)," Annu Rev Med, vol. 49, pp. 341-61, 1998.], and depressed patients show reduced left relative to right frontal resting EEG activity compared to controls [C. E. Schaffer, R. J. Davidson, and C. Saron, "[Frontal and parietal electroencephalogram asymmetry in depressed and nondepressed subjects](#)," Biol

Psychiatry, vol. 18, pp. 753-62, Jul 1983.]. In addition, stroke patients with damage to left prefrontal regions are more likely to display depressive symptoms [R. G. Robinson, K. L. Kubos, L. B. Starr, K. Rao, and T. R. Price, "[Mood disorders in stroke patients. Importance of location of lesion](#)," Brain, vol. 107 (Pt 1), pp. 81-93, Mar 1984.]. This has led to the hypothesis that anodal tDCS over left prefrontal regions may alleviate depression.

A number of studies in the last years suggest the efficacy of tDCS in depression. The studies in our search show in general positive results.

In the review [[Arul-Anandam2009a](#)] (studies with 522 subjects reviewed), the authors conclude that transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique, has emerged in the past decade as a useful investigative and therapeutic technique. A number of recent studies suggest that tDCS is safe and may be efficacious in the treatment of a variety of psychiatric and neurological disorders, including major depressive disorder, chronic neuropathic pain, and stroke. More evidence is necessary, however, before it can be recommended for general clinical application. Moreover, they indicate that mixed results in the 1960s and 70s may be due to the fact that concomitant antidepressant medications and psychotherapy were significant confounders in many studies from the 1960s and 1970s.

Similarly, in the review by [[Berlim2009](#)] (total of 141 subjects), the authors conclude that 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.

[[Brunoni2011a](#)] studied tDCS application in (31 patients) unipolar (MDD) and bipolar depression (BDD). They concluded that after the fifth tDCS session, depressive symptoms in both study groups diminished, and the beneficial effect persisted at one week and one month. In conclusion, our preliminary study suggests that tDCS is a promising treatment for patients with MDD and BDD.

[[Dell'Osso2011b](#)] studied efficacy and tolerability of tDCS of major depression patients with poor response to pharmacological treatment. They found a significant reduction of HAM-D and MADRS total scores was observed during the study ($P < 0.0001$). Treatment response (endpoint HAM-D reduction 50%) was obtained by four patients (17.4%) at T1 and by seven patients (30.4%) at T2 and remission (endpoint HAM-D < 8) by three patients (13.0%) at T1 and by four subjects (17.4%) at T2. They concluded that present findings support the efficacy and good tolerability of tDCS in the acute treatment of patients with TRD with clinical benefit being progressive and extended to the first week of follow-up. Further sham-controlled trials with longer follow-up are needed to confirm present results.

On the negative side, [[Palm2012a](#)] found that anodal tDCS, applied for 2 weeks, was not superior to placebo treatment in patients with treatment resistant depression. However, secondary outcome measures are pointing to a positive effect of tDCS on emotions. Therefore, modified and improved tDCS protocols should be carried out in controlled pilot trials to develop tDCS towards an efficacious antidepressant intervention in therapy-resistant depression.

[[Loo2012a](#)] report a study with 64 patients in which participants with current depression received active or sham anodal tDCS to the left prefrontal cortex (2 mA, 15 sessions over 3 weeks), followed by a 3-week

open-label active treatment phase. Mood and neuropsychological effects were assessed. They conclude that there was significantly greater improvement in mood after active than after sham treatment ($P < 0.05$), although no difference in responder rates (13% in both groups). Attention and working memory improved after a single session of active but not sham tDCS ($P < 0.05$). There was no decline in neuropsychological functioning after 3-6 weeks of active stimulation. One participant with bipolar disorder became hypomanic after active tDCS. Findings confirm earlier reports of the antidepressant efficacy and safety of tDCS. Vigilance for mood switching is advised when administering tDCS to individuals with bipolar disorder.

We provide next an updated list of recent publications on this subject.

Update (2012-2013)

Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial.

To further investigate the efficacy of tDCS in a double-blind, sham-controlled trial (registered at www.clinicaltrials.gov: NCT00763230). **64 participants with current depression** received **active** or **sham** anodal tDCS to the left prefrontal cortex (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 after sham treatment ($P < 0.05$), although no difference in responder rates (13% in both groups). Attention and working memory improved after a single session of active but not sham tDCS ($P < 0.05$). There was no decline in neuropsychological functioning after 3-6 weeks of active stimulation. One participant with bipolar disorder became hypomanic after active tDCS. Findings confirm earlier reports of the antidepressant efficacy and safety of tDCS. Vigilance for mood switching is advised when administering tDCS to individuals with bipolar disorder.

