

tDCS clinical research highlights: Depression

Neuroelectrics White Paper WP201303

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Released: Oct 17th 2013

Updated: April 24th 2015



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(released Oct 17th 2013 / updated March 2015)

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 Depression (from March 2009 and until March 2015).

As you can read below, there quite a few encouraging results in this area, and study group sizes (the famous N) are now 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 ill news from the safety point of view. This seems to be a common pattern of tDCS research (or tCS, in fact). See Neuroelectrics [wikipedia](#) (Safety section) for more information. **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 (see Neuroelectrics' Wikipedia section on [multi-focal montages](#) for more information).**

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

1. 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.

The studies reviewed demonstrate the efficacy of tDCS in non-TRD depression (non-treatment resistant depression). The studies in our search show positive results in this subgroup, while efficacy in TRD is still dubious. The total number of subjects in non-TRD studies was of 433, with 86% of subjects in studies with positive outcomes.

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

2. Update 2014-2015

In addition to the papers found in our previous search in 2012-2013, our search in 2015 has provided notable new studies with positive results for the use of tDCS in depression.

Brunoni AR1, Valiengo L, Baccaro A, Zanão TA, de Oliveira JF, Goulart A, Boggio PS, Lotufo PA, Benseñor IM, Fregni F. JAMA Psychiatry. 2013 Apr;70(4):383-91. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial.

In [Brunoni2013] (the tDCS-SELECT also discussed in Zanao2014, Brunoni 2014, Valiengo, clinicaltrials.gov Identifier: NCT01033084), the goal was to assess the combined safety and efficacy of tDCS vs a common pharmacological treatment (sertraline hydrochloride, 50 mg/d). This was a double-blind, controlled trial. Participants were randomized using a 2 × 2 factorial design to sertraline/placebo and active/sham tDCS. A total of **120 antidepressant-free patients with moderate to severe, nonpsychotic, unipolar MDD** were recruited. The intervention consisted of a 6 week treatment of 2-mA anodal left/cathodal right prefrontal tDCS (twelve 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). In this intention-to-treat analysis, the **primary outcome measure was the change in Montgomery-Asberg depression rating scale** score at 6 weeks (end point). The study considered a difference of at least 3 points to be clinically relevant. The analysis plan was previously published. Safety was measured with an adverse effects questionnaire, the young mania rating scale, and cognitive assessment. Secondary measures were rates of clinical response and remission and scores on other scales. *At the main end point, there was a significant difference in Montgomery-Asberg depression rating scale scores when comparing the combined treatment group (sertraline/active tDCS) vs sertraline only (mean difference, 8.5 points; 95% CI, 2.96 to 14.03; P = .002), tDCS only (mean difference, 5.9 points; 95% CI, 0.36 to 11.43; P = .03), and placebo/sham tDCS (mean difference, 11.5 points; 95% CI, 6.03 to 17.10; P < .001). Analysis of tDCS only vs sertraline only presented comparable efficacies (mean difference, 2.6 points; 95% CI, -2.90 to 8.13; P = .35). 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. 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.

Brunoni AR, Boggio PS, De Raedt R, Benseñor IM, Lotufo PA, Namur V, Valiengo LC, Vanderhasselt MA. Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. J Affect Disord. 2014 Jun;162:43-9.

In a separate study [Brunoni2014, Clinicaltrials.gov identifier: NCT01434836.], the authors investigated whether tDCS enhanced the effects of CCT in a double-blind trial, in which participants were randomized to sham tDCS and cognitive control therapy CCT (n=17) vs. active tDCS and CCT (n=20). CCT and tDCS were applied for 10 consecutive workdays. *Both CCT alone and combined with tDCS ameliorated depressive symptoms after the acute treatment period and at follow-up, with a response rate of approximately 25%. Older patients and those who presented better performance in the task throughout the trial (possibly indicating greater engagement and activation of the DLPFC) had greater depression improvement in the combined treatment group. Within the limitations of the study size, the authors conclude that CCT and tDCS combined might be beneficial for older depressed patients, particularly for those who have cognitive resources to adequately learn and improve task performance over time. This combined therapy might be specifically relevant in this in this subgroup that is more prone to present cognitive decline and prefrontal cortical atrophy.*

