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

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Background
Anodal transcranial direct current stimulation (tDCS) of the prefrontal cortex has been proposed as therapeutic intervention in major depression. According to clinical needs, this study addresses the question whether tDCS is effective in treatment resistant major depressive episodes.

Methods
Twenty-two 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. The parameters of active tDCS were: 1 or 2 mA for 20 minutes/day, anode over the left dorsolateral prefrontal cortex, cathode over the contralateral supraorbital region. Active and placebo tDCS was applied for 2 weeks using indistinguishable DC stimulators. Patients, raters, and operators were blinded to treatment conditions.

Results
There was no significant difference in depression scores after 2 weeks of real compared with 2 weeks of sham tDCS. Scores on the Hamilton Depression Rating Scale were reduced from baseline by 14.7%

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for active tDCS and 10% for placebo tDCS. In contrast, subjective mood ratings showed an increase in positive emotions after real tDCS compared with sham tDCS.

Conclusions

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.

Keywords noninvasive brain stimulation; prefrontal cortex; antidepressant treatment; major depression; cognition

Transcranial direct current stimuation (tDCS) is a noninvasive brain stimulation approach that has been widely used as experimental intervention in neuroscience research and discussed as potential treatment for neuropsychiatric disorders. Early studies in animals have shown that applying a polarizing current to the cerebral cortex modulates neuronal firing and the size of evoked potentials, i.e., a surface-positive current was found to enhance and a surface-negative current to reduce both.[1] These effects have been related to a polarization-induced shift of resting membrane-potentials toward de- or hyperpolarization.[2] More recently, Nitsche and Paulus[3] have rediscovered direct current (DC) stimulation in humans and found that tDCS leads to changes of motor cortex excitability depending on current direction and density. Anodal tDCS enhances motor cortex excitability as measured by the amplitudes of motor evoked potentials, whereas cathodal tDCS reduces it with poststimulation effects being maintained for minutes up to hours depending on duration and repetition rates.[3-6] Moreover, neuroimaging studies have demonstrated cortical and subcortical changes in regional brain activity after tDCS of the primary motor cortex[7,8] and the prefrontal cortex.[9] Several studies have shown an improvement of behavioral and cognitive measures, e.g., working memory performance and reaction time after prefrontal tDCS,[3,10] which was accompanied by specific changes of event-related potentials.[11]

Because of the growing interest in therapeutic applications of noninvasive brain stimulation as repetitive transcranial magnetic stimulation (rTMS), prefrontal tDCS was also investigated as novel treatment for psychiatric disorders with prefrontal pathophysiology, i.e., major depression. Indeed, controlled pilot studies suggest that anodal tDCS of the dorsolateral prefrontal cortex (DLPFC) exerts beneficial effects on clinical symptoms and cognition in major depression. Table 1 provides an overview of previous studies investigating DC stimulation in depression.[12-22] The majority of studies have been conducted in mild to moderate depression, whereas very few of those studies focussed on severe and/or therapy-resistant depression. Thus, the current randomized, placebo-controlled trial investigates the safety and efficacy of prefrontal tDCS in therapy-resistant major depressive episodes.

Methods and materials

Subjects

Twenty-two in- and outpatients of the Department of Psychiatry at the Ludwig-Maximilians University, Munich, Germany (14 female, mean age 57 years, range 36-79), having a major depressive episode (DSM-IV criteria; based on a clinical interview by an experienced psychiatrist) were recruited. Twenty patients had a unipolar depressive disorder (three first episode, 17 recurrent), two had bipolar disorder. Therapy resistance and previous medication were assessed using the Antidepressant Treatment History Form (ATHF).[23] All patients had failed to respond to at least two trials of antidepressant pharmacotherapy from different classes[24]: they were treated with antidepressants (tricyclics, selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, monoamine oxidase inhibitors, combinations) and in addition received antipsychotics, mood stabilizers, or anxiolytics (for a detailed patient description see Supplemental Table 1). Concomitant medication was kept stable for 3 weeks before tDCS and maintained during the entire study period. All patients gave their written informed consent. The study was approved by the medical ethics committee of the Ludwig-Maximilians University and carried out in accordance with the declaration of Helsinki. Further information regarding screening, randomization, design, and reporting is shown in Figure 1.

