Journal of Affective Disorders ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Brief report

Serum levels of brain-derived neurotrophic factor are unchanged after transcranial direct current stimulation in treatment-resistant depression

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ARTICLE INFO

Article history:
Received 14 February 2013
Received in revised form
13 March 2013
Accepted 14 March 2013

Keywords:
BDNF serum levels
Transcranial direct current stimulation
tDCS
Major depressive disorder

ABSTRACT

Background: Brain-derived neurotrophic factor (BDNF) plays an important role in differentiation and repair of neurons in the adult brain. BDNF serum levels have been found to be lower in depressed patients than in healthy subjects. In a couple of studies, effective antidepressant treatment including electroconvulsive therapy led to an increase in BDNF serum levels. As transcranial direct current stimulation (tDCS) is currently discussed as novel therapeutic intervention in major depression, we investigated BDNF serum levels during tDCS in therapy-resistant depression.

Methods: Twenty-two patients with a major depressive episode participated in a double-blind placebo-controlled trial and received randomized cross over treatment with 2 weeks active and 2 weeks sham tDCS (1 or 2 mA for 20 min, anode over the left dorsolateral prefrontal cortex, cathode right supraorbital cortex).

Results: Clinical assessment only showed a modest and non-significant improvement in HAMD, BDI and CGI in both groups. BDNF serum levels were measured at baseline, after 2 and after 4 weeks. There was neither a significant change of BDNF levels following active tDCS, nor were severity of depressive symptoms and BDNF levels correlated.

Limitations: The small sample size, its heterogeneity, the short observation period and a cross-over design without an interval between both conditions.

Conclusions: tDCS did not change BDNF serum levels unlike other established antidepressant interventions in this treatment resistant sample. However, larger studies are needed.

1. Background

Brain-derived neurotrophic factor (BDNF), discovered in 1980, is an important regulator for neuronal growth, survival and differentiation, stabilizing neuronal synapses and enhancing axonal growth (Duman and Monteggia, 2006). BDNF serum levels are hypothesized to reflect BDNF regulation in the CNS and have been investigated in various psychiatric disorders.

BDNF serum levels were reduced in major depressive disorder (MDD) and negatively correlated with depression severity (Duman and Monteggia, 2006; Sen et al., 2008; Bocchio-Chiavetto et al., 2010). This was also the case in depressed subjects treated with antidepressants (Satomura et al., 2011) and peripheral BDNF levels were lower in patients with greater severity of depression (Dell'Osso et al., 2010; Wolkowitz et al., 2011). Clinical improvement due to antidepressant therapy seems to be associated with BDNF-induced hippocampal neurogenesis (Laske and Eschweiler, 2006). A meta-analysis by Brunoni et al. (2008) showed a more pronounced increase of peripheral BDNF levels after pharmacological treatment than after non-pharmacological interventions. Moreover, the lack of an early increase of BDNF levels is associated with a failure of antidepressant treatment (Tadic et al., 2011) and responders to antidepressant treatment had higher pre-treatment BDNF levels than non-responders (Wolkowitz et al., 2011). Dreimüller et al. (2012) could show that an early increase of BDNF plasma levels within 7 days of antidepressant treatment positively predicted the treatment outcome in MDD. However, changes in sBDNF were not necessarily correlated with changes in depression ratings (Wolkowitz et al., 2011).

Several studies have investigated the effects of therapeutic brain stimulation on peripheral BDNF levels in MDD. Electroconvulsive therapy (ECT) led to an increase of BDNF levels after treatment (Bocchio-Chiavetto et al., 2006; Okamoto et al., 2008;

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http://dx.doi.org/10.1016/j.jad.2013.03.015

Marano et al., 2007). Repetitive transcranial magnetic stimulation (rTMS) exerted a similar effect in one study (Zanardini et al., 2006), whereas no change of BDNF levels was detected in another trial (Lang et al., 2005). Neither did vagus nerve stimulation (VNS) lead to an increase of BDNF levels in the same study (Lang et al., 2005).