Alonzo A, Chan G, Martin D, Mitchell PB, Loo C. Transcranial direct current stimulation (tDCS) for depression: analysis of response using a three-factor structure of the Montgomery-Åsberg depression rating scale. J Affect Disord. 2013 Aug 15;150(1):91-5. doi: 10.1016/j.jad.2013.02.027. Epub 2013 Mar 15.

In [Alonzo2013] (N=64) the authors analyzed scores on the Montgomery-Åsberg depression rating scale (MADRS) from a randomised, sham-controlled trial of tDCS (Loo et al., 2012. British Journal of Psychiatry. 200, 52-59) using a three-factor model of MADRS items (Suzuki et al., 2005. Depression and Anxiety. 21, 95-97) encompassing dysphoria, retardation and vegetative symptoms. *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. Both groups also showed improvement in vegetative symptoms but there were no between-group differences. tDCS appears to be particularly effective in treating dysphoria and retardation, but not vegetative symptoms of depression. This may have implications for selection of types of depression most likely to respond to this treatment.*

Wolkenstein L, Zeiller M, Kanske P, Plewnia C. Induction of a depression-like negativity bias by cathodal transcranial direct current stimulation. Cortex. 2014 Oct;59:103-12.

In [Wolkenstein2013] (N=44), a double-blinded, balanced, randomized, sham-controlled crossover trial, authors 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, they 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 authors conclude that 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.

With regard to meta-analysis, the following one is the most recent and therefore relevant:

Shiozawa P, Fregni F, Benseñor IM, Lotufo PA, Berlim MT, Daskalakis JZ, Cordeiro Q, Brunoni AR. Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. Int J Neuropsychopharmacol. 2014 Sep;17(9):1443-52.

In [Shiozawa2014] the aim was to assess the efficacy of tDCS as a treatment for MDD. Authors performed a systematic review in Medline and other databases from the first RCT available until January 2014. The main outcome was the Hedges' g for continuous scores; secondary outcomes were the odds ratio (ORs) to achieve response and remission. They used a random-effects model. Seven RCTs (n = 259) were included, most with small sample sizes that assessed tDCS as either a monotherapy or as an add-on therapy. **Active vs. sham tDCS was significantly superior for all outcomes** (g = 0.37; 95% CI 0.04-0.7; ORs for response and remission were, respectively, 1.63; 95% CI = 1.26-2.12 and 2.50; 95% CI = 1.26-2.49). Risk of publication bias was low. No predictors of response were identified, possibly owing to low statistical power. In summary, active tDCS was statistically superior to sham tDCS for the acute depression treatment, although its role as a clinical intervention is still unclear owing to the mixed findings and heterogeneity of the reviewed studies. Further RCTs with larger sample sizes and assessing tDCS efficacy beyond the acute depressive episode are warranted. We include below Tables 1 and Table 2 from this study.