Design and treatment

Within a placebo-controlled cross-over design, patients were randomized in two groups (active → sham; sham → active) by the principal investigator (F.P.) using a PC-generated random number list. Two undistinguishable CE-certified programmable constant current DC-stimulators (*Eldith*© DC-Stimulator, Neuroconn GmbH, Ilmenau, Germany) were used for active and placebo tDCS. The anode was placed over the left DLPFC according to F3 (10-20 EEG system) and the cathode over the right supraorbital region.

Table 1 Synopsis of previous open and controlled clinical trials investigating tDCS as antidepressant intervention

Double-blind randomized placebo controlled trials

Author	Study design	N Mean age	MDD/BD treatment resistance	Medication	Electrode position	Reference electrode	Current strength electrode size	Duration	Results
Fregni et al.[12]	Double-blind placebo-controlled randomized (each 9 patients active/ sham)	n = 18 47 ± 10 y	MDD, no treatment resistance required, no data on failed trials	No antidepressant treatment in the last 3 mon	F3 (anodal)	Supraorbital right (cathodal)	1 mA, 35 cm^2	20 min/d for 5 d	Significant cognitive and mood improvement after active tDCS. No correlation between both conditions and HDRS/BDI ratings
Fregni et al.[13]	Double-blind placebo-controlled randomized (each 5 patients active/ sham)	n = 10 46 ± 9 y	MDD, no treatment resistance required, no data on failed trials	No antidepressant treatment in the last 3 mon	F3 (anodal)	Supraorbital right (cathodal)	1 mA, 35 cm^2	20 min/d for 5 d	Significant improvement of depressive symptoms in active group versus Sham group in HDRS/ BDI ratings
Boggio et al.[15]	Major depression Double-blind placebo controlled randomized (12 patients active, 7 occipital, 7 sham)	n = 26 48 ± 8	MDD, no treatment resistance required, no data on failed trials	No antidepressant treatment	F3 (anodal) [occipital: 2 cm above Inion (anodal)]	Supraorbital right (cathodal)	2 mA, 35 cm^2	20 min/dy for 10 d	Significant improvement of working memory (go-nogo-task) after active tDCS. No correlation with mood changes (HDRS)
Boggio et al.[16]	Double-blind placebo-controlled randomized (20 patients active, 10 occipital, 10 sham)	n = 40 49 ± 7 y	MDD, no treatment resistance required (avg. 1.7 failed trials)	No antidepressant treatment in the last 2 mon	F3 (anodal) [occipital: 2 cm above Inion (anodal)]	Supraorbital right (cathodal)	2 mA, 35 cm^2	20 min/d for 10 d	Significant mood improvement (HDRS/ BDI) after active anodal tDCS versus sham/occipital tDCS. Effects lasting up to 30 d
Rigonatti et al.[14]	Double-blind placebo-controlled randomized (21 patients active, 11 Fluoxetine 20 mg/d, 10 sham)	n = 42 49 ± 7	MDD, no treatment resistance required (avg. 1.6 failed trials in active group versus 1.2 in fluoxetine and 1.5 in sham group)	No antidepressant treatment in the last 2 mon	F3 (anodal)	Supraorbital right (cathodal)	2 mA, 35 cm^2	20 min/d for 10 d	Anodal tDCS showed faster improvement than Fluoxetine. Same improvement for active tDCS and Fluoxetine after 6 wk

