



CASE REPORT

Transcranial direct current stimulation in a patient with therapy-resistant major depression

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Abstract

Transcranial direct current stimulation (tDCS) of the prefrontal cortex (PFC) has been reported to exert significant antidepressant effects in patients with major depression. Several recent studies found an improvement of depressive symptoms in drug-free patients. Here we report the case of a 66-year-old female patient suffering from recurrent major depressive episodes who underwent anodal tDCS of the left dorsolateral PFC over 4 weeks as an add-on treatment to a stable antidepressant medication. Only a modest improvement of depressive symptoms was observed after tDCS, i.e. reduction of the baseline scores in the Hamilton Depression Rating Scale from 23 to 19 and in the Beck Depression Inventory from 27 to 20. However, there was an increase from 52 to 90% in the Regensburg Verbal Fluency Test. In addition, EEG was used to assess the acute effects of tDCS. Low resolution brain electromagnetic tomography (LORETA) showed a left unilateral focal effect (25–40% reduced power) in the delta, theta and alpha frequency bands. The same effect appeared in the surface analysis of the EEG. The absolute, as well as the relative power decreased significantly in the delta, theta and alpha bands after a comparison of the spectral analysis. Though tDCS over 4 weeks did not exert clinically meaningful antidepressant effects in this case of therapy-resistant depression, the findings for cognitive measures and EEG suggest that beneficial effects may occur in depressed subjects and future studies need to further explore this approach also in therapy-resistant major depression.

Key words: Major depressive disorder, transcranial direct current stimulation, tDCS

Introduction

The method of transcranial direct current stimulation (tDCS) is known since the 1960s and based on experimental research in animal models (Bindman 1962). In humans, anodal tDCS enhances working memory and reaction time due to excitability alteration in neurons (Nitsche et al. 2005). Several studies suggested that tDCS may be helpful in post-stroke rehabilitation (Hummel et al. 2005) and in the treatment of central pain in traumatic spinal cord injury (Fregni et al. 2006c). The reduction of depressive symptoms has been shown in consecutive studies by Fregni and co-workers. Fregni et al. (2006a) found a significant decrease in the Hamilton Depression Rating Scale and Beck Depression Inventory after 5 days of active stimulation in comparison to a group of patients with sham stimulation. In another study (Fregni et al. 2006b) including 18 antidepressant-free patients with recurrent major

depressive episodes, a significant reduction in the Hamilton depression score was found after 5 days of active tDCS. Interestingly, mood improvement and cognitive improvement were not correlated suggesting that independent mechanisms are responsible for cognitive and mood changes. This finding has been replicated by Boggio et al. (2007a). In 40 antidepressant-free patients suffering from unipolar major depression, Boggio et al (2007b) found a significant reduction in the Hamilton and Beck depression scores after DLPFC tDCS over 2 weeks compared to occipital and sham tDCS. Despite the particular need for novel effective antidepressant interventions in therapy-resistant depression there are no published data on tDCS in this difficult-to-treat group to our knowledge.

Here, we report the case of a 66-year-old woman suffering from a drug-resistant recurrent major depressive episode who was treated with anodal

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(Received 30 June 2008; accepted 17 September 2008)

ISSN 1563-2875 print/ISSN 1814-1412 online © 2009 Informa UK Ltd. (Informa Healthcare, Taylor & Francis AS)
15622970802480905

tDCS of the left dorsolateral prefrontal cortex over 4 weeks.

Case report

The 66-year-old female patient was suffering from a recurrent major depression (DSM-IV: 296.33) and had depressive episodes in 1986 and 1990. The current episode began in 2006 following a treatment of tinnitus with corticoids. The patient had undergone several failed antidepressant trials: the first combination of mirtazapine, venlafaxine and olanzapine had no obvious effect on the improvement of depressive symptoms. The second combination of paroxetine 40 mg, reboxetine 4 mg, mirtazapine 30 mg, risperidone 1 mg and lithium 800 mg brought a partial response of the depressive syndrome. When tDCS was considered the patient was still suffering from anhedonia, lack of energy and concentration. ECT was rejected by the patient. The treatment regime had been stable for 6 weeks and was carried on during tDCS treatment.

In accordance with the safety criteria of tDCS in humans, we used the protocol suggested by Nitsche et al. (2003a,b). We applied a weak direct current of 1 mA to the cortex. We used a CE-certified DC-stimulator (eldith DC-stimulator, neuroconn, Ilmenau, Germany). The anode was placed over the left dorsolateral prefrontal cortex (DLPFC – EEG F3/int. 10–20 system), the cathode was placed over the right supraorbital region. The sponges (35 cm²) were soaked with physiological 144 mmol/l NaCl solution. After 10 stimulations we changed to water-soaked sponges. The duration of the each stimulation was 20 min with phases of 15 s ramp up and 15 s ramp down. Over all we performed 16 stimulations in a period of 27 days, initially daily, and afterwards two-daily when the patient changed to outpatient status.