Study	Demographics			Depression			tDCS					
	N (active/sham)	Age (s.d.)	Gender (%fem)	Scale	Number (s.d.) of failed antidepressant therapies	AD use	Current (mA)	Duration (min/d)	Anode	Cathode	Number of sessions	Current density (A/m ²)
Boggio et al. (2008)	21/10	49 (7.4)	67.5	HAMD	1.6 (1.2)	No	2	20 min	F3	RSO	10	0.57
Loo et al. (2010)	20/20	47.3 (11.3)	55	MADRS	1.3 (1.6)	Yes	1	20 min	F3	RSO	5	0.28
Loo et al. (2012)	33/31	48.2 (12.5)	46.6	MADRS	1.7 (1.2)	Yes	2	20 min	F3	F8	15	0.57
Palm et al. (2012)	11/11	57 (12)	50	HAMD	2.9 (1.6)	Yes	1 or 2	20 min	F3	RSO	10	0.28/0.57
Blumberger et al. (2013)	13/11	42.7 (11.6)	45.6	HAMD	4.2 (2.3)	Yes	2	20 min	F3	F4	15	0.57
Fregni et al. (2006)	9/9	48.2 (10)	NR	MADRS	NR	No	1	20 min	F3	RSO	5	0.28
Brunoni et al. (2013) (group analysis)	30/30	43.7 (13.5)	68.5	MADRS	1.7(2.3)	No	2	30 min	F3	F4	12	0.8
Brunoni et al. (2013) (factor analysis)	60/60	42 (12)	68	MADRS	1.7(2.3)	Yes	2	30 min	F3	F4	12	0.8

s.d.: standard deviation; HAMD: Hamilton Depression Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; F3: left dorsolateral prefrontal cortex (according to the EEG 10/20 system); F4: right dorsolateral prefrontal cortex (according to the EEG10/20 system); F8: right lateral aspect of the supraorbital area (according to the EEG 10/20 system); RSO – right supraorbital area; AD: antidepressant drug. Two different analyses were performed, once at a time, for the Brunoni et al. study. In the 'group analysis' we compared the active-transcranial direct cranial stimulation tDCS/placebo vs. sham-tDCS/placebo; whereas in the 'factor analysis' we compared tDCS vs. sham-tDCS (regardless of drug use). Please refer to the main text for further details.

Table 1 from <http://www.ncbi.nlm.nih.gov/pubmed/24713139>

Table 2. Clinical results of each study

Study	Mean baseline depression scores		Mean endpoint depression scores		Response (%)		Remission (%)	
	Sham (s.d.)	Active (s.d.)	Sham (s.d.)	Active (s.d.)	Sham	Active	Sham	Active
Boggio et al. (2008)	21.9 (4.8)	21.1 (4.4)	21.2 (5.4)	13.8 (9.2)	20	38.1	0	23.8
Loo et al. (2010)	28.4 (4.4)	29.2 (4.9)	22.5 (8.1)	23.6 (7.7)	20	30	15	25
Loo et al. (2012)	29.5 (5)	30.4 (6)	24.9 (7.6)	20.6 (7.6)	12.9	12.1	3	3
Palm et al. (2012)	34.6 (5.4)	33 (7.3)	28.2 (8.8)	30.2 (7.4)	9	9	9	9
Blumberger et al. (2013)	24.1 (2.9)	24.9 (3.1)	18.1 (5.5)	18.8 (4.8)	9	7.7	9	7.7
Fregni et al. (2006)	25.9 (4.2)	23.5 (5)	22.5 (13.6)	9.8 (4.8)	0	77.7	–	–
Brunoni et al. (2013) (group analysis)	30.8 (5.3)	30.8 (5.8)	24.7 (8.6)	19.1 (12.2)	16.7	43.3	13.3	40
Brunoni et al. (2013) (factor analysis)	30.7 (5.6)	30.8 (6.4)	23.2 (11.1)	16.1 (10.8)	25	53.3	21.7	43.3

s.d.: standard deviation; NR: not reported. The column ‘Depression scores’ refers to the depression scale used for the primary outcome, as described in Table 1. All studies defined response as >50% depression improvement (from baseline to endpoint). Remission was defined as the absence of clinically relevant symptoms although different criteria were used in the the studies, as described in the main text. Two different analyses were performed, once at a time, for the Brunoni et al. study. In the ‘group analysis’ we compared the active-transcranial direct cranial stimulation (tDCS)/placebo vs. sham-tDCS/placebo, whereas in the ‘factor analysis’ we compared tDCS vs. sham-tDCS (regardless of drug use). Please refer to the main text for further details.