Loo et al.[19]	Double-blind placebo-controlled. 5 d active or sham followed by 5 d active tDCS.(20 active→19 active; 20 sham→16 active)	n = 40 45 ± 12 (sham) 48 ± 10 (active)	MDD, no treatment resistance required (avg. 1.7 failed trials in sham group versus 1.0 in active group)	With or without antidepressant treatment, stable dose > 4 wk	F3 (anodal)	Supraorbital right (cathodal)	1 mA, 35 cm^2	20 min/d, 3×/wk, totally 5 treatments per condition	Significant improvement in HAMD, MADRS, BDI after sham/active and active/active tDCS. No improvement in CORE
Ferrucci et al.[17]	Open label, no placebo control	n = 14 52 ± 2	MDD, treatment resistance after multiple drug trials (no data on avg. trials)	antidepressant treatment, stable dose > 4 wk	F3 (anodal)	Supraorbital right (cathodal)	2 mA, 32 cm^2	2 × 20 min/ d for 5 d	30% improvement in HDRS and BDI, lasting 4 weeks after study end. Improvement in VAS. No cognitive enhancement
Ferrucci et al.[18]	Open label, no placebo control	n = 32 49 ± 12	13 mild/moderate MDD, 19 severe MDD, treatment resistance in 19 patients (2 failed trials)	Antidepressant treatment in stable dose	F3 (anodal)	Supraorbital right (cathodal)	2 mA, 35 cm^2	2 × 20 min/ d for 5 d	50% BDI and HDRS improvement in severe depression, 5-10% in mild/moderate depression
Brunoni et al.[22]	Open label, no placebo control	n = 31 54 ± 11	17 MDD (14 treatment resistant), 14 BD (11 treatment resistant), no data on avg. trials	Miscellaneous psychiatric drugs except 2 patients, stable dosage > 2 wk	F3 (anodal)	DLPFC right (cathodal)	2 mA, 35 cm^2	2 × 20 min/ d for 5 d	Significant mood improvement for MDD and BDD patients, lasting up to 4 wk
Martin et al.[21]	Open label, no placebo control	n = 11 46 ± 13	9 MDD, 2 BD, moderate treatment resistance required (avg. 2.6 failed trials)	With or without psychiatric drugs, stable dose > 4 wk	F3 (anodal)	Supraorbital right (cathodal, 35 cm^2); right upper arm (cathodal, 100 cm^2)	2 mA, 35 cm^2	20 min/ d for 20 d	More rapid response and possibly more potent effect after tDCS with extracephalic electrode compared to BF montage
Dell'Osso et al.[20]	Open label, no placebo control.	n = 23 51 ± 13	15 MDD, 8 BD, no treatment resistance required (1 failed trial, no data on avg. trials)	Miscellaneous psychiatric drugs, stable dose > 4 wk	F3 (anodal)	Supraorbital right (cathodal)	2 mA, 35 cm^2	2 × 20 min/ d over 5 d	Significant improvement in HAMD, MADRS