A further novel brain stimulation technique is transcranial direct current stimulation (tDCS). The method of changing membrane potentials in neurons by a weak direct current is known since the 1960s and has been re-discovered by Nitsche and Paulus (2000). Since, tDCS has been investigated as therapeutic intervention in various neuropsychiatric disorders including MDD (Palm et al., 2012). The neurophysiological background of tDCS-elicited changes in synaptic plasticity is not fully understood, but may involve BDNF-mediated mechanisms (Ventimiglia et al., 1995). Enhanced BDNF secretion has been proposed to influence long-lasting synaptic potentiation during tDCS-induced neuronal excitability shifts (Fritsch et al., 2010). As no study has addressed the effect of tDCS on BDNF serum levels in major depressive disorder to date, we investigated BDNF levels in patients with a treatment-resistant major depressive episode participating in a double-blind placebo-controlled tDCS trial (Palm et al., 2012).

2. Methods

2.1. Subjects

Twenty-two patients (14 female, 8 male, mean age 57 years, range 36–79) were included in the study (see CONSORT flowchart —Supplemental information Fig. 1). All patients suffered from a major depressive episode (DSM-IV criteria) and had undergone at least two antidepressant treatment trials without achieving remission of depressive symptoms (avg. 2.9 failed trials in the ATHF score). Twenty patients had a unipolar depressive disorder (3 first episodes, 17 recurrent), two had bipolar disorder. Pharmacological treatment of the past 3 weeks was continued in stable dose during the study. All patients had various antidepressants (TCA, SSRI, SNRI, MAOI, and combinations), some of them were additionally treated with standard or second generation antipsychotics (aripiprazole, quetiapine, olanzapine, melperone), mood stabilizers (lamotrigine, lithium, pregabaline) and benzodiazepines ($_{max}$. 1.5 mg lorazepam or equivalent). The detailed description together with the clinical outcome of the study has been published elsewhere (Palm et al., 2012). In brief, all patients received 10 sessions of active and 10 sessions of sham tDCS for 2 weeks each in random order and counterbalanced across subjects. Stimulation intensity was either 1 mA ($n=10$) or 2 mA ($n=12$). The trial was in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical Faculty at the Ludwig-Maximilians-University. All patients gave their written informed consent.

2.2. Transcranial direct current stimulation

Two identical CE-certified programmable constant current DC-stimulators (*eldith*© DC-Stimulator, Neuroconn GmbH, Ilmenau, Germany) were used for active and placebo tDCS. The sham stimulation initiates ramp-in and -out phases of the active stimulation mode without delivering a short stimulation period. Both conditions were indistinguishable to the patients and the operator and patients were not able to differentiate between the two conditions (Palm et al., 2012). Active and sham tDCS were each applied over the dorsolateral prefrontal cortex (DLPFC) for 20 min on 10 days. The anode was placed over the left dorsolateral prefrontal cortex (DLPFC) according to F3 (10–20 EEG system) and the cathode over the right supraorbital region. This electrode montage has been a standard in a variety of clinical trials of tDCS in major depressive episode with active changes under the anode over the left DLPFC and the reference electrode over the right supraorbital region (for a synopsis see Palm et al., 2012). Electrodes (35 cm^2) were covered by tap water- or saline-soaked sponges and fixed by rubber bands.

2.3. BNDF measurement

BDNF was measured at beginning of the trial before first tDCS, after 2 weeks of tDCS, after 4 weeks of tDCS (after completion of tDCS series), and a follow-up measure was made 2 weeks after the end of the tDCS series. Venous blood was centrifuged after clotting for 15 min at 4000 turns per minute. 500 μl of the serum were given in an *Eppendorf cup* and stored at −80 °C. BDNF was measured using a *Quantikine Human BDNF Immunoassay* (R&D Systems, Minneapolis, MN, USA). This enzyme linked immunosorbent assay (ELISA) uses a monoclonal antibody specific for BDNF, pre-coated onto a microplate. Samples were pipetted into the wells and BDNF was bound by the immobilized antibody. An enzyme-linked monoclonal antibody specific for BDNF was added to the wells. Following a wash to remove any unbound antibody–enzyme reagent, a substrate solution was added to the wells and color developed in proportion to the amount of BDNF bound in the initial step. The color development was stopped and the intensity of the color was measured at 450 nm wavelength.