In advance of the stimulation we performed several neuropsychological tests and ratings: Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HAMD) and Clinical Global Impression (CGI) for clinical assessment, the Regensburg Word Fluency Assessment (RWT) and the Verbal Learning and Memory Test A/B (VLMT in four parallel versions A–D) for neuropsychological assess-

ment. After a cycle of five stimulations we measured again BDI, HAMD, CGI, RWT and VLMT-C. After the second cycle of five stimulations we rated BDI, HAMD, CGI, RWT, VLMT-D. The rater was not blinded to the treatment. After the 16th stimulation the patient refused to continue treatment and ratings for personal reasons.

tDCS was started at 1 mA over 20 min with a ramp up and a ramp down of each 15 s (in toto 1230 s). The measured impedance initially showed variations between 50 and 70 k Ω in accordance to the skin contact and the pressure applied to the sponges and dropped to 10–20 k Ω during ramp-up-phase. During the stimulation all parameters were supervised constantly by the Eldith DC Stimulator. An excess of limitations, e.g., impedance rise by drying up or chute of the electrodes the stimulation was automatically finished. The itching sensation under tDCS application with 144 mmol/l NaCl solution was reported as uncomfortable but not painful. The duration of the sensation was about 2 min. After changing to water-soaked sponges, the duration of the itching sensation diminished to ~1 min. Stimulation with water was reported more comfortable due to less itching sensation. Skin lesions did not appear (Palm et al. in press).

Overall, clinical rating showed a modest improvement of depressive symptoms (Table I). We found a reduction of the baseline HAMD score from 25 points at baseline to 22 after five stimulations and to 19 points after 10 stimulations. Further ratings did not take place as the patient wanted to stop the treatment. The BDI showed a reduction from 27 to 20 or 21 points after five and 10 stimulations, respectively. In the Regensburg word fluency assessment (RWT) in different versions, we found a percentage of 90% after 10 stimulations in comparison to 52% at baseline. The VLMT was constant at 27 points. The CGI was constant at 4. Although CGI showed no difference from baseline to the end, there has been a mild subjective and objective cognitive improvement. The further antidepressant treatment was moderately changed after end of tDCS and consisted in lithium 800 mg, reboxetine 4 mg and paroxetine 40 mg, but there was no improvement of depressive symptoms in the follow-up examinations.

Table I. Scores in measures of psychopathology and cognition.

	HAMD	BDI	CORE	PANAS	VLMT W-F	RWT	CGI	MMST
Baseline	25	27	12	16/16	A: 27 B: 42	PR 52	4	28/30
5 tDCS stimulations								
1. rating	22	20		18/12	C: 27		4	
5 tDCS stimulations								
2. rating	19	21	12	20/17	D: 27	PR 90	4	

Acute effects of tDCS on the EEG were assessed with a Neuroscan Synamps apparatus using an electrode cap with 33 electrodes (all referred to channel Cz). After EEG baseline recording, we measured after treatment with 20 min sham tDCS (Eldith sham device), the patient was blinded to this condition. Fifteen minutes after the first active tDCS treatment EEG recording was repeated, the time was needed for drying the hair to avoid malfunction. Electrode skin impedance was always less than 5 k Ω . We used an electrooculogram below the left eye. The electrodes were placed according to the International 10/20 system (Jasper 1958) with the additional electrodes FC1, FC2, FC5, FC6, CP5, CP6, P09, P010. Fpz served as ground electrode. The patient was instructed to remain in an alert state with her eyes closed in a sound-attenuated room. The EEG was recorded for 10 min with a sampling rate of 1000 Hz and an analogous banpass filter (0.16–200 Hz). Offline we changed the sampling rate to 250 Hz and used a 70-Hz low-pass filter. Before analysis, artefact detection was performed visually with the exclusion of all EEG segments that contained obvious eye or muscle artefacts or a decrease in alertness. The scalp sites were grouped into three sagittal regions, frontal (Fp1, Fp2, F3, FC1, F4, FC2, FC5, F7, F8, FC6, Fz), central (T3, T4, CP5, CP6, C3, C4, Cz) and posterior (T5, T6, P3, P4, Pz, O1, O2) for the surface EEG analysis. After recomputation to the average reference, spectral analysis was performed for 27 electrodes (we excluded the electrodes T1, T2, P09 and P010 due to bad quality). The EEG was Fourier transformed for at least 2-s epochs using the Brain Vision Analyzer software Version 1.05. Epochs were reduced to 80 epochs (2 min 40 s). The EEG was analyzed in four frequency bands: delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz) and beta (13–25 Hz). A summary of real versus placebo treatment results are presented in Table II.

In addition we carried out a source analysis with LORETA (Pascual-Marqui et al. 1994). The LORETA changes showed up an asymmetric and focal effect (25–40% reduced activity) in the following frequency bands: delta (1.0–6.0 Hz), theta (6.5–8.0

Hz), alpha 1 (8.5–10.0 Hz) and alpha 2 (10.5–12.0 Hz) (see Figure 1).