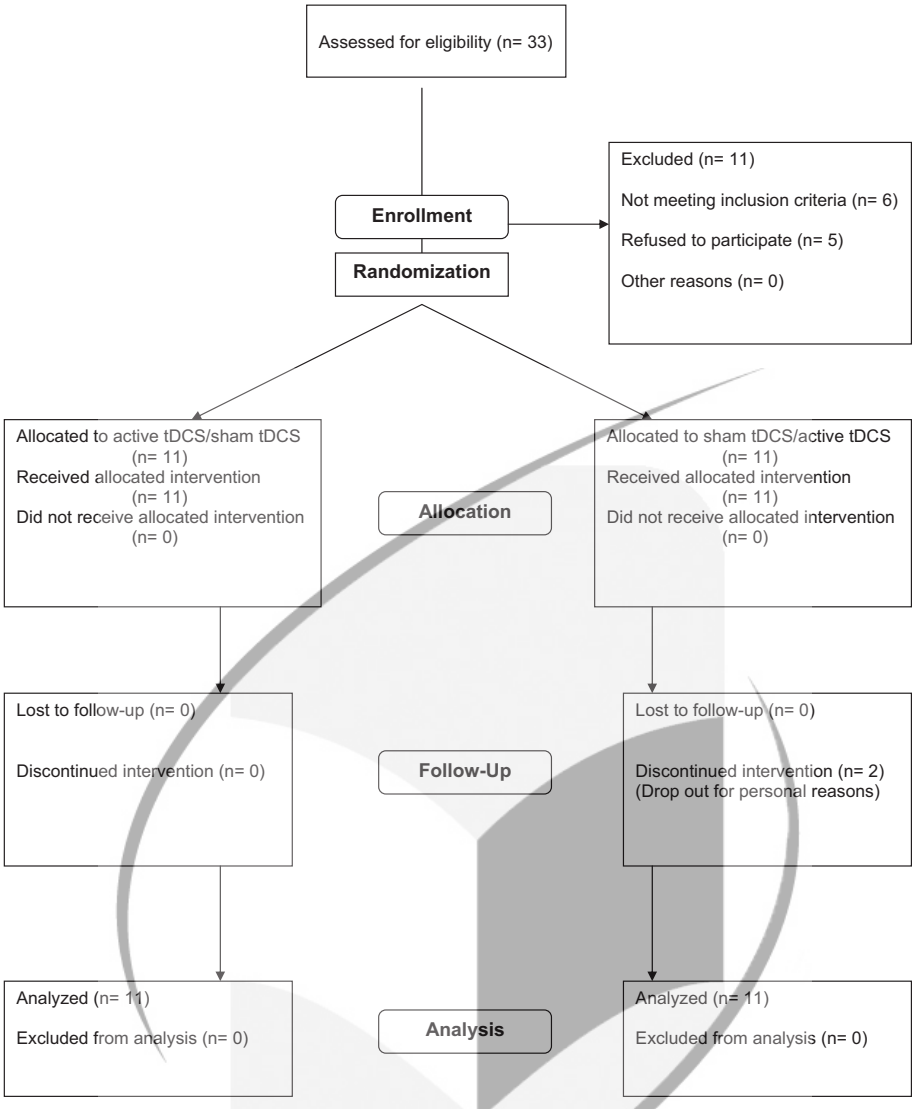

Figure 1 CONSORT flow chart of the study. The study was registered at URL:http://clinicaltrials.gov/show/NCT00667680(ID: NCT00667680).

Electrodes (7 × 5 cm = 35 cm^2) were covered by tap water or saline-soaked sponges and fixed with rubber bands. All patients underwent 20 tDCS sessions (10 active, 10 sham) for 20 minutes/day within 4 weeks without a break between the two conditions. The first 10 patients were treated with 1 mA and the following 12 with 2 mA intensity. This sequential increase of stimulation intensity was chosen because the dose response relationship for tDCS has not been clarified yet. One study comparing 1 and 2 mA intensities in healthy subjects showed an improvement of verbal fluency at 2 mA, whereas 1 mA intensity did not lead to any significant changes.[25] Fregni and his coworkers applied 1 mA intensity in their first pilot studies on tDCS in depression (12, 13). In their later study, however, they switched to 2 mA intensity and reported a significant improvement of depressive symptoms.[15,16] Therefore, we decided to compare both intensities as our study was designed to explore the potential of tDCS as intervention in more severe therapy-resistant depression. The sequential approach was chosen to assess tDCS safety at a lower intensity level first.

The placebo stimulator was programmed with a 20-minute off interval between ramp in and out periods of 15 seconds to produce identical skin sensations to the active device. All operators, tDCS trained MD or PhD students (C.S., Z.F., E.R., D.K.), were blind to treatment conditions.

Clinical assessment and cognitive tasks

The following rating scales and cognitive tests were administered by experienced raters blind to treatment conditions at baseline, after the first 2 weeks and after week 4 with additional depression ratings after week 1 and 3: Hamilton Rating Scale for Depression, 24-item version (HAMD-24, primary outcome criterion), positive and

negative affect scale (PANAS), 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 in parallel versions were repeated after week 1, 2, 3, and 4 VLMT in parallel versions (A/B) was repeated after week 2 and 4. After completion of tDCS, subjects were asked to guess treatment conditions (active or sham) to ascertain the integrity of the blinding.

Statistical analysis

Univariate group comparisons were performed using Student *t* tests. To account for the longitudinal format of the data, mixed effect models for scale courses were performed with patient effects in terms of random intercepts. For model selection, a backward method was performed; the initial mixed effect model included all variables of interest, which were treatment, time and baseline score (including interactions), and which were reduced step by step referring to the results likelihood quotient tests. The final model was validated by a 10-fold cross-validation with the root mean square error (RMSE) as an estimate for the standard deviation of the fit, and Pearson's correlation coefficient as loss functions. The statistical software package R 2.9.1 was used for all analyses.

Results

Subjects

Half of the patients (n = 11) received active tDCS and half of the patients (n = 11) placebo tDCS as first treatment. Both groups were comparable in terms of demographic measures, clinical characteristics, and cognitive performance at baseline (Table 2).