2.4. Clinical assessment

Rating scales and cognitive tests were administered by experienced raters blind to treatment conditions at baseline, after 2 weeks and after 4 weeks: Hamilton Rating Scale for Depression, 24-item version (HAMD-24, primary outcome criterion), Clinical Global Impression (CGI) and Beck Depression Inventory (BDI), Verbal Learning Memory Test (VLMT), Letter Number Sequencing Task of the Wechsler Adult Intelligence Scale (LNS_{WAIS}), Regensburg Word Fluency Test (RWT) and the Mini-Mental-Status-Test (baseline only). LNS_{WAIS} and RWT were repeated after 5, 10, 15 and 20 stimulations, VLMT in parallel versions was repeated after 2 and 4 weeks. The detailed description of the clinical ratings and cognitive tests was already reported elsewhere (Palm et al., 2012).

2.5. Statistical analysis

Univariate group comparisons were performed using *t*-tests. Accounting for the longitudinal format of the data, mixed effect models for scale courses were applied with patient effect in terms of random intercepts. For model selection a backward method was performed: the initial mixed effect model included thereby all variables of interest, which are treatment, time and baseline score including interactions, and was reduced step by step referring to the results of likelihood quotient tests. Spearman's correlation coefficients were performed for BDNF levels and demographic/clinical variables at baseline, after 2 and 4 weeks with regard to changes from baseline and within the two treatment periods. The statistical software environment R 2.13.2 (R Development Core Team, 2011) was used for all analyses.

3. Results

3.1. Subjects

Half of the patients ($n=11$) received active tDCS (group A) and half of the patients ($n=11$) received sham tDCS (group B) as first

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treatment. Both groups were comparable in terms of demographic measures, clinical characteristics, and cognitive performance at baseline (Table 1). From twenty-two patients enrolled, twenty patients completed the study, nineteen patients completed BDNF measurements (2 drop-outs for personal reasons, 1 refused blood examination). The data of 20 subjects were included in the observation (last observation carried forward [LOCF]).

3.2. Efficacy outcomes

Comparing the primary endpoints (HAMD at week 2 and 4), there was no significant difference between active and sham tDCS. Median HAMD showed a modest reduction by 13.7% after active tDCS and by 14.6% after sham tDCS. BDI and CGI ratings were not different between active→sham and sham→active groups. Results in verbal learning (VLMT), verbal fluency (RWT), and working memory (LNS_{WAIS}) did not change significantly. Detailed clinical and neuropsychological results have already been reported by Palm et al. (2012).

3.3. BDNF results

3.3.1. BDNF levels in the cross-over groups

With regard to cross-over order (group A: active→sham, group B: sham→active), median BDNF levels in both groups were comparable at the respective baseline [before active stimulation (includes group A: baseline→week 2 and group B: week 2→week 4): 11.6 ng/nl; before sham stimulation (includes group A: week 2→week 4 and group B: baseline→week 2): 11.3 ng/ml]. BDNF levels did not differ after each 2-week treatment period with either active or sham tDCS (after active stimulation: 11.6 ng/ml; after sham stimulation: 11.8 ng/ml). Without regard to cross-over order, BNDF differences between both intervention groups were not significant at baseline (group A: 14.4 ng/ml vs. group B: 10.5 ng/ml; $p=0.24$) and there was no change of BDNF levels in the active first or sham first group after 4 weeks (Fig. 1).

The follow-up measures, 6 weeks after beginning and 2 weeks after end of tDCS, showed inconsistent results and no trend towards an increase of BDNF levels and therefore were excluded from further statistical analyses. Current strength had no impact on BDNF levels after 2 weeks of active stimulation (1 mA group: 10.4→12.6 ng/dl; 2 mA group: 11.0→13.0 ng/ml). Detailed demographical/clinical data and BDNF levels at baseline are reported Table 1. The mixed linear model showed no influence of baseline BDNF levels ($t=1.89$, $p=0.08$, d.f. 15), active stimulation ($t=0.61$, $p=0.55$, d.f. 15), and the interaction of active stimulation and time course (t −0.86, p 0.40, d.f. 15) on outcome BDNF level.