Enhancement of Affective Processing Induced by Bifrontal Transcranial Direct Current Stimulation in Patients With Major Depression

Randomized, double-blind, sham-controlled, parallel design enrolling **24** age-, gender-matched, drug-free, **depressed subjects**. Anode and cathode were placed over the left and right dorsolateral prefrontal cortex. *Active but not sham tDCS significantly modified the negative attentional bias. These findings add evidence that a single tDCS session transiently induces potent changes in affective processing, which might be one of the mechanisms of tDCS underlying mood changes.*

The Sertraline vs Electrical Current Therapy for Treating Depression Clinical Study

Results From a Factorial, Randomized, Controlled Trial

The goal was to assess the combined safety and efficacy of tDCS vs a common pharmacological treatment (sertraline hydrochloride, 50 mg/d). **120 antidepressant-free patients with moderate to severe, nonpsychotic, unipolar major depressive disorder (MDD)**. **Six-week treatment** of 2-mA anodal left/cathodal right prefrontal tDCS (12 30-minute sessions: 10 consecutive sessions once daily from Monday to Friday plus 2 extra sessions every other week) and sertraline hydrochloride (50 mg/d). *Use of tDCS only (but not sertraline only) was superior to placebo/sham tDCS.* Common adverse effects did not differ between interventions, except for skin redness on the scalp in active tDCS ($P = .03$). There were 7 episodes of treatment-emergent mania or hypomania, 5 occurring in the combined treatment group. *Conclusions and Relevance: In MDD, the combination of tDCS and sertraline increases the efficacy of each treatment. The efficacy and safety of tDCS and sertraline did not differ.*

Acute working memory improvement after tDCS in antidepressant-free patients with major depressive disorder.

28 age- and gender-matched, antidepressant-free depressed subjects received a **single-session of active/sham tDCS** in a randomized, **double-blind**, parallel design. The anode was positioned over the left and the cathode over the right dorsolateral prefrontal cortex. The n-back task was used for assessing working memory and it was performed immediately before and 15min after tDCS onset. *All effect sizes were large. In other words, one session of tDCS acutely enhanced WM in depressed subjects, suggesting that tDCS can improve "cold" (non affective-loaded) working memory processes in MDD.*

Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind, placebo-controlled study.

22 patients with a major depressive episode were randomly assigned to a cross-over protocol comparing tDCS and placebo stimulation add-on to a stable antidepressant medication. *Anodal tDCS, applied for 2 weeks, was not superior to placebo treatment in patients with treatment resistant depression. However, secondary outcome measures are pointing to a positive effect of tDCS on emotions. Therefore, modified and improved tDCS protocols should be carried out in controlled pilot trials to develop tDCS towards an efficacious antidepressant intervention in therapy-resistant depression.*

Bifrontal tDCS prevents implicit learning acquisition in antidepressant-free patients with major depressive disorder.

The findings for implicit (procedural) learning impairment in major depression are mixed. We investigated this issue using transcranial direct current stimulation (tDCS), a method that non-invasively increases/decreases cortical activity. **28 age- and gender-matched, antidepressant-free depressed subjects** received a **single-session of active/sham tDCS**. We used a bifrontal setup - anode and cathode over the left and the right dorsolateral prefrontal cortex (DLPFC), respectively. The probabilistic classification-learning (PCL) task was administered before and during tDCS. *The percentage of correct responses improved during sham; although not during active tDCS. Procedural or implicit learning acquisition between tasks also occurred only for sham.* We discuss whether DLPFC activation decreased activity in subcortical structures due to the depressive state. The deactivation of the right DLPFC by cathodal tDCS can also account for our results. *To conclude, active bifrontal tDCS prevented implicit learning in depressive patients. Further studies with different tDCS montages and in other samples are necessary.*

Amelioration of cognitive control in depression by transcranial direct current stimulation.

Deficient cognitive control over emotional distraction is a central characteristic of major depressive disorder (MDD). Hypoactivation of the dorsolateral prefrontal cortex (dlPFC) has been linked with this deficit. In this study, we aimed to enhance the activity of the dlPFC in MDD patients tDCS and thus ameliorate cognitive control. In a **double-blinded**, balanced, randomized, **sham-controlled** crossover trial, we determined the effect of a single-session tDCS to the left dlPFC on the cognitive control in **22 MDD patients** and **22 healthy control subjects**. To assess the cognitive control, we used a delayed response working memory task with pictures of varying content (emotional vs. neutral) presented during the delay period. Emotional pictures presented during the delay period impaired accuracy and response time of patients with MDD, indicating an attentional bias for emotional stimuli. *Anodal tDCS to the dlPFC was associated with an enhanced working*

memory performance both in patients and control subjects. Specifically in subjects with MDD, the attentional bias was completely abolished by anodal tDCS. The present study demonstrates that anodal tDCS applied to the left dlPFC improves deficient cognitive control in MDD. Based on these data, tDCS might be suitable to support the effects of behavioral training to enhance cognitive control in MDD.

Continuation transcranial direct current stimulation for the prevention of relapse in major depression.