Efficacy outcomes

Twenty patients completed the study, two dropped out because of personal reasons. The data of all 22 subjects were included in the analysis (last observation carried forward [LOCF]). In the Active→Sham group baseline HAMD scores decreased by 16% during active tDCS and by 8% during sham treatment. In the Sham→Active group HAMD scores decreased by 12% during sham tDCS and by 14% during active treatment. Regarding primary endpoints (HAMD at week 2 and week 4), there was no significant difference between active and placebo tDCS (Figure 2A). Modeling the HAMD-course via mixed model analysis showed that active tDCS was slightly superior to placebo treatment ($P = 0.0492$). However, this difference was restricted to the first study phase, i.e., weeks 1 and 2, as there was also a significant ($P = 0.0271$) influence of the study phase and a trend toward a significant ($P = 0.0864$)

Table 2 Demographic and clinical variables at baseline and outcome measures during and after tDCS (mean ± SD)

	Active tDCS → sham tDCS n = 11	Sham tDCS → active tDCS n = 11	df, F/χ^2	*P*
Age (y)	56 ± 12	58 ± 12	21, 0.63	0.70
Gender (female/male)	6/5	8/3	0.14	0.40
Age of onset (y)	44 ± 10	43 ± 15	21, 0.96	0.68
Duration of current episode (mon)	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
$HAMD_{24}$ baseline	33.0 ± 7.3	34.6 ± 5.4	62, 0.29	0.41
$HAMD_{24}$ week 1	28.6 ± 7.7	33.2 ± 7.2	62, 0.50	0.14
$HAMD_{24}$ week 2	28.2 ± 8.8	30.2 ± 7.4	62, 0.50	0.79
$HAMD_{24}$ week 3	26.8 ± 7.1	26.7 ± 10.2	62, 0.58	0.89
$HAMD_{24}$ week 4	23.1 ± 5.2	26.5 ± 11.7	62, 0.25	0.62
BDI baseline	27.9 ± 7.2	31.3 ± 12.1	17, 0.45	0.32
BDI week 2	23.3 ± 8.8	27.7 ± 13.5	17, 0.58	0.45
BDI week 4	21.7 ± 7.0	26.4 ± 14.5	17, 0.39	0.60
CGI baseline	4.6 ± 1.7	4.5 ± 2.3	17, 0.64	0.65
CGI week 2	4.9 ± 0.7	5.2 ± 0.6	17, 0.48	0.34
CGI week 4	4.6 ± 0.5	4.6 ± 0.8	17, 0.27	>0.99
PANAS pos. Baseline	17.5 ± 2.3	17.3 ± 2.6	17, 0.56	0.60
PANAS pos. week 2	20.6 ± 1.9	16.9 ± 2.2	17, 0.40	0.08
PANAS pos. week 4	19.4 ± 2.6	17.8 ± 2.9	17, 0.50	0.28
PANAS neg. Baseline	26.8 ± 3.4	23.4 ± 4.6	17, 0.52	0.58
PANAS neg. week 2	22.3 ± 3.1	26.7 ± 4.2	17, 050	0.20
PANAS neg. week 4	22.4 ± 3.7	25.1 ± 4.5	17, 0.45	0.34

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

interaction between treatment and study phase. The cross-validation of the mixed model showed a good performance with a correlation of 0.78 and a RMSE of 5.16. BDI and CGI ratings showed no significant difference at all between Active→Sham and Sham→Active groups. There were no significant changes in measures of verbal learning, verbal fluency, and working memory (VLMT, RWT, LNS_{WAIS}, Table 3).

Subjective mood ratings showed a significant increase in positive emotions (PANAS pos.) after real tDCS compared with sham tDCS ($P = 0.0145$), and a statistical trend for a reduction of negative emotions (PANAS neg.) after real tDCS compared with sham tDCS ($P = 0.0735$).

Impact of stimulation intensity and electrode preparation

Within this protocol, active tDCS conditions were varied in terms of stimulation intensity and electrode solutions: (1) tDCS stimulation intensity of 1 mA in the first 10 patients was compared with 2 mA in the subsequent 12 patients, (2) tap water was used in the first 15 patients and substituted with saline solution after skin lesions occurred. However, neither stimulation intensity (Figure 2B) nor electrode preparation had a significant impact on HAMD scores ($P = 0.38$ and $P = 0.83$, respectively). HAMD reduction was 20% after 1 mA stimulation and 29% after 2 mA stimulation.

Safety measures and adverse effects

All patients were systematically asked for adverse effects and reported only few and mild side effects such as slight headaches and itching skin sensations during stimulation. As long as tap water was used for electrode preparation, one patient of the 1 mA group and five patients of the 2 mA group showed brown and crusty skin lesions under the cathode, which had been reported previously.[26] No more skin lesions were observed in the last seven patients, when physiologic saline solution was used instead. Because of these unexpected adverse effects, a questionnaire similar to that proposed by Brunoni et al.[27] will be applied in subsequent studies.