3.3.2. Correlations at baseline and over the first treatment period

Spearman's correlation analysis for BDNF levels in relation to demographic/clinical variables showed no significant effects at

Table 1
Demographic data, BDNF levels and depression scores at baseline (mean ± SD) with regard to order of intervention.

	Active tDCS→sham tDCS $n=11$	Sham tDCS→active tDCS $n=11$	d.f., F/χ^2	P
Age (yrs)	56 ± 12	58 ± 12	21, 0.63	0.70
Gender (female/male)	6/5	8/3	0.14	0.40
Age of onset (yrs)	44 ± 10	43 ± 15	21, 0.96	0.68
Duration of current episode (months)	7 ± 10	9 ± 15	21, 0.74	0.51
Antidepressant trials failed (ATHF score)	2.9 ± 2.0	2.91 ± 1.22	0.60	0.62
BDNF	14.4[a] ± 4.7	10.46 ± 4.65	20, 0.58	0.24
HAMD	33.0 ± 7.3	34.6 ± 5.4	62, 0.29	0.41
BDI	27.9 ± 7.2	31.3 ± 12.1	17, 0.45	0.32
CGI	4.6 ± 1.7	4.5 ± 2.3	17, 0.64	0.65
PANAS pos.	17.5 ± 2.3	17.3 ± 2.6	17, 0.56	0.60
PANAS neg.	26.8 ± 3.4	23.4 ± 4.6	17, 0.52	0.58

ATHF-Antidepressant Treatment History Form, HAMD-Hamilton Rating Scale for Depression, 24-item version, CGI-Clinical Global Impression, BDI-Beck Depression Inventory, PANAS-positive and negative affect scale.

[a] $n=9$

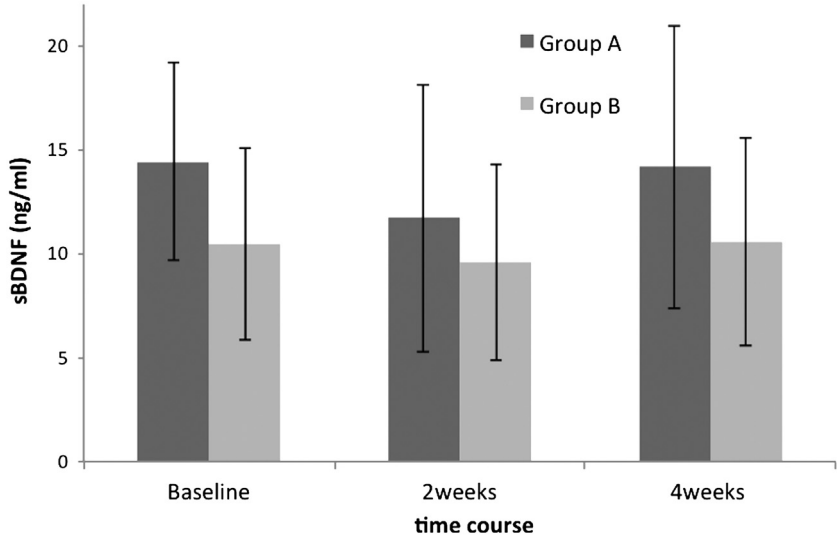

Fig. 1. Median Serum BDNF levels in both intervention groups over the time course. Legend: sBDNF levels (ng/ml) in Group A (2 weeks real→2 weeks sham tDCS) and Group B (2 weeks sham→2 weeks real tDCS) at baseline, after 2 and after 4 weeks of tDCS treatment.