Table 2 from <http://www.ncbi.nlm.nih.gov/pubmed/24713139>

The authors make the additional important points:

The effect size hereby found is comparable to those obtained by a recent repetitive transcranial magnetic stimulation (rTMS) meta-analysis (Schutter, 2009) (0.37 vs. 0.39, respectively), although it should be underscored that the rTMS meta-analysis reviewed a much larger number of studies.

Previous tDCS meta-analyses [Kalu2012; Berlim2013 discussed below] presented different results on the efficacy of tDCS for MDD, possibly owing to methodological discrepancies in the assessment of the primary outcome – [Kalu2012] used a continuous outcome and found positive results whereas [Berlim2013], which included the study of [Blumberger2012] and used categorical outcomes, did not reveal a difference between active vs. sham tDCS. It should be underscored, though, that the non-significant results of the meta-analysis by [Berlim2013] could have occurred owing to the relatively low sample size addressed, since their results were marginally significant. In the present study, we analyzed both continuous and categorical (response and remission rates) measures as outcomes, all results showing that active tDCS was significantly superior to sham tDCS in depression treatment.

[Shiozawa2014] extends and supersedes [Berlim2013] and [Kalu2012], including additional more recent studies, which we include here for completeness:

Berlim MT1, Van den Eynde F, Daskalakis ZJ. 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. J Psychiatr Res. 2013 Jan;47(1):1-7.

In [Berlim2013] the authors 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 ($p = 0.043$).** Finally, the risk of publication bias in this meta-analysis was found to be low. 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.

Kalu UG1, Sexton CE, Loo CK, Ebmeier KP, Transcranial direct current stimulation in the treatment of major depression: a meta-analysis, Psychol Med. 2012 Sep;42(9):1791-800

In [Kalu2012], 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. For randomized controlled trials, effect size (Hedges' g) was calculated and the relationships between study variables and effect size explored using meta-regression.

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 ($Q=15.52$, $df=6$, $p=0.017$, $I^2=61.35$). Meta-regression did not reveal any significant correlations. 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.

3. Update 2012-2013

Loo CK, Alonzo A, Martin D, Mitchell PB, Galvez V, Sachdev P. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. Br J Psychiatry. 2012 Jan;200(1):52-9

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.*

Brunoni AR1, Zanao TA, Vanderhasselt MA, Valiengo L, de Oliveira JF, Boggio PS, Lotufo PA, Benseñor IM, Fregni F. Enhancement of Affective Processing Induced by Bifrontal Transcranial Direct Current Stimulation in Patients With Major Depression Neuromodulation. 2014 Feb;17(2):138-42

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.*

Oliveira JF1, Zanão TA, Valiengo L, Lotufo PA, Benseñor IM, Fregni F, Brunoni AR. Neurosci Lett. 2013 Mar 14;537:60-4. 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.*

Palm U1 Schiller C, Fintescu Z, Obermeier M, Keeser D, Reisinger E, Pogarell O, Nitsche MA, Möller HJ, Padberg F. Brain Stimul. 2012 Jul;5(3):242-51. 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.*

Brunoni AR1, Zanao TA, Ferrucci R, Priori A, Valiengo L, de Oliveira JF, Boggio PS, Lotufo PA, Benseñor IM, Fregni F. Bifrontal tDCS prevents implicit learning acquisition in antidepressant-free patients with major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2013 Jun 3;43:146-50.

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.*

Martin DM1, Alonzo A, Ho KA, Player M, Mitchell PB, Sachdev P, Loo CK. , Continuation transcranial direct current stimulation for the prevention of relapse in major depression, J Affect Disord. 2013 Jan 25;144(3):274-8

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.

Loo CK, Martin DM., Could transcranial direct current stimulation have unexpected additional benefits in the treatment of depressed patients? Expert Rev Neurother. 2012 Jul; 12(7):751-3

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.

4. Update 2009-2012

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.