Transcranial direct current stimulation (tDCS) is gaining attention as an effective new treatment for major depression. Little is known, however, of the duration of antidepressant effects following acute treatment. In this study, we describe the use of continuation tDCS treatment for up to 6 months following clinical response to an acute treatment course. **26 participants pooled from two different studies involving different tDCS protocols received continuation tDCS treatment on a weekly basis for 3 months and then once per fortnight for the final 3 months.** Mood ratings were completed at 3 and 6 months. Analyses examined clinical predictors of relapse during continuation tDCS treatment. The cumulative probability of surviving without relapse was 83.7% at 3 months and 51.1% at 6 months. Medication resistance was found to be a predictor of relapse during continuation tDCS. This was an **open label prospective study with no control group**. Two different forms of tDCS were used. *Similar to other antidepressant treatments, continuation tDCS appears to be a useful strategy to prevent relapse following clinical response. These preliminary data suggest that the majority of patients maintained antidepressant benefit with a continuation schedule of at least weekly treatment. Future controlled studies are required to confirm these findings.*

Transcranial direct current stimulation (tDCS) for depression: Analysis of response using a three-factor structure of the Montgomery–Åsberg depression rating scale

There is growing evidence that tDCS may be an effective treatment for depression. However, no study to date has profiled the antidepressant effects of tDCS using items or factors on depression symptom severity rating scales. *Participants in the active tDCS treatment group showed significant improvement in dysphoria while participants in the sham treatment group did not. While both groups showed improvement in retardation symptoms, improvement was significantly greater in the active tDCS group.*

Reviews

Could Transcranial Direct Current Stimulation Have Unexpected Additional Benefits in the Treatment of Depressed Patients?

The application of novel brain stimulation techniques to treat depression, and possibly other neuropsychiatric disorders, is a new and rapidly growing field. Among these techniques, transcranial direct current stimulation (tDCS) is emerging as one of the most promising approaches because of its relative ease of use, safety and neurobiological effects. One of the most promising therapeutic applications of tDCS has been in the treatment of depression. *A recent meta-analysis suggested that tDCS may have robust and clinically meaningful effects in treating depression (see below).* This group recently published the largest and most definitive sham-controlled trial of tDCS in depression (see above). Active stimulation was more effective than sham stimulation, and 48% of subjects who received 30 treatments of tDCS (given every weekday over a period of 6 weeks) responded to treatment. In the course of conducting this trial, it has been observed that tDCS may induce additional benefits that appeared to be independent of mood improvement. These observations are consistent with reports in the literature of cognitive enhancement and pain relief with tDCS.

Anodal stimulation of the left dorsolateral prefrontal cortex (the same region stimulated for the treatment of depression) has been shown to enhance task performance across a number of 'executive' cognitive tasks, tapping higher-level cognitive functions, such as working memory, verbal fluency and planning.

Transcranial direct current stimulation in the treatment of major depression: a meta-analysis.

Medline and Embase were searched for open-label and randomized controlled trials of tDCS in depression using the expressions ('transcranial direct current stimulation' or 'tDCS') and ('depression' or 'depressed'). Study data were extracted with a standardized data sheet. A total of 108 citations were screened and 10 studies included in the systematic review. Six randomized controlled trials were included in the meta-analysis, with a cumulative sample of 96 active and 80 sham tDCS courses. *Active tDCS was found to be more effective than sham tDCS for the reduction of depression severity (Hedges' $g=0.743$, 95% confidence interval 0.21-1.27), although study results differed more than expected by chance ($Q=15.52$, $df=6$, $p=0.017$, $I^2=61.35$). Our study was limited by the small number of studies included, which often had small sample size. Future studies should use larger, if possible representative, health service patient samples, and optimized protocols to evaluate the efficacy of tDCS in the treatment of depression further.*

Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: A systematic review and meta-analysis of randomized, double-blind and sham-controlled trials

We carried out a systematic review and meta-analysis on randomized, double-blind and controlled trials of tDCS in MD with a focus on clinically relevant outcomes, namely response and remission rates. We searched the literature for English language randomized, double-blind and sham-controlled trials (RCTs) on tDCS for treating MD from 1998 through July 2012 using MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials and SCOPUS. We also consulted the Web of Science's Citations Index Expanded for the selected RCTs up to July 2012. The main outcome measures were response and remission rates. We used a random-effects model and Odds Ratios (OR). Data were obtained from 6 RCTs that included a total of 200 subjects with MD. After an average of 10.8 ± 3.76 tDCS sessions, *no significant difference was found between active and sham tDCS in terms of both response (23.3% [24/103] vs. 12.4% [12/97], respectively; OR = 1.97; 95% CI = 0.85-4.57; $p = 0.11$) and remission (12.2% [12/98] vs. 5.4% [5/92], respectively; OR = 2.13; 95% CI = 0.64-7.06; $p = 0.22$). Also, no differences between mean baseline depression scores and dropout rates in the active and sham tDCS groups were found. Furthermore, sensitivity analyses excluding RCTs that involved less than 10 treatment sessions or stimulus intensity of less than 2 mA did not alter the findings. However, tDCS used as monotherapy was associated with higher response rates when compared to sham tDCS ($p = 0.043$). CONCLUSIONS: *The clinical utility of tDCS as a treatment for MD remains unclear when clinically relevant outcomes such as response and remission rates are considered. Future studies should include larger and more representative samples, investigate how tDCS compares to other therapeutic neuromodulation techniques, as well as identify optimal stimulation parameters.**