Integrity of the blinding

After completion of the treatment, 19 patients were asked which sequence of treatment conditions they had received. In the group receiving active first (n = 8), five patients rated "active condition first," no one rated "sham condition first," three patients did not notice any difference between the two conditions. In the group receiving sham first (n = 11), two patients rated "active condition first," two patients rated "sham condition first," seven patients did not feel any difference. Differences between ratings in both groups were not significant ($\chi^2 = 4.545$; df = 2; $P = 0.104$). Neither the occurrence of skin lesions nor that of itching sensations had any significant impact on patients' guesses, because patients did not attribute skin lesions necessarily to real tDCS, and the ramp in and out periods of the sham stimulator provoked skin sensations similar to those of active stimulator.

Discussion

This study shows that prefrontal tDCS for a period of only 2 weeks failed to exert any meaningful therapeutic effect in treatment resistant depression compared with placebo treatment. In contrast to clinical depression ratings, subjective mood ratings using PANAS showed an increase in positive emotions and a trend towards a reduction of negative emotions after real tDCS, which may point to an influence of real tDCS on emotional regulation in major depression similar to the findings of Nahas et al.[28] for rTMS. Cognitive tasks showed no significant difference between active or sham stimulation.

It is important to emphasize that the negative finding of our study should not be generalized to tDCS as a potential therapeutic method for treating therapy-resistant depression. Indeed, our results are in contrast to other tDCS pilot trials in depression. Fregni et al.[13] reported antidepressant

Table 3 Performance in neuropsychologic tasks during and after tDCS (mean ± SD)

	Active tDCS → sham tDCS n = 11	Sham tDCS → active tDCS n = 11	df, F/χ^2	*P*
VLMT baseline	11.0 ± 4.9	13.2 ± 3.0	17, 0.47	0.17
VLMT week 2	13.1 ± 4.7	14.6 ± 4.9	17, 0.35	0.36
VLMT week 4	12.0 ± 3.4	12.8 ± 4.1	17, 0.54	0.22
RWT baseline	10.1 ± 3.7	10.8 ± 6.7	17, 0.28	0.72
RWT week 2	8.8 ± 4.5	9.3 ± 5.2	17, 0.38	0.97
RWT week 4	10.0 ± 3.8	12.0 ± 5.2	17, 0.56	0.33
LNS_{WAIS} baseline	7.4 ± 3.7	7.7 ± 3.6	17, 0.97	0.94
LNS_{WAIS} week 2	8.6 ± 4.0	7.9 ± 3.0	17, 0.39	0.72
LNS_{WAIS} week 4	7.6 ± 2.7	8.4 ± 3.1	17, 0.23	0.49

VLMT = Verbal Learning Memory Test; RWT = Regensburg Word Fluency Test; LNS_{WAIS} = Letter Number Sequencing Task of the Wechsler Adult Intelligence Scale.

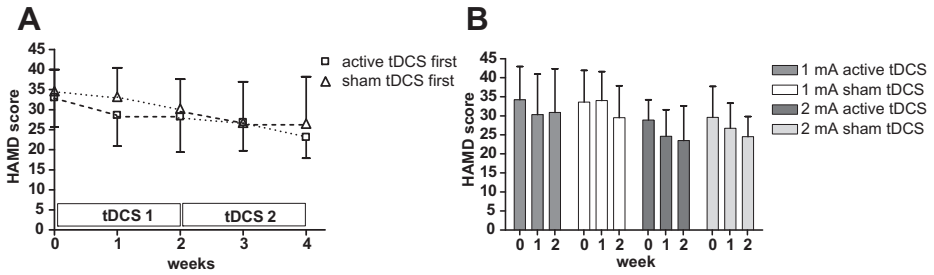

Figure 2 **A**, Time course of mean HAMD scores (± SD) during active and sham tDCS. The respective sequence of active and sham tDCS is indicated by active tDCS first (followed by sham) or sham tDCS first (followed by active). **B**, Mean HAMD scores of patients receiving 1 mA or 2 mA real tDCS compared with their respective sham condition.

effects of prefrontal tDCS (1 mA, 20 minute/session, only five sessions) superior to sham treatment in 18 drug-naïve patients with major depression. Boggio et al.[16] confirmed these findings in medication-free patients (2 mA, 20 minute/session, 10 sessions).