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baseline for age, treatment resistance (ATHF), HAMD, BDI, and CGI scores. There was no correlation between BDNF levels and neuropsychological performance (VLMT, RWT, LNSWAIS) at baseline. Analyzing changes of BDNF levels within the first 2 weeks in relation to demographic/clinical variables at baseline, no correlation with age, treatment resistance, HAMD, BDI, CGI and neuropsychological scores was observed. Correlation analysis of changes in BDNF levels and changes in clinical variables from baseline to week 2 showed no significant correlation for demographic/clinical variables (age, HAMD, BDI, CGI scores) and neuropsychological performance (RWT, VLMT, LNSWAIS).

3.3.3. Correlations over the second and the whole treatment period

From week 2 to week 4, only reduction in BDI ($r=-0.46$, $p=0.06$) showed a trend towards significance. Correlation analysis showed a significant and strong negative correlation between the change of BDNF levels from week 2 to week 4 and the HAMD score at baseline ($r=-0.85$, $p=0.004$). Although RWT increased by 22% between week 2 and 4, neuropsychological data showed no correlation with BDNF levels in this period. BDNF level changes from baseline to week 4 showed no significant correlation with age, treatment resistance, HAMD, BDI and CGI scores at baseline. Neuropsychological scores at baseline showed no correlation with changes of BDNF levels over the study period. Over the whole period from base line to week 4, correlation between changes in BDNF levels and clinical variables/neuropsychological tests showed no significant effects except for improvement in the RWT($r=0.68$, $p=0.002$).

4. Discussion

To our knowledge, this study is the first to investigate the effect of tDCS on BDNF serum levels in depression. We observed no significant effect of real tDCS on BDNF serum levels in therapy-resistant depressed patients compared to sham stimulation. Changes of BDNF levels were neither correlated with a change of depression scores nor with a change in neuropsychological performance except for minor improvement of verbal fluency (RWT), whereas other neuropsychological parameters were unchanged.

Compared to findings for established antidepressant interventions like rTMS (Zanardini et al., 2006), there was no increase of BDNF levels after tDCS. Okamoto et al. (2008) reported a significant increase of BDNF levels in responders to ECT whereas non-responders showed no increase. However, ECT is the most potent tool in non-invasive brain stimulation and clinical outcome is probably largely superior to tDCS. These results in ECT non-responders are in line with the lack of changes in BDNF levels possibly related to the modest clinical outcome in our study. Similar to Okamoto et al. (2008) and Wolkowitz et al. (2011) we did not find a correlation between changes in BDNF levels and changes in HAMD scores before and after treatment.

4.1. Limitations

In our study, tDCS did not turn out to be an efficient treatment in severe, treatment-resistant depression, shown by the only modest clinical improvement and possibly reflected by the lack of a BDNF increase. This might be due to several reasons: First, the higher degree of therapy-resistance shown by an average of 2.9 failed antidepressant trials that hampers quick and strong changes of illness severity. Second, it could also be due to the elevated age range (up to 79 years) in our patient sample as BDNF expression seems to decrease in higher age (Lommatzsch et al., 2005; Ziegenhorn et al., 2007) and might be responsible for a reduction of neuroplastic capacity. A lower increase of sBDNF levels in non-remitters than in remitters (Piccinni et al., 2009) and higher pre-treatment sBDNF levels in responders vs. non-responders have been reported (Wolkowitz et al., 2011). In our study, sBDNF levels showed no correlation at all neither with severity of depression at baseline nor with changes of severity after active and sham treatment.

A critical issue may be the method chosen for determining BDNF in serum samples. Measurements were made by an experienced laboratory technician with a generally sound standard procedure. However, we cannot completely rule out that the duration of sample storage had an effect on sBDNF levels as low BDNF levels occurred in samples after longer storage (maximum 3 months at −80 °C; 40% of samples) as well as in samples with rather immediate BDNF measurement (60% of samples). Similarly, the time of the day in relation to the biophysical or emotional activation of the subject might have influenced BDNF levels, though blood samples were mostly drawn in the morning. Furthermore it is still in discussion whether serum or plasma BDNF measures lead to more stable and reliable results (Lommatzsch et al., 2005). In addition, the high inter-individual variability of plasma BDNF reported by Piccinni et al. (2008) was also observed in our serum BDNF samples. Taken together, these methodological imponderabilities may partially explain the variation of results in previous studies.