Discussion

In our case, tDCS had very limited effects on the course of a therapy-resistant depressive episode. The improvement in clinical symptoms was modest. Verbal fluency improved after ten tDCS sessions, but no effect was observed on verbal memory performance. A placebo effect on cognitive tasks may be possible, but the cognitive enhancement by tDCS has frequently been reported. Learning effects are not likely due to different versions of the tasks. Interestingly, the acute effects of a single session of tDCS on the EEG were rather pronounced. The differences between EEG effects after sham and after active tDCS suggest a specific efficacy of tDCS on neuromodulation and are probably more intensive after a couple of stimulations. Moreover, we observed similar somatosensory side effects as described by Dundas et al. (2007) in their trial of perception of comfort during tDCS. The use of water showed no other methodological and functional difficulties than the use of NaCl, in both cases the measured impedances depended on the skin contact of the sponges, and in both cases an erythema was found under the sponges after stimulation. In summary, tDCS was well tolerated and no adverse effects were reported.

Boggio et al. (2007b) found a decrease of depressive symptoms in the HAMD from 21 to 13 after 2 weeks of 2 mA treatment which means an average reduction by 8 points. Fregni et al. (2006b) found a decrease by 58% in the HAMD from the baseline score of 23.5 (stimulation with 1 mA over 5 days). In our case, the HAMD decreased from 25 to 19 (6 points) after 2 weeks of 1 mA treatment. In contrast to the studies of Boggio et al. (2007), Fregni et al. (2006a,b) we applied tDCS in a patient with therapy-resistant major depression and continuous psychopharmacological treatment. The moderate effects that we found suggest a lower efficacy of weak tDCS in this case of chronic and therapy-resistant depressive disorder. Another question is whether an antidepressant or

Table II. Summary of significant differences in the surface EEG after active tDCS compared to sham treatment.

Comparison tDCS EEG vs. baseline EEG	Absolute power (μV^2)			Relative power (%)		
	Delta	Theta	Alpha	Delta	Theta	Alpha
Frontal	** ↓		*** ↓	** ↓	* ↓	*** ↓
Central			** ↓			** ↓
Posterior						

Paired *t*-test significance: * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$; ↓ = significantly decreased.

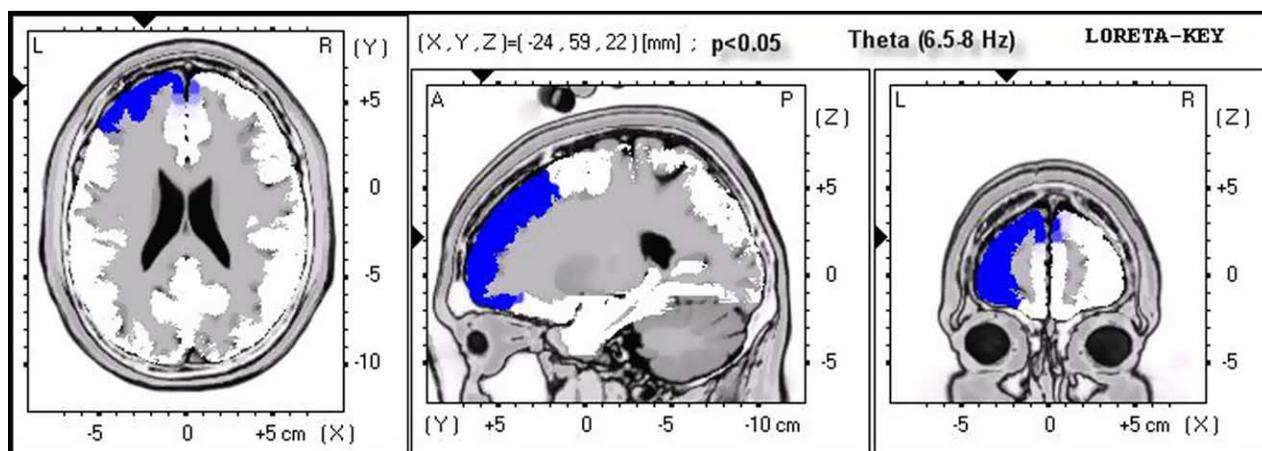


Figure 1. The acute effect of real tDCS on the current densities measured by LORETA. The signal measured about 15 min after the real prefrontal tDCS at the EEG Point F3 decreased the current density in the delta, theta and alpha bands. The figure shows the significant effect between real versus sham measurements for the theta frequency band. The effect was laterally in the superior frontal gyrus ($xyz = -24, 59, 22$; BA 9). The paired t -test was used with corrected P values: $P \leq 0.05$. $xyz =$ maximum in the Talairach space. TF, converted z -value.

phase-prophylactic medication may alter the effect of tDCS on neuroplasticity and result in lower antidepressant effects.

However, tDCS has been proven to be a powerful tool for changing cortex excitability. The acute EEG changes following tDCS point in this direction and even more pronounced changes are probable when tDCS is repeated over a longer period. In contrast to former studies with antidepressant-free patients, the application of tDCS in this single case of a multi-drug-resistant and chronic depressive patient seems to have not the same quick and significant effects. The protocol we used was restricted to 1 mA for reasons of safety, and higher stimulation intensity and/or longer tDCS sessions may yield more robust results.

In conclusion, there is further need for studies evaluating tDCS as an add-on-treatment in therapy-resistant patients.

Acknowledgements

None.

Statement of interest

The authors have not declared any conflicts of interest.

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