A higher degree of treatment resistance might be one reason for the discrepancies between previous studies and our data. Except for the study by Martin et al.,[21] treatment resistance was not an explicit inclusion criterion in previous studies. Moreover, the number of failed adequate antidepressant trials in previous studies was lower compared with our study, i.e., 1.0-2.6 versus 2.9 (Table 1). This higher degree of therapy-resistance in our patients might also have contributed to the rather low placebo response rate.[29] Very little data have been published on tDCS in treatment resistant depression. Recently, Ferrucci et al.[17] reported in an open trial that tDCS applied twice daily (2 mA, 20 minutes) led to a 30% reduction of baseline HAMD scores after only 5 days, whereas we found an improvement of only 25% altogether after 4 weeks placebo and real tDCS.

Another reason for the lack of efficacy could be the relatively higher mean age of our patient sample compared with previous tDCS studies (56 versus 46-54 years, Table 1), as age may be generally associated with a poorer antidepressant response to transcranial brain stimulation.[30]

A third reason for the lack of tDCS efficacy in our study could be the interaction between tDCS and antidepressant medication. Loo et al.[19] also recently failed to confirm antidepressant efficacy of tDCS in not explicitly treatment-resistant patients at similar stimulation parameters as applied by Fregni et al.[12] However, half of these patients were not free of antidepressant medication. Indeed, tDCS trials in healthy subjects suggest a marked impact of serotonergic or dopamine-modulating medication on nonfocal plasticity.[31,32]

The interpretation of our findings is limited by the small sample size and we cannot fully exclude missing a therapeutic action because of a type II error. Larger placebo-controlled trials are definitely required in this field. In addition, we would like to recommend extending the treatment period to 4 or 6 weeks, as we did not observe any clinically meaningful effect in our study after a 2-week treatment period.[21] Another limitation is the lack of randomization for current strengths. tDCS was applied with 1 mA or 2 mA in sequential patient groups as the dose-response relationship for tDCS in depression has not been clarified yet. As mentioned previously, we started with a lower intensity and switched to 2 mA after 1 mA had turned out to be considerably safe. The size of antidepressant effects did not differ between 1 mA and 2 mA intensity. However, a solid conclusion is hampered by both the lack of randomization and the small group sizes.

A third limitation is the cross-over design without an interval between the two conditions. Thus, carry-over effects from active treatments may have occurred during sham tDCS, blurring differences between the two conditions. In this case, we would expect, that the Active→Sham condition differs from the Sham→Active condition regarding the outcome after 4 weeks. This was not the case., Moreover, our study design exactly followed an early milestone study demonstrating the antidepressant efficacy of rTMS in therapy-resistant depression.[33]

The most unexpected adverse effect of the study was the occurrence of skin lesions underneath the anode in six patients of the active group (one patient with 1 mA and generally irritable skin, five patients with 2 mA). In these patients, tap water was used for soaking the sponges. After changing to saline solution, which has been proposed to provoke less uncomfortable sensations,[34] no more skin lesions occurred. These lesions were interpreted as skin burnings caused by drying of the tap water soaked sponge electrodes, including the occurrence of a bacterial superinfection.[26] It is possible that the ionic binding of the NaCl solution prevents sponge electrodes from drying out and keeps impedance at a low level. Another explanation could be that the degree of water hardness plays a role, because water hardness is high in Munich and Regensburg (Frank and colleagues[35]) compared with Göttingen (Nitsche and colleagues) and Perth (Dundas and colleagues[34]). This question will be addressed in a separate study on safety and tolerability of tDCS (Palm et al., in preparation) and should be subject to further systematic assessments.

Conclusions

Taking into account the small sample size and the possible carry-over effects, anodal tDCS of the DLPFC for 2 weeks did not produce a clinically relevant antidepressant effect in our patients having therapy-resistant depression. However, changes in the PANAS subscales may point to tDCS-mediated effects on the emotional regulation in depressed subjects. A longer period of stimulation could have led to more pronounced results. Nevertheless, tDCS is a promising intervention for noninvasive stimulation of the human cortex and larger sham-controlled studies at optimized parameters are needed to explore its potential for therapeutic brain stimulation in therapy-resistant depression. Because of its economic advantages, tDCS should systematically be explored in trials comparing tDCS and pharmacotherapy, as previously published and ongoing in the SELECT tDCS study.[14,36]

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.brs.2011.08.005.

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