The most prominent limitation of our study is definitely the small sample size of only 19 completers. With the subgroups of unipolar (first episode and recurrent) and bipolar depressed patients, there is no sufficient statistical power to draw any firm conclusion. Furthermore, the different concomitant medication of various antidepressants and antipsychotics with their different mechanisms of action could have had crucial influence on the heterogeneous outcome, and the use of benzodiazepines and mood stabilizers such as lamotrigine and pregabaline could have reduced excitability effects of tDCS (Nitsche et al., 2012). Another limitation may be the cross-over design of the study. The key-mechanism of neuroplasticity changes is possibly driven by long-term potentiation like mechanisms which lead to a later onset of antidepressant efficacy, as reported by Piccinni et al. (2009) after ECT. In our study, the cross-over sequence of real and sham treatment without an observational interval could have led to carry-over effects, blurring the difference between real and sham tDCS. However, if real tDCS would have had a pronounced carry-over effect, one could expect a larger difference between the “2 weeks real→2 weeks sham tDCS” and “2 weeks sham→2 weeks real tDCS” groups in favor of real tDCS first. For real tDCS, however, we did not even observe a non-significant, but promising signal towards a reduction of depressive symptoms or an increase of BDNF levels compared to sham tDCS. However, on the one hand, it seems reasonable that a lack of antidepressant efficacy in our sample is not associated with BDNF changes. On the other hand there could be a decoupling of clinical and neurobiological/neurochemical measures. Thus, a longer observation period could have shown more pronounced results as neuroplasticity changes may not be observable within the first treatment weeks. Brunoni et al. (2008) suggest a 4–8 weeks period for this reason. Furthermore, the possible role of the *Val66Met* polymorphism in the BDNF gene has not been assessed in our sample which may have a diminishing effect on the efficacy of tDCS (Cheeran et al., 2008; Antal et al., 2010).

The meta-regression of BDNF level changes by Brunoni et al. (2008) reveals a correlation with the change of depressive symptoms, period of treatment and previous treatment with antidepressants. Antidepressant treatment of major depressive disorder and the increase of peripheral BDNF levels were consequently hypothesized to be associated with enhanced neuroplasticity (Brunoni et al., 2008). It is likely that ineffective antidepressant

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treatment as add-on tDCS in our study is not sufficient to provoke improvement in clinical assessments together with an increase of sBDNF levels. From this point of view, the negative BDNF results are coherent and underline the hypothesis that a failure in treatment response is linked to missing BDNF increase (Tadic et al., 2011). Although this pilot study showed no significant effect of tDCS on BDNF levels in treatment resistant depression, this negative finding should not be overestimated due to the limitations mentioned above. As tDCS has shown to be a promising treatment option for various neuropsychiatric disorders due to its ability of non-focally shifting neuronal excitability in target regions, the interaction between tDCS-induced neuroplasticity changes and BDNF level should be further investigated.

5. Conclusions

In our sample, tDCS did not alter BDNF serum levels in therapy-resistant depression corresponding to a lack of meaningful therapeutic effects. There is a need for further studies to clarify the inconsistent results of BDNF blood levels in severe psychiatric disorders such as therapy resistant major depressive disorders, and there is need for comparison of pharmacological versus non-pharmacological treatments, taking into account the possible role of BDNF gene polymorphisms.

Role of funding source

The corresponding author and all co-authors declare no conflict in terms of funding bodies.

Conflict of interest

F. Padberg has received grant/research support from Brainsway Inc. and Aspect Medical Systems. O. Pogarell has received grant/research support from Lundbeck. M.A. All other authors declare no conflict of interest concerning their affiliations.

Acknowledgments

This work is part of the MD thesis of Zoe Fintescu. The *eldith* DC-stimulators were provided by neuroConn GmbH for rent.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2013.03.015.

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Please cite this article as: Palm, U., et al., Serum levels of brain-derived neurotrophic factor are unchanged after transcranial direct current stimulation in treatment-resistant depression. Journal of Affective Disorders (2013), http://dx.doi.org/10.1016/j.jad.2013.03.015